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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA Complete Response
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Reviewer Name(s)	Valerie S.W. Pratt, M.D.
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Established Name	Alogliptin and alogliptin/pioglitazone FDC
(Proposed) Trade Name	Nesina and Oseni
Therapeutic Class	DPP4 inhibitor and DPP4 inhibitor/TZD FDC
Applicant	Takeda

Formulation(s)	Tablet
Dosing Regimen	Alogliptin: 6.25, 12.5, or 25 mg daily FDC: 12.5/15, 12.5/30, 12.5/45, 25/15, 25/30, 25/45 mg daily
Indication(s)	Type 2 diabetes mellitus
Intended Population(s)	Adults

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Abbreviations

ADA	Antidiabetic agent
ACEI	Angiotensin converting enzyme inhibitor
AE	Adverse event
Alo or A	Alogliptin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AP	Alkaline phosphatase
ARB	Angiotensin II receptor blocker
AUC	Area under the curve
BE	Bioequivalence
BID	Twice daily
Bili	Bilirubin
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CG	Cockcroft-Gault
CHF	Congestive heart failure
CI	Confidence interval
C _{max}	Maximum concentration
CMC	Chemistry Manufacturing and Controls
CR	Complete response
Cr	Creatinine
CrCl	Creatinine clearance
CRF	Case report form
CV	Cardiovascular
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DMC	Data monitoring committee
DMEP	Division of Metabolism and Endocrinology Products
DMEPA	Division of Medication Error Prevention and Analysis
DMF	Drug master file
DMPP	Division of Medical Policy Programs
DPP-4	Dipeptidyl peptidase 4
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOR	End of Review
ESRD	End stage renal disease
FAS	Full analysis set
FDC	Fixed dose combination

FPG	Fasting plasma glucose
GGT	γ-glutamyl-transferase
GIP	Glucose-dependent insulintropic polypeptide
GLP-1	Glucagon-like polypeptide-1
HCl	Hydrochloride
Hct	Hematocrit
HDL	High-density lipoproteins
HEV	Hepatitis E virus
Hgb	Hemoglobin
HgA1c	Hemoglobin A1c
HOMA-BCF	Homeostasis model assessment – beta cell function
HTN	Hypertension
IAS	Integrated analysis of safety
IND	Investigational new drug
IRB	Institutional review board
IV	Intravenous
K-M	Kaplan-Meier
LDL	Low-density lipoproteins
LOCF	Last observation carried forward
LS	Least squares
LSEC	Liver safety evaluation committee
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
Met or M	Metformin
NAI	No action indicated
MI	Myocardial infarction
MTD	Maximum tolerated dose
MMRM	Mixed model repeat measures
NDA	New drug application
NME	New molecular entity
NYHA	New York Heart Association
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PCDR	Potential cutaneous drug reaction
PD	Pharmacodynamics
PDCO	EMA's pediatric committee
PeRC	Pediatric Review Committee
PI	Prescribing information
PIP	Pediatric investigation plan
Pio	Pioglitazone
PK	Pharmacokinetics
PMR	Postmarketing requirement
PPARγ	Proliferator-activated receptor γ

PPG	Postprandial glucose
PPS	Per protocol set
PREA	Pediatric Research Equity Act
PRN	As needed
PSUR	Periodic Safety Update Report
PT	Pharmacology/toxicology
QD	Daily
RBC	Red blood cells
REMS	Risk evaluation and mitigation strategies
RI	Renal insufficiency
SAE	Severe adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SD	Standard deviation
SMQ	Standardized MedDRA query
SOC	Systems organ class
Study 402	CV study SYR-322_402
SU	Sulfonylurea
SY	Subject-years
T1/2	Half-life
T2DM	Type 2 diabetes mellitus
Tg	Triglycerides
TID	Three times daily
Tmax	Time to peak plasma concentration
TZD	Thiazolidinedione
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection
URI	Upper respiratory tract infection
VAI	Voluntary action indicated
WBC	White blood cells

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of the following two NDAs, pending an approvable recommendation from the Office of Compliance for the GMP status of manufacturing/testing sites:

- NDA 22-271: Alogliptin (SYR-322) for the use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM
- NDA 22-426: Alogliptin/pioglitazone FDC for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both alogliptin and pioglitazone is appropriate

1.2 Risk Benefit Assessment

The efficacy of alogliptin and alogliptin/pioglitazone FDC was previously demonstrated in the original NDA submissions. Alogliptin results in a 0.4% - 0.6% reduction in HbA1c from baseline at week 26 relative to placebo. Alogliptin/pioglitazone FDC results in an additional reduction of 0.4% - 0.6% over pioglitazone monotherapy and 0.4% - 0.9% over alogliptin monotherapy.

As agreed at the EOR meeting, 20 controlled phase 2 and 3 studies were pooled for the safety analysis (003, 007, 008, 009, 010, 011, 303, 301, 402, OPI-001, OPI-002, OPI-004, CCT-001, CCT-003, CCT-004, CCT-005, CCT-006, MET-302, 308, and 305). (See Table 4 for relevant cutoff dates.) Studies entitled "CCT" were conducted in Japan. Study 308 was conducted in China. Study 402 enrolled subjects with acute coronary syndrome. A total of 5987 subjects received comparators, 6626 received alogliptin 25 mg, and 9857 subjects received alogliptin. A total of 2421 subjects have been exposed to alogliptin for ≥ 1 year.

The risks of alogliptin and alogliptin/pioglitazone FDC are as follows:

- Hepatotoxicity: On April 25, 2012, a second CR was issued to the alogliptin and alogliptin/pioglitazone FDC NDAs due to 1) numerical imbalances not favoring alogliptin for serum ALT elevations $>5x$, $>10x$, and $>20x$ the ULN compared to control and 2) five probable cases of alogliptin hepatotoxicity among the estimated 219,000 patient-years of postmarketing experience in Japan. As agreed at the EOR meeting, the sponsor submitted safety data from 20 controlled phase 2 and 3 studies and the fourth Japanese PSUR. In controlled phase 2 and 3 studies which contain 9857 subjects exposed to alogliptin, the incidence of transaminase elevations was low and lower than with active

comparators (glipizide, metformin, and pioglitazone) and all comparators (active comparators and placebo). The number and percentage of alogliptin subjects who had ALT ≤ 3 x ULN at baseline and shifted to >10 x ULN during treatment or at endpoint was similar to placebo (<0.1 and 0, respectively). Although 1) K-M curves indicate that cumulative rate of ALT elevations >10 x ULN is greater in the all alogliptin group than the all comparator group during the first 120 days of treatment and 2) there are cases of probable alogliptin hepatotoxicity, these cases are infrequent and, according to Leonard Seeff's first review "trivial" once the drug is discontinued. Therefore, in my opinion, review of the current clinical database supports approval of alogliptin. The sponsor proposes including hepatic enzyme elevations in the labeling section 6.2 Postmarketing Experience. I agree with this proposal and also recommend a hepatotoxicity warning. Hepatotoxicity should be monitored as an adverse event (AE) of special interest in the controlled CV study 402, the PSURs, and an enhanced pharmacovigilance PMR.

- Hypersensitivity: Serious hypersensitivity events were observed under the alogliptin IND and NDA. When compared by treatment group, the incidence of all events in the severe cutaneous adverse reactions, angioedema, and anaphylactic SMQs was similar between treatment groups. The occurrence of these events is consistent with other DPP-4 inhibitors and is not an approvability issue but needs to be adequately labeled when alogliptin is approved. I recommend that the use of alogliptin be contraindicated in subjects with a history of serious hypersensitivity reaction to alogliptin. I also recommend a warning and description of the events. Hypersensitivity should be monitored as an adverse event (AE) of special interest in the controlled CV study 402, the PSURs, and an enhanced pharmacovigilance PMR.
- Skin lesions: The percentage of subjects reporting PCDR events was higher in the alogliptin 25 mg and all alogliptin groups when compared to all comparators (6.9% and 7.4% versus 5.7%). (The list of preferred terms comprising PCDRs was agreed upon with the sponsor prior to resubmission.) The most common events were rash and pruritis. Although these skin reactions are not likely related to the necrotic lesions seen with other DPP4 inhibitors, they suggest that some individuals may be hypersensitive to alogliptin. This is not an approvability issue but needs to be adequately labeled when alogliptin is approved.
- Pancreatitis: The incidence of acute pancreatitis events was similar between treatment groups when stratified by narrow and/or broad events, serious events, and events leading to discontinuation of study drug. This is consistent with other DPP4 inhibitors and is not an approvability issue but needs to be adequately labeled when alogliptin is approved. I recommend labeling contain an acute pancreatitis warning consistent with that for other DPP4 inhibitors. I also recommend that the applicant analyze pancreatitis events as an AE of special interest in controlled CV safety study 402 (as is planned), the PSURs, and an enhanced pharmacovigilance PMR.

- Infection: Due to its mechanism of action, there is a theoretical concern that DPP-4 inhibition may increase the risk for infections. The incidence of events in the infection and infestation SOC was higher in the alogliptin 25 mg and all alogliptin groups than the all comparator group (25.6% and 27.0% versus 23.6%, respectively). The incidence of nasopharyngitis and URI was greater in the alogliptin groups when compared to the all comparators group. This is consistent with the prescribing information for approved DPP-4 inhibitors which describes an increase in common infections, such as nasopharyngitis, UTI, and URI.
- Malignancy (including bladder, thyroid, and pancreatic cancer): The incidence of these AEs was similar in the three treatment groups (0.6-0.7%). The incidence of AEs of malignancy which led to discontinuation was also similar between the treatment groups (0.1-0.2%). Therefore, in the population and for the duration studied, alogliptin does not appear to increase the risk of malignancy. Although pioglitazone is associated with a potential risk for bladder cancer, relatively short-term trials with limited exposures are not the best way to assess this safety risk.
- Fractures: No additional studies were conducted with alogliptin + pioglitazone. Therefore, no additional bone fracture analyses were submitted in the second CR. In the first resubmission, the use of alogliptin with pioglitazone did not increase the risk of fracture significantly more than the use of pioglitazone alone (FDC 0.8% vs. pioglitazone 0.5%).
- Hypoglycemia: Alogliptin does not appear to increase one's risk of hypoglycemia when compared to placebo. However, a lower dose of insulin or sulfonylurea may be required to reduce the risk of hypoglycemia when used with alogliptin. This is consistent with other DPP4 inhibitors and is not an approvability issue but should be adequately labeled when alogliptin is approved.

The most common AEs associated with alogliptin were similar in the second and first resubmissions and are as follows, respectively. More alogliptin subjects experienced nasopharyngitis, URI, headache, and HTN when compared to comparator subjects.

- Nasopharyngitis (5.0% versus 3.9%)
- Hypertension (4.0% versus 2.9%)
- Headache (3.9% versus 3.9%)
- Diarrhea (3.5% versus 2.7%)
- Urinary tract infection (3.3% versus 3.7%)
- Upper respiratory tract infection (3.9% versus 3.5%)

The applicant proposes alogliptin 25 mg daily for use in subjects with normal renal function and 12.5 mg and 6.25 mg for subjects with moderate and severe RI, respectively. There is no renal safety signal in the controlled phase 2 and 3 study data using these doses. The sponsor's proposed alogliptin dosage adjustment for RI is acceptable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Although I do not recommend postmarket risk evaluation and mitigation strategies (REMS), I recommend the following information be conveyed in MGs:

- Alogliptin
 - The risk of pancreatitis (as was done for sitagliptin and saxagliptin).
 - The risk of hepatotoxicity
- Alogliptin/pioglitazone FDC
 - A MG
 - Similar to alogliptin (see above)
 - Similar to pioglitazone to ensure that the benefits of the drug outweigh the risk of CHF

1.4 Recommendations for Postmarket Requirements and Commitments

I recommend the following alogliptin postmarketing requirements (PMRs).

- An assessment and analysis of spontaneous reports of serious hepatic abnormalities, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, and severe hypersensitivity in patients treated with alogliptin. Specialized follow up should be obtained on these cases to collect additional information on the events.
- Completion of SYR-322_402 (402, EXAMINE): *A multicenter, randomized, double-blind, placebo-controlled study to evaluate CV outcomes following treatment with alogliptin in addition to standard of care in subjects with T2DM and acute coronary syndrome.* The trial should include an assessment of hepatotoxicity, hypersensitivity reactions (including severe cutaneous reactions), serious hypoglycemia, pancreatitis, and renal safety. The trial must include at least 200 alogliptin-treated patients with moderate renal impairment and 100 alogliptin-treated patients with severe renal impairment.
- Pediatric studies under the Pediatric Research Equity Act (PREA) and as further described in section 7.6.3:
 - SYR-322_104 (104): *A comparative, randomized, open-label, multicenter, single dose, pharmacokinetic, pharmacodynamic and safety study of alogliptin (12.5 mg and 25 mg) between children, adolescents, and adults with type 2 (non-insulin dependent) diabetes mellitus*
 - SYR-322_307 (307): *A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of alogliptin compared with placebo as monotherapy (with a metformin control arm) in pediatric subjects with T2DM*
 - SYR-322_309 (309): *A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of alogliptin compared with placebo when added on to metformin in pediatric subjects with type 2 diabetes*

I would also recommend the PSURs summarize the AEs of interest (e.g., hepatotoxicity, hypersensitivity [including skin lesions], pancreatitis, infection, malignancy, fracture [when used with pioglitazone], and hypoglycemia). Specifically for malignancy, the applicant should summarize pancreatic malignancy for alogliptin and pancreatic and bladder malignancy for the FDC.

2 Introduction and Regulatory Background

2.1 Product Information

Takeda Global Research and Development Center, Inc. (TGRD) has submitted class 2 CRs to NDAs 22-271 and 22-426 for NME alogliptin (a DPP-4 inhibitor) and alogliptin/pioglitazone FDC, respectively. On August 16, 2012, the same information was also submitted as a Major Amendment to alogliptin/metformin FDC NDA 203-414. (See also my NDA 203-414 review.)

In NDA 22-271, the applicant proposes use of 6.25, 12.5, or 25 mg alogliptin daily as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The recommended dose of alogliptin is 25 mg daily, taken with or without food as mono- or combination therapy. The sponsor recommends dosage adjustment in patients with moderate or severe RI and in patients with ESRD requiring dialysis as shown in Table 1.

Table 1. NDA 22-271: Sponsor-proposed alogliptin dosage adjustment for moderate, severe, and ESRD

Degree of renal insufficiency	Serum creatinine levels (mg/dl)	Creatinine clearance (ml/min)	Recommended dosing
Moderate	Men > 1.7 to ≤ 3.0 Women > 1.5 to ≤ 2.5	≥ 30 to < (b) (4)	12.5 mg once daily
Severe/ESRD	Men > 3.0 Women > 2.5	< 30	6.25 mg once daily*

*Without regard to timing of dialysis in patients with ESRD

In NDA 22-426, the applicant proposes the use of alogliptin/pioglitazone FDC 12.5/15, 12.5/30, 12.5/45, 25/15, 25/30, or 25/45 mg daily as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both alogliptin and pioglitazone is appropriate. Pioglitazone is a TZD, specifically a PPAR γ agonist. The applicant recommends a dose reduction for the alogliptin component from 25 mg to 12.5 mg daily in patients with moderate RI. Use of the FDC is not recommended in patients with severe RI or ESRD, because a FDC formulation has not been developed that provides the dose of alogliptin (6.25 mg) required for these patients. On February 23,

2010, the agency agreed that, due to low expected use (<2%), the applicant need not manufacture FDC doses containing 6.25 mg alogliptin. Product labeling can appropriately address dosing of patients with severe RI through co-administration of alogliptin and pioglitazone.

2.2 Tables of Currently Available Treatments for Proposed Indications

Medications currently approved for the treatment of T2DM include the following:

- Insulin
- Sulfonylureas (SUs)
 - Tolazamide (Tolinase)
 - Chlopropramide (Diabinese)
 - Glyburide (Micronase)
 - Glipizide (Glucotrol and Glucotrol XL)
 - Glimepiride (Amaryl)
- Meglitinide analogs: Repaglinide (Prandin)
- D-Phenylalanine: Nateglinide (Starlix)
- Biguanides: Metformin (e.g., Glucophage and Glucophage XR)
- Thiazolidinediones
 - Rosiglitazone (Avandia)
 - Pioglitazone (Actos)
- α -Glucosidase inhibitors
 - Acarbose (Precose)
 - Miglitol (Glyset)
- GLP-1 receptor agonists
 - Exenatide (Byetta and Bydureon)
 - Liraglutide (Victoza)
- Amylinomimetics
 - Pramlintide (Symlin)
- Dipeptidyl peptidase 4 inhibitors
 - Sitagliptin (Januvia)
 - Saxagliptin (Onglyza)
 - Linagliptin (Tradjenta)
- Bile acid sequestrants
 - Colesevelam (WelChol)
- Dopamine receptor agonists
 - Bromocriptine mesylate (Cycloset)
- FDCs of the various oral medications listed above

2.3 Availability of Proposed Active Ingredient in the United States

Alogliptin is not currently approved for use in the United States (US). Pioglitazone has been approved for the treatment of T2DM since July 15, 1999.

Alogliptin was approved for use in Japan on April 16, 2010. The alogliptin/pioglitazone FDC was approved for use in Japan on July 1, 2011.

2.4 Important Safety Issues With Consideration to Related Drugs

Labeled safety issues for other DPP4 inhibitors include the following:

- A contraindication for patients with a history of a serious hypersensitivity reaction, such as anaphylaxis or angioedema
- Pancreatitis
- Acute renal failure, sometimes requiring dialysis
- Hypoglycemia when used with insulin or an insulin secretagogue
- Serious allergic and hypersensitivity reactions
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with DPP4 inhibitors or any other anti-diabetic drug

Additional safety concerns with DPP4 inhibitors include the following:

- Infections: DPP4 has many substrates other than GIP and GLP-1, including chemokines involved in immune development and function. DPP-4 is expressed on a subset of CD4+ and CD8+ T-cells and natural killer cells. Thus, there is a theoretical concern that DPP-4 inhibition may increase the risk for infections.
- Skin lesions: Necrotizing skin lesions, which have been observed in monkeys given other DPP4 inhibitors, were not seen in alogliptin studies in mice, rats, dogs, or monkeys. The NOAEL for skin-related toxicity in the 13 week monkey study was 30 mg/kg/d (the highest tested dose), which provided approximately 31x expected human exposure. The lack of cutaneous toxicity may be due to alogliptin's high selectivity for DPP4, as opposed to DPP8 and/or DPP9.
- Hepatotoxicity: Vildagliptin, another DPP4 inhibitor may cause hepatotoxicity.
- Malignancy: Studies suggest that DPP4 (CD26) may have a role in human tumor progression.¹ Diabetic individuals may be at increased risk of malignancy. Furthermore, long-acting GLP-1 analogues, such as liraglutide and exenatide once-weekly, increase thyroid C-cell adenomas and/or carcinomas in rats and/or mice. The alogliptin NOAEL for rat thyroid C-cell tumors was 32x. Exposure multiples were higher ($\geq 188x$) for doses that caused increased combined thyroid C-cell adenomas and carcinomas in male rats. There is no evidence of increased C-cell tumors with 3 other DPP4 inhibitors, sitagliptin, (b) (4) and saxagliptin. There was an absence of other drug-related tumors in rats ($>400x$ female MRHD) or mice (60x MRHD).

¹ Kajiya H, Shibata K, Ino K, Mizutani S, Nawa A, Kikkawa F. The expression of dipeptidyl peptidase IV (DPPIV/CD26) is associated with enhanced chemosensitivity to paclitaxel in epithelial ovarian carcinoma cells. Cancer Sci 2010;101(2):347-54.

Labeled safety issues for pioglitazone include the following:

- A boxed warning for congestive heart failure (CHF) and contraindication for patients with established New York Heart Association (NYHA) Class III or IV heart failure
- A contraindication for patients with a history of serious hypersensitivity reaction to pioglitazone or its ingredients
- Warnings and precautions for the following:
 - Dose-related edema
 - Hepatic effects
 - Increased incidence of fractures in female patients
 - Bladder cancer
 - Hypoglycemia when used with insulin or an insulin secretagogue
 - Macular edema
 - Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with pioglitazone or any other anti-diabetic drug

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On April 25, 2012, a second CR was issued for the alogliptin and alogliptin/pioglitazone FDC NDAs. The applicant adequately addressed the deficiencies communicated in action letters dated June 6, 2009 and September 2, 2009 for NDA 22-271 and 22-426, respectively. However, alogliptin has a concerning signal for DILI that is stronger than that seen with other DPP4 inhibitors. In the controlled phase 2/3 clinical trial database, there are numerical imbalances not favoring alogliptin for serum ALT elevations >5x, >10x, and >20x the ULN compared to control. In addition, five probable cases of alogliptin hepatotoxicity were identified among the estimated 219,000 patient-years of postmarketing experience in Japan, the only country where alogliptin is approved. Yet, alogliptin has not been shown to have a unique benefit over already approved DPP4 inhibitors. Based on the available data, we concluded that the potential benefit of alogliptin did not exceed its risk.

We advised the applicant to provide additional postmarketing data from countries where alogliptin is approved as well as additional clinical trial data to provide reassurance that alogliptin hepatotoxicity is of limited clinical significance. We also encouraged the applicant to perform enhanced pharmacovigilance for all potential cases of DILI reported.

The following agreements regarding the resubmission were made at the EOR meeting on June 29, 2012:

- The April 2012 IAS exposure sufficiently exceeds that of the July 2011 submission, so as to justify submission of the data for a complete review.
- A case of hepatotoxicity need not be devoid of all confounding factors prior to attributing the event of alogliptin therapy.

- The structure and contents of the resubmission were agreed upon.
 - A revised CSE will not be included in the submission.
 - Safety data for the following will be submitted: CV safety, renal safety, hypersensitivity, skin lesions, pancreatitis, infections, malignancy, fractures, and hypoglycemia.
- Data from uncontrolled, open-label extension study OLE-012 will not be summarized within Module 2.7.4.
- Efficacy data from completed study MET-302 will be included in the PI.
- (b) (4) will not be included in the PI, although the associated safety data will be included.
- The Agency's regulations favor disclosure of information in an application (including CV safety data) after the application has been approved. However, the Agency is not inclined to place CV safety data in the label.
- The process for enhanced monitoring of postmarketing liver-related cases was agreed upon. The LSEC will review new cases on a monthly basis, and their assessments will be subsequently submitted to the Agency. The applicant, LSEC, and Agency may discuss these cases.
- The applicant may submit data from the April 2012 IAS to the alogliptin/metformin FDC NDA as a major amendment.
- As approval of the FDC NDAs is contingent on the Agency's conclusion that the deficiencies for the alogliptin NDA have been adequately addressed, discretion may be taken with regard to the completion dates for NDAs 22-271, 22-426, and 203-414.

2.6 Other Relevant Background Information

On July 27, 2012, the applicant requested elimination of the REMS for the alogliptin/pioglitazone FDC due to the May 17, 2012 approval of a supplemental NDA for pioglitazone NDA 21-073, which released the REMS requirement.

Liver safety reports were submitted on the following dates:

- August 14, 2012: Follow up TCI2011A02933
- September 13, 2012: Follow up TPG2012A01058
- September 25, 2012: Initial TCI2012A05429
- October 10, 2012: Follow up TCI2012A05586 and TCI2012A05429
- November 15, 2012: Follow up report TCI2012A05586
- November 30, 2012: Initial report TCI2012A06036

On August 27, 2012, the applicant submitted a comparison document (b) (4).

However, on October 22, 2012, the applicant withdrew this amendment.

On October 5, 2012, the applicant submitted a response to our September 24 and 26, 2012 liver safety information requests. It also submitted an updated SCS Table 3.d, which did not include placebo subject 8481-010/402.

October 11, 2012, the applicant submitted a response to our September 21, 2012 inquiry regarding pediatric study SYR-322_309.

On November 1, 2012, the applicant submitted the LSEC's assessment of liver safety case TCI2012A05586.

On November 7, 2012, the applicant submitted a revised pediatric deferral request.

On November 9, 2012, the applicant submitted a response to our October 29 liver safety information request.

On November 27, 2012, the applicant submitted the LSEC's consensus adjudication of hepatic case TCI2012A05429.

On January 7 and 9, 2013, the applicant submitted responses to our information requests.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The electronic submissions were of reasonable quality. The information was well organized.

3.2 Compliance with Good Clinical Practices

The key clinical studies that are part of the alogliptin and alogliptin/pioglitazone FDC resubmissions [Chinese study 308, study 305 [cutoff 4/24/12], and study 402 [cutoff 4/18/12]] were conducted according to the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP).

As 1) OSI already investigated study 402 sites and 2) (b) (4)
(b) (4) OSI was not consulted to inspect study sites.

3.3 Financial Disclosures

All active clinical investigators certified that no financial interests or arrangements existed during the conduct of the clinical study, except for the following:

(b) (6)

Financial information for all studies except 305 was previously reviewed. (b) (4)
Finally, potential bias was minimized by the studies' large, randomized, double-blind design.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

As the second CR was issued due to a clinical safety finding, only clinical information was submitted in the July 26, 2012 CR.

Because an issue was identified at the Osaka, Japan manufacturing site, the sponsor received a Form 483. The recommendation from the Office of Compliance for the GMP status of alogliptin manufacturing/testing sites is still pending.

4.1 Chemistry Manufacturing and Controls

Please refer to John Hill's January 4, 2012 review of the first alogliptin and alogliptin/pioglitazone FDC CR, which recommends approval.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Please refer to David Carlson's and Todd Bourcier's January 18, 2012 reviews, which include discussion of the alogliptin/metformin rat embryofetal development study. No drug-related fetal abnormalities considered relevant to human subjects were identified in the combination embryofetal toxicology study conducted in rats. The non-clinical pharmacology/toxicology reviewers recommended approval of the alogliptin and alogliptin/pioglitazone FDC NDAs.

4.4 Clinical Pharmacology

Please refer to Sang Chung's January 18, 2012 reviews. He accepted the applicant's proposed dosing regimen (including the use of alogliptin 25 mg daily in patients with mild RI) based on the pharmacokinetic data and recommended approval.

4.4.1 Mechanism of Action

Alogliptin is a DPP4 inhibitor, which slows the inactivation of incretin hormones (including GLP-1 and GIP) and thus increases insulin levels and decreases glucagon levels in a glucose-dependent manner. Pioglitazone is a PPAR γ agonist. Activation of PPAR γ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism. Please refer to my May 13 and July 1, 2009 reviews of the alogliptin and alogliptin/pioglitazone FDC NDAs for full details.

4.4.2 Pharmacodynamics

Single-dose administration of alogliptin to healthy subjects produced rapid and nearly complete inhibition of DPP-4. Peak inhibition occurred within 2 to 3 hours after dosing and exceeded 93% across doses of 12.5 mg to 800 mg. Inhibition of DPP-4 remained above 80% at 24 hours for doses of 25 mg and above.

Comment: There is no clear relationship between degree or duration of GLP-1 inhibition and glycemic control. Although applicants often use the percent inhibition data for early potential dose selection, it is unclear how these findings and GLP-1 concentrations relate to changes in glycemic control in T2DM patients. Therefore, the change in HbA1c compared to baseline remains to be the most significant information when determining efficacy.

Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, and improves hepatic sensitivity to insulin. In patients with T2DM, the decreased insulin resistance produced by pioglitazone results in lower plasma glucose concentrations, lower plasma insulin concentrations, and lower A1C values.

Please refer to my May 13 and July 1, 2009 reviews of the alogliptin and alogliptin/pioglitazone FDC NDAs as well as the clinical pharmacology reviews for full details.

4.4.3 Pharmacokinetics

The absolute bioavailability of alogliptin is approximately 100%. As total and peak exposures were not altered by administration with a high-fat meal, alogliptin may be administered with or without food. It is well distributed into tissues and negligibly bound

to plasma proteins (20%). Alogliptin does not undergo extensive metabolism and 60-71% of the dose is excreted as unchanged drug in the urine.

Following oral administration of pioglitazone hydrochloride, peak concentrations of pioglitazone were observed within 2 hours. Food slightly delays the time to peak serum concentration (T_{max}) to 3 to 4 hours, but does not alter the extent of absorption (AUC). Pioglitazone is extensively protein bound (>99%) in human serum, mainly to serum albumin. Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Following once daily administration of pioglitazone, steady-state serum concentrations of both pioglitazone and its major active metabolites are achieved within 7 days.

Please refer to my May 13 and July 1, 2009 reviews of the alogliptin and alogliptin/pioglitazone FDC NDAs as well as the clinical pharmacology reviews for full details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2. Controlled phase 2 and 3 studies conducted in the CR

Study	Study Design Primary Objective	Population No. and Type	Treatment Duration	Treatment
Previously Submitted and Reviewed				
SYR-322-003 Dose-ranging	Randomized, double blind, placebo controlled, comparison Efficacy (HbA1c)	265 T2DM on no treatment, SU, Met or a combination of SU + Met	12 weeks	Placebo Alogliptin 6.25, 12.5, 25, 50, or 100 mg QD
SYR-322-SULF-007 Add-on to SU	Randomized, double blind, placebo controlled, 3 treatment arm Efficacy (HbA1c)	500 T2DM receiving SU	26 weeks	Alogliptin 12.5 + SU Alogliptin 25 + SU Placebo + SU
SYR-322-MET-008 Add-on to Met	Randomized, double blind, placebo controlled, 3 treatment arm Efficacy (HbA1c)	527 T2DM receiving Met	26 weeks	Alogliptin 12.5 + Met Alogliptin 25 + Met Placebo + Met
SYR-322-TZD-009 Add-on to TZD	Randomized, double blind, placebo controlled, 3 treatment arm Efficacy (HbA1c)	493 T2DMs receiving pioglitazone alone or in combination with Met or SU	26 weeks	Alogliptin 12.5 + pioglit Alogliptin 25 + pioglit Placebo + pioglit
SYR-322-PLC-010 Monotherapy	Randomized, double blind, placebo controlled, 3 treatment arm Efficacy (HbA1c)	329 T2DM	26 weeks	Alogliptin 12.5 Alogliptin 25 Placebo
SYR-322-INS-011 Add-on to insulin	Randomized, double blind, placebo controlled, 3 treatment arm	390 subjects with T2DM receiving insulin alone or in combination with Met	26 weeks	Alogliptin 12.5 + insulin Alogliptin 25 + insulin Placebo + insulin

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	Efficacy (HbA1c)			
SYR-322_303 (303) Elderly	Randomized, double blind, active controlled Efficacy (HbA1c)	441 T2DM aged 65-90 years	52 week	Alogliptin 25 Glipizide 5 or 10
SYR-322_301 (301) Postprandial lipids	Randomized, double blind, active and placebo controlled Efficacy (triglycerides)	71 T2DM on no treatment, Met, SU, nateglinide, or repaglinide	16 weeks	Alogliptin 25 Alogliptin 25 + pioglit 30 Placebo
SYR-322_402 (402) CV outcomes with 4/18/12 cutoff*	Randomized, double blind, placebo controlled Safety (CV outcomes)	2149 T2DM (interim) 5400 T2DM (planned)	Up to 4.75 years	Alogliptin 25 or placebo + standard of care
01-05-TL-322OPI-001 Combination add-on to Met	Randomized, double blind, placebo controlled, parallel group factorial Efficacy (HbA1c)	1554 T2DM on Met	26 weeks	Placebo + placebo or pioglit 15, 30, or 45 Alogliptin 12.5 + placebo or pioglit 15, 30, or 45 Alogliptin 25 + placebo or pioglit 15, 30, or 45
01-06-TL-322OPI-002 Initial combination therapy	Randomized, double blind, active controlled Efficacy (HbA1c)	655 T2DM	26 weeks	Alogliptin 12.5 + placebo or pioglit 30 Alogliptin 25 + placebo or pioglit 30
01-06-TL-322OPI-004 (OPI-004) Add-on to pioglitazone and Met	Randomized, double blind, active controlled Efficacy (HbA1c)	803 T2DM on Met + pioglitazone	52 week	Alogliptin 25 + pioglit 30 Pioglitazone 45
CCT-001 Japanese monotherapy	Randomized, double blind, placebo controlled Efficacy (HbA1c)	480 T2DM	12 week	Alogliptin 6.25 Alogliptin 12.5 Alogliptin 25 Alogliptin 50 Placebo Voglibose 0.2 mg TID
CCT-003 Japanese add-on to voglibose (α -glucosidase inhibitor)	Randomized, double blind, placebo controlled Efficacy (HbA1c)	230 T2DM on voglibose	12 week	Alogliptin 12.5 Alogliptin 25 Placebo
CCT-004	Randomized, double blind,	339 T2DM on pioglitazone	12 week	Alogliptin 12.5

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Japanese add-on to pioglitazone	placebo controlled Efficacy (HbA1c)			Alogliptin 25 Placebo
CCT-005 Japanese add-on to glimepiride	Randomized, double blind, placebo controlled Efficacy (HbA1c)	312 T2DM on glimepiride	12 week	Alogliptin 12.5 Alogliptin 25 Placebo
CCT-006 Japanese add-on to metformin	Randomized, double blind, placebo controlled Efficacy (HbA1c)	288 T2DM on metformin (500 or 750 mg/d)	12 week	Alogliptin 12.5 Alogliptin 25 Placebo
MET-302 Alo + met factorial	Randomized, double blind, placebo controlled Efficacy (HbA1C)	784 T2DM	26 week	Placebo Alogliptin 25 mg QD Alogliptin 12.5 mg BID Metformin 500 mg BID Metformin 1000 mg BID A12.5 + Met 500 BID A 12.5 + M 1000 BID
Newly Submitted				
308 Chinese monotherapy, add-on to met, & add-on to pio (± met)	Randomized, double blind, placebo controlled Efficacy (HbA1c)	506 T2DM on diet, metformin, or pioglitazone (± met)	16 week	Alogliptin 25 Placebo
305 Add-on to met Ongoing (cutoff 4/24/12, week 52)	Randomized, double blind, active (SU) controlled Efficacy (HbA1c)	2638 T2DM on metformin	2 year	Alogliptin 12.5 Alogliptin 25 Glipizide 5-20 mg

* Previous cutoff was April 29, 2011

5.2 Review Strategy

The applicant submitted the following new phase 3, randomized, double-blind, controlled data in the CR, which were reviewed along with Japanese PSUR 4 (10/16/11 – 4/15/12):

- SYR-322_308 (308): *An international, multicenter, randomized, double-blind, placebo-controlled, phase 3 study to determine the efficacy and safety of SYR-322 when used in subjects with type 2 diabetes* (Study was conducted in China, Taiwan, and Hong Kong.)
- Ongoing SYR-322_305 (305, cutoff 4/24/12, week 52): *A multicenter, randomized, double-blind, active-controlled study to evaluate the durability of the efficacy and safety of alogliptin compared to glipizide when used in combination with metformin in subjects with type 2 diabetes*
- SYR-322_402 (402, EXAMINE, cutoff 4/18/12): *A multicenter, randomized, double-blind, placebo-controlled study to evaluate CV outcomes following treatment with alogliptin in addition to standard of care in subjects with T2DM and acute coronary syndrome*

The sponsor also submitted the following data which was previously reviewed:

- Study 402 (cutoff 4/29/11) was reviewed under the first alogliptin CR.
- MET-302 was reviewed under alogliptin/metformin FDC NDA 203-414 and the first alogliptin CR.
- Liver safety data from Japanese CCT studies were submitted on November 7, 2011 and reviewed under the first alogliptin CR.
- Relevant liver and hypersensitivity safety data from SYR-322-OLE-012, *A long-term, open-label extension study to investigate the long-term safety of SYR110322 (SYR-322) in subjects with type 2 diabetes*, was reviewed under alogliptin/metformin FDC NDA 203-414.

As agreed at the EOR meeting, additional efficacy data were not submitted.

5.3 Discussion of Individual Studies/Clinical Trials

1) SYR-322_308: *An international, multicenter, randomized, double-blind, placebo-controlled, phase 3 study to determine the efficacy and safety of SYR-322 when used in subjects with type 2 diabetes* (Amendment 3, June 8, 2011)

Study Phase and Dates Conducted: This phase 3 study was conducted from December 23, 2010 to December 19, 2011.

Objectives:

Primary: To evaluate the efficacy of alogliptin compared to placebo when given as monotherapy, add-on to metformin, or add-on to pioglitazone (with or without metformin) on the HbA1c change from baseline at Week 16 (or Early Termination).

Secondary:

- To evaluate other measures of glycemic control between alogliptin and placebo including change from baseline at Week 16 (or Early Termination) of FPG, incidence of marked hyperglycemia (FPG ≥ 200 mg/dL), and incidence of clinical HbA1c response within each of the 3 therapy groups (monotherapy, add-on to metformin, and add-on to pioglitazone with or without metformin).
- To evaluate change from baseline at Week 16 (or Early Termination) in body weight between alogliptin and placebo within each of the 3 therapy groups (monotherapy, add-on to metformin, and add-on to pioglitazone with or without metformin).

Safety: To evaluate the safety of alogliptin compared to placebo by measuring the incidence of adverse events, clinical laboratory evaluations, physical examinations, vital signs, 12-lead ECG, and the incidence of hypoglycemic events.

Study Design: This study was a multicenter, randomized, double-blind, placebo-controlled, 16-week study in T2DM subjects. The study compared alogliptin 25 mg once daily versus placebo when used alone (monotherapy), as add-on to metformin, or as add-on to pioglitazone with or without metformin. The study was conducted in 506 T2DM subjects who had HbA1c between 7-10% and were between the ages of 18–75, inclusive.

All subjects entered into a screening period of up to 2 weeks, followed by a 4 week placebo run-in period. Following the 4 week placebo run-in period, subjects were stratified into one of the three therapy groups based upon their background antidiabetic therapy before being randomized 1:1 to receive either alogliptin 25mg QD or matching placebo QD.

- Monotherapy group: Subjects who were treated with diet and exercise for at least 2 months prior to Screening (subject received less than 7 days of any antidiabetic medication within 2 months prior to Screening).
- Add-on to metformin therapy group: Subjects who were treated with metformin for at least 3 months and at a stable dose (≥ 1000 mg/day) for at least 8 weeks prior to Screening, unless there was documentation that the subject's current dose was his or her maximum tolerated dose and MTD was ≤ 1000 mg/day.
- Add-on to pioglitazone therapy group: Subjects who were treated with a stable dose of pioglitazone alone or in combination with metformin. Both the pioglitazone and metformin were stable for at least 8 weeks prior to Screening.

There was a 16 week treatment period and a follow-up visit 2 weeks after the end of treatment. The duration of the study for these subjects was approximately 24 weeks.

Main Inclusion Criteria:

- The subject has a historical diagnosis of T2DM.
- The subject is male or female and aged 18 to 75 years, inclusive. (Legal age of consent from 21 to 75 years in Taiwan)
- The subject has a body mass index (BMI) between 20 and 45 kg/m², inclusive.
- Subject is experiencing inadequate glycemic control defined as a HbA1c concentration between 7.0% and 10.0%, inclusive, and meets one of the following criteria at Screening:
 - Monotherapy group: The subject has been treated with diet and exercise for at least 2 months prior to Screening (subject has received less than 7 days of any antidiabetic medication within 2 months prior to Screening).
 - Add-on to metformin therapy group: The subject has been treated with metformin for at least 3 months and at a stable dose (≥ 1000 mg/day) for at least 8 weeks prior to Screening, unless there is documentation that the subject's current dose is his or her MTD and MTD is ≤ 1000 mg/day).
 - Add-on to pioglitazone therapy group: The subject has been treated with a stable dose of pioglitazone alone or in combination with metformin. Both the pioglitazone and metformin must be at a stable dose for at least 8 weeks prior to Screening.
- Body weight keeps constant (fluctuation range of body weight over at least 3 months before screening is no more than 10%).
- A female subject of childbearing potential and males who are sexually active agree to use routinely adequate contraception* from signing of informed consent throughout the duration of the study and for 30 days after last dose.
- Male hemoglobin ≥ 12 g/dL and female hemoglobin ≥ 10 g/dL at screening.
- Male serum creatinine < 1.5 mg/dL and female serum creatinine < 1.4 mg/dL, or creatinine clearance > 60 mL/min based on calculation using the MDRD approximation at Screening.
- In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
- The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
- Able and willing to monitor their own blood glucose concentrations with a home glucose monitor and complete subject diary.

Main Exclusion Criteria:

- The subject has participated in another clinical study within the past 90 days or has received any investigational compound within 30 days prior to randomization

- Systolic blood pressure ≥ 180 mmHg and/or diastolic pressure ≥ 110 mmHg at Screening visit.
- Subject has a history of any hemoglobinopathy or diagnosed with a chronic anemia.
- Subject has New York Heart Association Class III or IV heart failure regardless of therapy. Currently treated subjects who are stable at Class I or II are candidates for the study.
- Subject has a history of coronary angioplasty, coronary stent placement, coronary bypass surgery, or myocardial infarction within the 6 months prior to Screening visit.
- Subject has an active or untreated malignant tumor, or having clinical remission of malignant tumor within last 5 years prior to Screening (except for basal cell carcinoma or skin squamous cell carcinoma, cervical carcinoma in situ or prostate carcinoma in situ).
- Subject has a significant clinical sign or symptom of hepatopathy, acute or chronic hepatitis, or ALT is 3 times more than upper limit of normal value.
- Subject has a history of angioedema in association with use of ACEI or ARB.
- Subject has a history of alcohol or substance abuse within the 2 years prior to Screening.
- Subject has an active proliferative retinopathy.
- Subject has been using medicine for weight loss within one month prior to screening (such as Xenical, Sibutramine, Phenylpropanolamine or similar nonprescription drugs).
- Subject has a history of organ transplantation.
- The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
- The subject has any major illness or debility that in the investigator's opinion prohibits the subject from completing the study.
- The subject has a history of hypersensitivity or allergies to any DPP-4 inhibitor.
- If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 30 days after participating in this study.

Treatments and Management: Alogliptin 25 mg or placebo daily by mouth

Study Sites Including Enrollment: 506 subjects were randomized at 30 centers in China, Taiwan, and Hong Kong.

- 185 monotherapy (92 alogliptin 25 mg daily and 93 placebo)
- 197 add-on to metformin (99 alogliptin 25 mg daily and 98 placebo)
- 124 add-on to pioglitazone with or without metformin (61 alogliptin 25 mg daily and 63 placebo)

Efficacy Assessments:

Primary: Change from baseline in HbA1c at week 16

Secondary:

- FPG
- Incidence of marked hyperglycemia (FPG \geq 200 mg/dL)
- Incidence of clinical HbA1c response

Safety Assessments: Clinical laboratory results, vital sign measurements, physical examination findings, 12-lead ECG readings, AEs, and hypoglycemia

2) SYR-322_305 (cutoff 4/24/12, week 52): A multicenter, randomized, double-blind, active-controlled study to evaluate the durability of the efficacy and safety of alogliptin compared to glipizide when used in combination with metformin in subjects with type 2 diabetes

Study Phase and Dates Conducted: This phase 3 study was initiated on March 5, 2009 and is ongoing.

Objectives:

Primary: To evaluate the durability (for up to two years) of the efficacy of alogliptin plus metformin as compared to glipizide plus metformin as measured by HbA1c change from baseline to week 52 or 104 in adults with T2DM

Secondary:

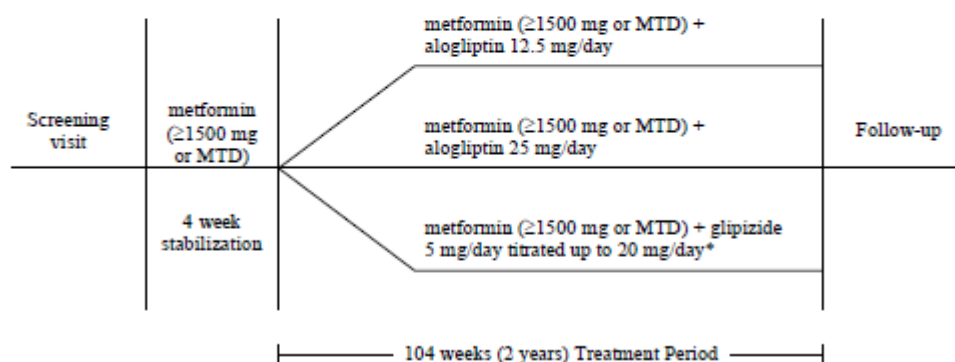
- To evaluate other measures of glycemic control after treatment with alogliptin plus metformin as compared with glipizide plus metformin, including HbA1c change from Baseline in other visit and FPG change from Baseline in all visits.
- To evaluate clinically meaningful levels of response in HbA1c after treatment with alogliptin plus metformin as compared with glipizide plus metformin.
- To evaluate changes in body weight after treatment with alogliptin plus metformin as compared with glipizide plus metformin.

Study Design: This is an international, randomized, double-blind, active-controlled, 3-treatment arm design, 2-year study using alogliptin (12.5 mg and 25 mg once daily) plus metformin versus glipizide (total daily dose of 5 mg titrated up to 20 mg) plus metformin to be conducted in 2445-2691 subjects (815-897 per arm) with a history of T2DM who are between the ages of 18 and 80, inclusive, and who are currently treated with a stable daily dose of metformin alone but experienced inadequate glycemic control (with an HbA1c between 7.0% and 9.0%, inclusive). Subjects could be randomized (1:1:1) to alogliptin 12.5 mg QD, alogliptin 25 mg QD, or glipizide 5 mg QD if they successfully completed the Stabilization Period.

Subjects who were experiencing inadequate glycemic control with HbA1c between 7.0% and 9.0%, inclusive, while on a treatment regimen of metformin at a daily dose level \geq 1500 mg (or MTD) followed Schedule A (see Figure 1). Subjects who were experiencing inadequate glycemic control with higher HbA1c levels (between 7.5%

and 10%, inclusive) with a lower metformin daily dose (<1500 mg) with no documentation of MTD followed Schedule B (see Figure 2).

Assess- ments	Screening Period (Up to 2 weeks)	Stabilization Period				Treatment Period															Follow- Up
Week	-6 to -5	-4	-3	-2	-1	baseline	1	2	4	8	12	16	20	26	39	52	65	78	91	104/ ET	106
Day		-29	-22	-15	-8	1	8	15	29	57	85	113	141	183	274	365	456	547	638	729	743

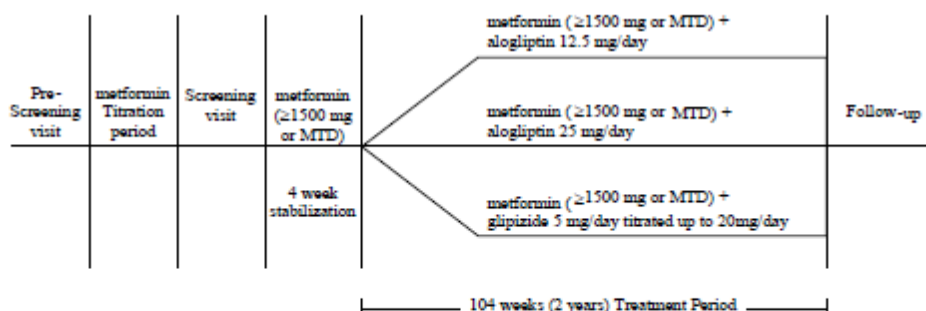


*: titration of glipizide from 5mg to 20 mg total daily dose only for subjects who demonstrate persistent hyperglycemia after at least 2 weeks but prior to Week 20.

Figure 1. Study 305: Design schedule A: If a subject is experiencing inadequate glycemic control (with HbA1c between 7.0 and 9.0%, inclusive) with metformin therapy (daily dose ≥1500 mg or MTD)

Source: Protocol 305 Amendment 14 Figure 6.a

Assess-ments	Pre-Screening Period (Up to 2 weeks)	Titration Period 8 weeks	Screening Period (Up to 1 week)	Stabilization Period	Treatment Period																			Follow-Up
Week	-15 to -14	-13 to -6	-5	-4	-3	-2	-1	baseline	1	2	4	8	12	16	20	26	39	52	65	78	91	104	ET	106
Day				-29	-22	-15	-8	1	8	15	29	57	85	113	141	183	274	365	456	547	638	729	743	



*: titration of glipizide from 5mg to 20 mg total daily dose only for subjects who demonstrate persistent hyperglycemia after at least 2 weeks but prior to Week 20.

Figure 2. Study 305: Design schedule B: If a subject is experiencing inadequate glycemic control (with HbA1c between 7.5% and 10.%, inclusive) with metformin therapy daily dose <1500 mg without documented MTD

Source: Protocol 305 Amendment 14 Figure 6.a

After at least 2 weeks of treatment but prior to Week 20, subjects demonstrating persistent hyperglycemia (defined as FPG ≥ 250 mg/dL; confirmed by a repeated FPG test within 7 days) underwent a dose titration (increase of glipizide or matching placebo from 5 mg to up to 20 mg in 5 mg increments in 4-week intervals). Alogliptin doses were not titrated but glipizide-matching-placebos were added or removed per protocol so as to maintain the double blind. Following any dose titration, a subject who experienced hypoglycemia was allowed to reduce the dose to as low as 5 mg glipizide (or matching placebo) and continue the study on that dose. Following down titration, subjects were not allowed to increase the dose again. Subjects who had continued hyperglycemia after reaching the maximum titration dose prior to Week 20 were rescued from the study.

During the Double-Blind Treatment Period (Weeks 1 through 104/Early Termination), subjects received blinded study drug as well as dietary and exercise coaching, and home glucose monitoring training. Subjects who were rescued or were discontinued from the study prior to Week 104 also underwent the end-of-

treatment assessments using an Early Termination Visit. Subjects returned to the study center 2 weeks later for a final Follow-Up Visit.

Main Inclusion Criteria: Eligible study participants are men or women aged 18 to 80 years, inclusive, with a historical diagnosis of T2DM. The subjects must have met one of the following criteria: inadequately controlled (as defined by an HbA1c concentration between 7.0% and 9.0%, inclusive) on a stable dose ≥ 1500 mg (or documented MTD) of metformin for at least 2 months prior to Screening or inadequately controlled (as defined by an HbA1c concentration between 7.5% and 10%, inclusive) on metformin < 1500 mg without documented MTD. At the Week -1 Visit, subjects were required to have an HbA1c concentration between 7.0% and 9.0%, inclusive, and a FPG < 275 mg/dL in order to be eligible for randomization.

Treatments and Management: Alogliptin 12.5 or 25 mg daily versus glipizide 5-20 mg daily

Study Sites including Enrollment: Approximately 2,445 - 2,691 subjects are planned at 310 study sites worldwide.

Efficacy Assessments:

Primary: HbA1c change from baseline at weeks 52 or 104

Secondary:

- Change from baseline in HbA1c
- Change from baseline in FPG
- Clinical response including the percentage of subjects with HbA1c $\leq 6.5\%$ and $\leq 7.0\%$
- Change from baseline in body weight

Safety Assessments: Hypoglycemia, AEs, clinical laboratory parameters, ECG, vitals, and physical examinations

6 Review of Efficacy

Efficacy Summary

The applicant proposes the following indications:

- NDA 22-271: Alogliptin for the use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM
- NDA 22-426: Alogliptin/pioglitazone FDC for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both alogliptin and pioglitazone is appropriate

The efficacy of alogliptin and alogliptin/pioglitazone FDC was demonstrated in the first NDA submission. Alogliptin results in a 0.4% - 0.6% reduction in HbA1c from baseline

at week 26 relative to placebo. Alogliptin/pioglitazone FDC results in an additional reduction of 0.4% - 0.6% over pioglitazone monotherapy and 0.4% - 0.9% over alogliptin monotherapy.

As agreed at the EOR meeting, additional efficacy data were not submitted in the second CR. Please refer to my original review of the NDAs 22-271 and 22-426 and the first CR.

6.1 Indication

The applicant proposes the following indications:

- NDA 22-271: Alogliptin for the use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM
- NDA 22-426: Alogliptin/pioglitazone FDC for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both alogliptin and pioglitazone is appropriate

6.1.1 Methods

As agreed at the EOR meeting, additional efficacy data was not submitted in the second CR. Please refer to my original review of the NDAs 22-271 and 22-426 and the first CR.

6.1.2 Demographics

Not applicable.

6.1.3 Subject Disposition

Not applicable.

6.1.4 Analysis of Primary Endpoint(s)

Not applicable.

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In my review of the first CR, I recommended that the 12.5 or 25 mg daily dose be used in subjects with normal renal function, because alogliptin 12.5 and 25 mg daily have similar efficacy in randomized clinical trials, as shown in Table 3.

Table 3. Primary efficacy results for the phase 2 and 3 clinical trials submitted to the original alogliptin NDA 22-271 (FAS population with LOCF)

Study	N	Baseline mean \pm SE	Change from baseline Adj. mean \pm SE	Difference in adjusted mean change 95% CI	p-value
Study 010 (monotherapy)					
Alo 25 mg	131	172 \pm 4	-16 \pm 4	-28 (-40, -15)	<0.001
Alo 12.5 mg	133	174 \pm 4	-10 \pm 4	-22 (-34, -9)	<0.001
Placebo	64	173 \pm 7	11 \pm 5		
Study 007 (add-on to sulfonylurea)					
Alo 25 mg	198	174 \pm 4	-8 \pm 3	-11 (-22, 1)	0.07
Alo 12.5 mg	201	172 \pm 4	-5 \pm 3	-7 (-18, 5)	0.24
Placebo	99	177 \pm 5	2 \pm 5		
Study 008 (add-on to metformin)					
Alo 25 mg	204	172 \pm 3	-17 \pm 3	-17 (-26, -9)	<0.001
Alo 12.5 mg	211	168 \pm 3	-19 \pm 3	-19 (-27, -10)	<0.001
Placebo	104	180 \pm 5	0 \pm 4		
Study 009 (add-on to pioglitazone)					
Alo 25 mg	197	170 \pm 3	-20 \pm 3	-14 (-23, -5)	0.003
Alo 12.5 mg	196	173 \pm 3	-20 \pm 3	-14 (-23, -5)	0.003
Placebo	97	171 \pm 5	-6 \pm 4		
Study 011 (add-on to insulin)					
Alo 25 mg	128	186 \pm 6	-12 \pm 6	-18 (-33, -2)	0.03
Alo 12.5 mg	131	190 \pm 5	2 \pm 6	-4 (-19, 12)	0.66
Placebo	127	196 \pm 7	6 \pm 6		
FAS=full analyses set; LOCF=last-observation-carried-forward; SE=standard error; CI=confidence interval					

Source: Dr. Hylton Joffe.

However, three NDAs containing alogliptin are now under review (alogliptin NDA 22-271, alogliptin/pioglitazone FDC NDA 22-426, and alogliptin/metformin FDC NDA 203-414). Alogliptin NDA 22-271 proposes 25, 12.5, or 6.25 mg daily, depending upon renal function. The FDC NDAs propose different alogliptin doses and dosing schemes. NDA 22-426 proposes 25 or 12.5 mg alogliptin daily, whereas NDA 203-414 proposes alogliptin 12.5 mg twice daily.

In my opinion, since three alogliptin products may enter the market at the same time with different available doses and frequencies of administration, I believe that adding another dose option (i.e. 12.5 mg daily for subjects with normal renal function), which was not proposed by the sponsor, will unnecessarily complicate the dosing of alogliptin products for prescribers and patients. It may increase the incidence of medication errors. For this reason, I support the dosing of alogliptin and alogliptin/pioglitazone as proposed by the sponsor.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

The safety review focused on the pooled, controlled phase 2 and 3 alogliptin data, with an emphasis on liver safety, as this deficiency was outlined in the CR letters. It also focused on the following AEs of special interest: hepatotoxicity, CV safety (including CHF), renal safety, hypersensitivity, pancreatitis, skin lesions, infections, malignancy (including bladder, thyroid, and pancreatic cancer), fractures, hypoglycemia, and interstitial lung disease.

As agreed at the EOR meeting, 20 controlled phase 2 and 3 studies were pooled for the safety analysis (003, 007, 008, 009, 010, 011, 303, 301, 402, OPI-001, OPI-002, OPI-004, CCT-001, CCT-003, CCT-004, CCT-005, CCT-006, MET-302, 308, and 305). (See Table 4 for relevant cutoff dates.) Studies entitled "CCT" were conducted in Japan. Study 308 was conducted in China. Study 402 enrolled subjects with acute coronary syndrome. A total of 5987 subjects received comparators, 6626 received alogliptin 25 mg, and 9857 subjects received alogliptin at any dose. A total of 2421 subjects have been exposed to alogliptin for ≥ 1 year.

Demographic data were similar between groups. More alogliptin subjects completed the studies, when compared to comparator subjects (71.7% versus 62.7%). More comparator subjects (which included placebo-treated subjects) received hyperglycemic rescue when compared to alogliptin subjects (20.7% versus 13.5%). A similar percentage of subjects were discontinued (12.4-13.3%).

Key safety findings were as follows:

- Alogliptin subjects were not at increased risk of death (2.0% placebo, 0.3% active comparator, 1.3% all comparators, 1.0% alogliptin 25 mg, and 0.7% all alogliptin).
- Alogliptin subjects experienced fewer SAEs (11.1% alogliptin 25 mg, 8.9% all alogliptin, and 12.0% all comparators). Cardiac and infection and infestation SAEs were most common. This was driven by CV study 402.
- Fewer alogliptin subjects were discontinued due to AEs (4.3% alogliptin 25 mg, 4.0% all alogliptin, and 4.8% all comparators). There was an increase in the number of subjects discontinued for renal AEs, due to the addition of metformin co-administration studies with renal rescue criteria.
- The required 1.8 CV safety margin is still met in the revised meta-analysis.
- Findings for AEs of special interest (hypersensitivity, skin lesions, pancreatitis, infections, fractures [when used with pioglitazone], and hypoglycemia) were generally consistent with those of the first resubmission.
- In the controlled clinical database, alogliptin does not appear to increase the risk of malignancy or interstitial lung disease.
- The most common alogliptin AEs were similar in the second and first resubmissions and were, respectively, as follows. More alogliptin subjects experienced nasopharyngitis, URI, headache, and HTN when compared to comparator subjects.
 - Nasopharyngitis (5.0% versus 3.9%)
 - Hypertension (4.0% versus 2.9%)
 - Headache (3.9% versus 3.9%)
 - Diarrhea (3.5% versus 2.7%)
 - Urinary tract infection (3.3% versus 3.7%)
 - Upper respiratory tract infection (3.9% versus 3.5%)
- The fourth Japanese PSUR postmarketing data was generally consistent with the clinical trial findings.

As agreed at the EOR meeting, the sponsor submitted hepatic safety data from 20 controlled phase 2 and 3 studies and the Fourth Japanese PSUR. In controlled phase 2 and 3 studies which contain 9857 subjects exposed to alogliptin, the incidence of transaminase elevation was low and lower than with active comparators (glipizide, metformin, and pioglitazone) and all comparators (active comparators and placebo). The number and percentage of alogliptin subjects who had ALT ≤ 3 x ULN at baseline and shifted to >10 x ULN during treatment or at endpoint was similar to placebo (<0.1 and 0, respectively). Although 1) K-M curves indicate that cumulative rate of ALT elevations >10 x ULN is greater in the all alogliptin group than the all comparator group during the first 120 days of treatment and 2) there are cases of probable alogliptin hepatotoxicity, these cases are infrequent and, according to Leonard Seeff's first review "trivial" once the drug is discontinued. Therefore, in my opinion, review of the current clinical database supports approval of alogliptin. The sponsor proposes including hepatic enzyme elevations in the labeling section 6.2 Postmarketing

Experience. I agree with this proposal and also recommend adding related text to Section 5 Warnings and Precautions. Hepatotoxicity should be monitored as an adverse event (AE) of special interest in the controlled CV study 402, PSURs, and a PMR.

There is no renal safety signal in the controlled phase 2 and 3 study data. The sponsor's proposed alogliptin dosage adjustment for RI is acceptable.

Alogliptin does not appear to be associated with clinically meaningful changes in vital signs or ECGs parameters. The interim analysis of ongoing CV study 402 demonstrated that alogliptin does not increase CV risk.

A full waiver of pediatric studies was granted for the alogliptin/pioglitazone FDC NDA. However, the applicant plans to conduct three alogliptin pediatric studies, as follows. (See section 7.6.2 for full details.)

- SYR-322_104 (104): *A comparative, randomized, open-label, multicenter, single dose, pharmacokinetic, pharmacodynamic and safety study of alogliptin (12.5 mg and 25 mg) between children, adolescents, and adults with type 2 (non-insulin dependent) diabetes mellitus.*
- SYR-322_307 (307): *A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of alogliptin compared with placebo as monotherapy (with a metformin control arm) in pediatric subjects with T2DM.*
- SYR-322_309 (309): *A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of alogliptin compared with placebo when added on to metformin in pediatric subjects with type 2 diabetes.*

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

My safety review focused on the pooled, controlled phase 2 and 3 alogliptin data, with an emphasis on liver safety, as this deficiency was outlined in the CR letters. As alogliptin 25 mg is the recommended dose, my safety review focused on comparing the alogliptin 25 mg and all comparators groups in the pooled studies. It also focused on the following AEs of special interest: hepatotoxicity, CV safety (including CHF), renal safety, hypersensitivity, pancreatitis, skin lesions, infections, malignancy (including bladder, thyroid, and pancreatic cancer), fractures, hypoglycemia, and interstitial lung disease. When appropriate, I included information specific to the safety of the alogliptin/pioglitazone FDC.

I also reviewed the 4th Japanese PSUR (October 16, 2011 – April 15, 2012) in section 8 Postmarket Experience.

7.1.2 Categorization of Adverse Events

The pooled safety analysis used MedDRA version 13.0. I generally agreed with the categorization of AEs.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The studies included in the 2011 and 2012 controlled phase 2 and 3 pool are shown in Table 4. Although safety data from Japanese CCT studies were included in the 2011 resubmission, they were not pooled at that time. The current pooling strategy was discussed and agreed upon at the EOR meeting. Please note however that in addition to the Japanese CCT studies, study 308 was conducted in China and study 402 enrolled subjects with acute coronary syndrome.

Table 4. Studies in controlled phase 2 and 3 pool

Studies in 2011 Resubmission (n=12)	Studies in 2012 Resubmission (n=20)
003, 007, 008, 009, 010, 011, 303, 301, 402(a), OPI-001, OPI-002, OPI-004	003, 007, 008, 009, 010, 011, 303, 301, 402(b), OPI-001, OPI-002, OPI-004, CCT-001, CCT-003, CCT-004, CCT-005, CCT-006, MET-302, 308, and 305(c)

(a) Interim data as of April 29, 2011; (b) Interim data as of April 18, 2012; (c) Interim data as of April 24, 2012

Source: SCS Table 1.a

In the pooled analysis, subjects were placed in one of the following three groups: all comparators (n=5987, received placebo, glipizide, metformin, or pioglitazone), alogliptin 25 mg (n=6626, received the 25 mg dose and all study 402 subjects randomized to receive alogliptin regardless of dose due to similar exposure determined in RI PK study), or all alogliptin (n=9857, received 6.25-100 mg).

Please see section 5.1 Tables of Studies/Clinical Trials for a full description of the pooled trials.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the original NDA, 1961 subjects were exposed to alogliptin. As shown in Table 5, in the first and second CRs, the numbers of subjects exposed to alogliptin were 5232 and

9857, respectively. When one year is defined as ≥ 365 days, 2421 subjects have been exposed to alogliptin for ≥ 1 year.

Table 5. Comparison of alogliptin exposure across submissions

Submission	Alogliptin total subject numbers (n)	Alogliptin cumulative exposure (subject-years)
July 11 NDA Resubmission	5232	2498
November 2011 Response to October 24, 2011 information request	7229	3378
July 2012 Resubmission	9857	6934

Source: SCS Table 1.d

Table 6. Exposure by dose and duration (controlled phase 2 and 3 studies)

Exposure	All Comparators (a) N=5987	Alogliptin 25 mg N=6626	All Alogliptin (b) N=9857
Duration in days (c)			
Mean (SD)	266.7 (202.74)	266.8 (197.48)	256.9 (203.15)
Median (min, max)	183.0 (1, 888)	183.0 (1, 942)	182.0 (1, 942)
Cumulative exposure (subject-years) (d)	4372.11	4840.19	6933.77
Number (%) of subjects exposed for (c)			
≤ 1 day	12 (0.2%)	11 (0.2%)	14 (0.1%)
> 1 to < 7 days	30 (0.5%)	25 (0.4%)	32 (0.3%)
≥ 7 to < 30 days	213 (3.6%)	198 (3.0%)	315 (3.2%)
≥ 30 to < 6 months	1899 (31.7%)	1806 (27.3%)	2903 (29.5%)
≥ 6 months to < 12 months	1831 (30.6%)	2466 (37.2%)	3823 (38.8%)
≥ 12 months to < 18 months	1091 (18.2%)	1153 (17.4%)	1270 (12.9%)
≥ 18 months	911 (15.2%)	967 (14.6%)	1500 (15.2%)
≥ 335 days	2002 (33.4%)	2120 (32.0%)	2770 (28.1%)
≥ 351 days	1932 (32.3%)	2053 (31.0%)	2697 (27.4%)
≥ 365 days	1685 (28.1%)	1779 (26.8%)	2421 (24.6%)

Source: IAS Tables 1.1 and 1.2.

Note: For exposure, 6 months is defined as 166 days, 12 months is defined as 335 days, and 18 months is defined as 518 days.

(a) The All Comparators grouping combines placebo and active comparator groups.

(b) The All Alogliptin grouping combines 25 mg with the 6.25, 12.5, 50, and 100 mg groups.

(c) Duration of exposure in days is calculated as date of last dose - date of first dose + 1. Last dose date is estimated for subjects ongoing in Study 402 using the earlier of the interim data cut date and the last study drug dispensing date plus the number of days in the dosing interval.

(d) Cumulative exposure in subject-years is defined as the sum of days for all subjects within a grouping divided by 365.25.

Source: SCS Table 1.e

Demographic and other baseline characteristics were well balanced between treatment groups. The majority of subjects were white with a mean age of 57-58 years, and approximately half had a BMI ≥ 30 . Mean HbA1c was $\sim 8.0\%$ and mean T2DM duration was ~ 7.0 years. These data are similar to that from the July 2011 resubmission.

In the controlled phase 2 and 3 study group, more alogliptin subjects completed the studies, when compared to comparator subjects (71.7% versus 62.7%). More comparator subjects (which included placebo-treated subjects) received hyperglycemic rescue when compared to alogliptin subjects (20.7% versus 13.5%). A similar percentage of subjects were discontinued (12.4-13.3%). The reasons for discontinuation were generally similar between groups (see Table 7).

Table 7. Disposition of subjects (Controlled phase 2 and 3 studies)

Disposition Category	n/N (%) of Subjects		
	All Comparators (a) N=5987	Alogliptin 25 mg N=6626	All Alogliptin (b) N=9857
Completed (c)	2389/3813 (62.7)	3089/4384 (70.5)	5255/7332 (71.7)
Hyperglycemic Rescue (d)	625/3026 (20.7)	465/3702 (12.6)	853/6307 (13.5)
Ongoing (c)	2172	2238	2521
Discontinued	799/5987 (13.3)	828/6626 (12.5)	1220/9857 (12.4)
Missing	2/5987 (<0.1)	6/6626 (<0.1)	8/9857 (<0.1)
Primary Reason for Discontinuation (e)			
Adverse Event	286/5734 (5.0)	286/6374 (4.5)	400/9605 (4.2)
Major Protocol Deviation	82/5734 (1.4)	76/6374 (1.2)	135/9605 (1.4)
Lost to Follow-Up	75/5734 (1.3)	75/6374 (1.2)	118/9605 (1.2)
Voluntary Withdrawal	221/5734 (3.9)	269/6374 (4.2)	382/9605 (4.0)
Study Termination	0	0	1/9605 (<0.1)
Pregnancy	2/5734 (<0.1)	3/6374 (<0.1)	5/9605 (<0.1)
Lack of Efficacy (f)	4/575 (0.7)	0	2/1145 (0.2)
Investigator Discretion (g)	64/4940 (1.3)	53/5633 (0.9)	87/8238 (1.1)
Other	43/5734 (0.7)	46/6374 (0.7)	70/9605 (0.7)

Source: IAS Table 2.

n=number of subjects with completion status, N=number of applicable subjects in population, %=(n/N)*100.

(a) The All Comparators grouping combines placebo and active comparator groups.

(b) The All Alogliptin grouping combines 25 mg with the 6.25, 12.5, 50, and 100 mg groups.

(c) Studies 305 and 402 are ongoing. Subjects who prematurely discontinued study drug in either study are counted in the denominator and subjects who completed study drug dosing in study 305 are counted in the numerator and denominator for completed study drug dosing. Subjects continuing study drug dosing in these studies are summarized as ongoing.

(d) Subjects who met the hyperglycemic rescue criteria as defined in the study protocol. These subjects are not included in the discontinuation summary. Studies 301, 402, CCT-001, CCT-003, CCT-004, CCT-005, and CCT-006 did not allow for hyperglycemic rescue, so these percentages are based on the number of subjects in each treatment grouping in all studies except these or 308.

(e) Percentages are based on the number of subjects in each treatment grouping for which the discontinuation reason was an available option. Study 308 is excluded because the reason for discontinuation of study drug was not collected.

(f) Studies 301, CCT-001, CCT-003, CCT-004, CCT-005, and CCT-006 were the only studies to include 'Lack of Efficacy' as an option for discontinuation without specified hyperglycemic rescue criteria.

(g) Studies 301, 303, CCT-001, CCT-003, CCT-004, CCT-005, and CCT-006 did not include 'Investigator Discretion' as a possible reason for discontinuation.

Source: SCS Table 1.c

7.2.2 Explorations for Dose Response

See section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations and my previous NDA reviews.

7.2.3 Special Animal and/or In Vitro Testing

No nonclinical data was included in the CR.

7.2.4 Routine Clinical Testing

The Sponsor obtained laboratory tests, vital signs, and ECGs at reasonable time points during the studies and under consistent settings, where applicable. I have reviewed the timing of these assessments in section 5.3 Discussion of Individual Studies/Clinical Trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to my previous alogliptin and alogliptin/pioglitazone FDC reviews.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As described in section 2.4 Important Safety Issues With Consideration to Related Drugs, AEs of special interest include the following: CV safety (including CHF), renal safety, hypersensitivity, pancreatitis, skin lesions, infections, malignancy (including bladder, thyroid, and pancreatic cancer), fractures, hepatotoxicity, and hypoglycemia.

The applicant analyzed CV events, hypersensitivity reactions, skin lesions, acute pancreatitis, malignancies, infections and infestations, and interstitial lung disease as AEs of interest in the SCS. It also analyzed hepatic and renal function parameters and hypoglycemia events.

Since the July 2011 resubmission, no additional studies have been conducted with alogliptin + pioglitazone. Therefore, no additional analyses were performed for bone fractures.

7.3 Major Safety Results

7.3.1 Deaths

In controlled phase 2 and 3 studies, the incidence of death was low and similar between treatment groups (2.0% placebo, 0.3% active comparator, 1.3% all comparators, 1.0% alogliptin 25 mg, and 0.7% all alogliptin) (see Table 8). The majority of deaths were due to cardiac disorders. This was driven by CV outcomes study 402.

Table 8. Deaths by SOC (controlled phase 2 and 3 studies)

SOC	Number (%) of Subjects		
	All Comparators (a) N=5987	Alogliptin 25 mg N=6626	All Alogliptin (b) N=9857
Any Death	79 (1.3)	64 (1.0)	69 (0.7)
Cardiac disorders	44 (0.7)	39 (0.6)	40 (0.4)
General disorders and administration site conditions	12 (0.2)	10 (0.2)	12 (0.1)
Infections and infestations	5 (<0.1)	5 (<0.1)	5 (<0.1)
Injury, poisoning and procedural complications	1 (<0.1)	1 (<0.1)	1 (<0.1)
Neoplasms benign, malignant, and unspecified	3 (<0.1)	0	1 (<0.1)
Nervous system disorders	3 (<0.1)	3 (<0.1)	4 (<0.1)
Psychiatric disorders	2 (<0.1)	0	0
Renal and urinary disorders	2 (<0.1)	1 (<0.1)	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	5 (<0.1)	5 (<0.1)	5 (<0.1)
Vascular disorders	2 (<0.1)	1 (<0.1)	1 (<0.1)
Uncoded	1 (<0.1)	0	0

Source: SCS Table 2.c

An additional 31 deaths were reported but are not considered treatment-emergent, because the deaths occurred more than 14 days after the last dose of study drug.

Alogliptin subjects were not at increased risk of death when compared to placebo.

7.3.2 Nonfatal Serious Adverse Events

A summary of SAEs reported by $\geq 0.1\%$ of subjects in any group in the 2011 and 2012 resubmissions is shown in Table 9. (Review of the complete list of SAEs did not reveal additional noteworthy findings, especially in light of the list of AEs of special interest described in Section 7.3.4.) As expected with the increased exposure, the incidence of any SAE was greater in the second CR. However, the incidence of SAEs was lower in the alogliptin groups (alogliptin 25 mg 11.1% and all alogliptin 8.9%) when compared to the all comparators group (12.0%).

SAEs were reported most often in the cardiac disorders SOC followed by the infections and infestations SOC. More cardiac disorder SAEs were observed in the second resubmission than the first (alogliptin 25 mg: 5.1% versus 2.9%, respectively; comparators 5.7% versus 4.1%). This is explained by the cardiac events contributed by CV study 402.

Table 9. SAEs reported by ≥0.1% of subjects in any group in the 2011 and 2012 resubmissions

SOC Preferred Term	Number (%) of Subjects					
	2011 NDA Resubmission			2012 NDA Resubmission		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232	All Comparators N=5987	Alogliptin 25 mg N=6626	All Alogliptin N=9857
Any SAE						(b) (4)
Blood and lymphatic system disorders	6 (0.2)	6 (0.2)	6 (0.1)	13 (0.2)	12 (0.2)	12 (0.1)
Anemia	5 (0.2)	5 (0.1)	5 (0.1)	9 (0.2)	10 (0.2)	10 (0.1)
Cardiac disorders						(b) (4)
Acute coronary syndrome						
Acute myocardial infarction						
Angina pectoris						
Angina unstable						
Atrial fibrillation						
Cardiac arrest						
Cardiac failure						
Cardiac failure congestive						
Coronary artery disease						
Coronary artery stenosis						
Myocardial infarction						
Myocardial ischemia						
Eye disorders	3 (0.1)	1 (<0.1)	1 (<0.1)	11 (0.2)	10 (0.2)	12 (0.1)
Cataract	2 (0.1)	0	0	7 (0.1)	3 (<0.1)	4 (<0.1)
Gastrointestinal disorders	17 (0.6)	17 (0.5)	22 (0.4)	46 (0.8)	65 (1.0)	79 (0.8)
Abdominal pain	1 (<0.1)	3 (0.1)	3 (0.1)	2 (<0.1)	7 (0.1)	8 (<0.1)
General disorders and administration site conditions	21 (0.7)	17 (0.5)	22 (0.4)	55 (0.9)	48 (0.7)	56 (0.6)
Non-cardiac chest pain	11 (0.4)	11 (0.3)	14 (0.3)	28 (0.5)	26 (0.4)	32 (0.3)
Infections and infestations	41 (1.4)	37 (1.1)	46 (0.9)	124 (2.1)	115 (1.7)	136 (1.4)
Bronchitis	1 (<0.1)	1 (<0.1)	1 (<0.1)	5 (<0.1)	9 (0.1)	9 (<0.1)
Cellulitis	2 (0.1)	2 (0.1)	2 (<0.1)	11 (0.2)	7 (0.1)	10 (0.1)
Pneumonia	9 (0.3)	6 (0.2)	6 (0.1)	32 (0.5)	25 (0.4)	26 (0.3)
Sepsis	2 (0.1)	1 (<0.1)	1 (<0.1)	9 (0.2)	5 (<0.1)	5 (<0.1)
Urinary tract infection	3 (0.1)	3 (0.1)	4 (0.1)	9 (0.2)	10 (0.2)	12 (0.1)
Injury, poisoning and procedural complications	17 (0.6)	16 (0.5)	17 (0.3)	43 (0.7)	53 (0.8)	61 (0.6)
In-stent coronary artery restenosis	2 (0.1)	1 (<0.1)	1 (<0.1)	5 (<0.1)	10 (0.2)	10 (0.1)
Metabolism and nutrition disorders	14 (0.5)	9 (0.3)	10 (0.2)	39 (0.7)	24 (0.4)	25 (0.3)
Hypoglycemia	2 (0.1)	5 (0.1)	6 (0.1)	7 (0.1)	10 (0.2)	11 (0.1)

Musculoskeletal and connective tissue disorders	11 (0.4)	14 (0.4)	17 (0.3)	30 (0.5)	38 (0.6)	50 (0.5)
Musculoskeletal chest pain	4 (0.1)	8 (0.2)	8 (0.2)	8 (0.1)	14 (0.2)	15 (0.2)
Osteoarthritis	2 (0.1)	3 (0.1)	4 (0.1)	6 (0.1)	7 (0.1)	10 (0.1)
Nervous system disorders	25 (0.9)	26 (0.7)	28 (0.5)	64 (1.1)	66 (1.0)	80 (0.8)
Cerebrovascular accident	4 (0.1)	5 (0.1)	5 (0.1)	13 (0.2)	10 (0.2)	10 (0.1)
Ischaemic stroke	4 (0.1)	2 (0.1)	2 (<0.1)	5 (<0.1)	10 (0.2)	11 (0.1)
Syncope	2 (0.1)	5 (0.1)	5 (0.1)	6 (0.1)	8 (0.1)	10 (0.1)
Renal and urinary disorders	15 (0.5)	19 (0.5)	21 (0.4)	54 (0.9)	56 (0.8)	65 (0.7)
Renal failure acute	7 (0.2)	6 (0.2)	6 (0.1)	23 (0.4)	22 (0.3)	24 (0.2)
Respiratory, thoracic and mediastinal disorders	17 (0.6)	21 (0.6)	22 (0.4)	54 (0.9)	62 (0.9)	67 (0.7)
Acute pulmonary edema	4 (0.1)	2 (0.1)	2 (<0.1)	8 (0.1)	15 (0.2)	15 (0.2)
Chronic obstructive pulmonary disease	5 (0.2)	5 (0.1)	5 (0.1)	12 (0.2)	10 (0.2)	12 (0.1)
Pulmonary edema	3 (0.1)	2 (0.1)	2 (<0.1)	8 (0.1)	6 (<0.1)	6 (<0.1)
Respiratory failure	3 (0.1)	0	0	7 (0.1)	3 (<0.1)	3 (<0.1)
Vascular disorders	15 (0.5)	7 (0.2)	9 (0.2)	47 (0.8)	30 (0.5)	36 (0.4)
Hypertension	3 (0.1)	0	0	11 (0.2)	5 (<0.1)	5 (<0.1)

Source: SCS Table 2.d

7.3.3 Dropouts and/or Discontinuations

A summary of AEs which led to discontinuation and were reported by ≥0.1% of subjects in any group in the 2011 and 2012 resubmissions is shown in Table 10. Alogliptin 25 mg did not increase the percentage of subjects discontinued due to an AE when compared to all comparators (4.3% versus 4.8%). However, there was an increase in the number of subjects discontinued for renal-related AEs. This is explained by the addition of studies MET-302 and 305, which contained renal rescue criteria due to the co-administration of metformin.

The alogliptin-treated patients who discontinued due to liver function test abnormal are discussed in 7.3.5 Submission Specific Primary Safety Concerns.

Table 10. AEs leading to discontinuation reported by ≥0.1% of subjects in any group in the 2011 and 2012 resubmissions

SOC Preferred Term	Number (%) of Subjects					
	2011 NDA Resubmission			2012 NDA Resubmission		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232	All Comparators N=5987	Alogliptin 25 mg N=6626	All Alogliptin N=9857
Any AE leading to discontinuation	87 (3.0)	90 (2.6)	131 (2.5)	287 (4.8)	282 (4.3)	390 (4.0)
Cardiac disorders	13 (0.4)	14 (0.4)	18 (0.3)	57 (1.0)	48 (0.7)	54 (0.5)
Acute myocardial infarction	4 (0.1)	2 (0.1)	2 (<0.1)	14 (0.2)	8 (0.1)	8 (<0.1)
Angina unstable	2 (0.1)	0	1 (<0.1)	5 (<0.1)	2 (<0.1)	3 (<0.1)
Myocardial infarction	3 (0.1)	5 (0.1)	5 (0.1)	9 (0.2)	12 (0.2)	12 (0.1)
Gastrointestinal disorders	8 (0.3)	9 (0.3)	13 (0.2)	24 (0.4)	29 (0.4)	40 (0.4)
Abdominal pain	0	2 (0.1)	2 (<0.1)	1 (<0.1)	2 (<0.1)	3 (<0.1)
Diarrhea	4 (0.1)	1 (<0.1)	2 (<0.1)	8 (0.1)	1 (<0.1)	5 (<0.1)
Nausea	2 (0.1)	1 (<0.1)	3 (0.1)	6 (0.1)	3 (<0.1)	6 (<0.1)
General disorders and administration site conditions	7 (0.2)	10 (0.3)	14 (0.3)	24 (0.4)	21 (0.3)	28 (0.3)
Edema	4 (0.1)	0	1 (<0.1)	4 (<0.1)	0	1 (<0.1)
Edema peripheral	2 (0.1)	4 (0.1)	4 (0.1)	2 (<0.1)	4 (<0.1)	5 (<0.1)
Investigations	9 (0.3)	11 (0.3)	17 (0.3)	31 (0.5)	63 (1.0)	92 (0.9)
Blood creatinine increased	1 (<0.1)	1 (<0.1)	1 (<0.1)	4 (<0.1)	6 (<0.1)	14 (0.1)
Creatinine renal clearance abnormal	1 (<0.1)	2 (0.1)	2 (<0.1)	1 (<0.1)	3 (<0.1)	4 (<0.1)
Creatinine renal clearance decreased	1 (<0.1)	0	0	11 (0.2)	22 (0.3)	31 (0.3)
Lipase increased	3 (0.1)	2 (0.1)	2 (<0.1)	5 (<0.1)	10 (0.2)	10 (0.1)
Liver function test abnormal	1 (<0.1)	1 (<0.1)	4 (0.1)	1 (<0.1)	2 (<0.1)	5 (<0.1)
Metabolism and nutrition disorders	12 (0.4)	4 (0.1)	5 (0.1)	47 (0.8)	5 (<0.1)	7 (<0.1)
Hyperglycemia	1 (<0.1)	3 (0.1)	3 (0.1)	3 (<0.1)	3 (<0.1)	3 (<0.1)
Hypoglycemia	8 (0.3)	0	1 (<0.1)	37 (0.6)	0	1 (<0.1)
Nervous system disorders	8 (0.3)	5 (0.1)	13 (0.2)	20 (0.3)	19 (0.3)	33 (0.3)
Dizziness	2 (0.1)	0	2 (<0.1)	4 (<0.1)	4 (<0.1)	6 (<0.1)
Headache	1 (<0.1)	1 (<0.1)	5 (0.1)	3 (<0.1)	2 (<0.1)	7 (<0.1)
Renal and urinary disorders	2 (0.1)	4 (0.1)	6 (0.1)	21 (0.4)	25 (0.4)	39 (0.4)
Renal failure chronic	0	0	1 (<0.1)	6 (0.1)	1 (<0.1)	2 (<0.1)
Renal impairment	0	1 (<0.1)	1 (<0.1)	3 (<0.1)	13 (0.2)	19 (0.2)
Skin and subcutaneous tissue disorders	5 (0.2)	11 (0.3)	18 (0.3)	11 (0.2)	18 (0.3)	27 (0.3)
Rash	2 (0.1)	1 (<0.1)	2 (<0.1)	5 (<0.1)	2 (<0.1)	4 (<0.1)
Rash pruritic	0	2 (0.1)	2 (<0.1)	0	3 (<0.1)	3 (<0.1)

Source: SCS Table 2.e

7.3.4 Significant Adverse Events

AEs of special interest include the following: CV safety, hypersensitivity, skin lesions, pancreatitis, infections, malignancy (including bladder, thyroid, and pancreatic cancer), fractures, hypoglycemia, and interstitial lung disease.

See also

- Section 7.3.5 Submission Specific Primary Safety Concerns for a discussion of hepatotoxicity
- Section 7.4.2 Laboratory Findings for a discussion of renal safety

- Section 8 Postmarket Experience.

CV Safety: The difference between the 2012 and 2011 CRs in terms of CV events is that the 2012 resubmission includes studies 302 and 305, which were not included in the 2011 CV meta-analysis. (b) (4)

As confirmed by Safety Statistics' Eugenio Andraca-Carrera, the 1.8 margin is still met in the meta-analysis after these data are accounted. There are no new CV data for study 402.

Table 11. Primary MACE composite (controlled phase 2 and 3 studies)

(b) (4)

Source: SCS Table 2.g

Hypersensitivity and Skin Lesions:

Hypersensitivity has been associated with other DPP4 inhibitors, such as sitagliptin, saxagliptin, and vildagliptin. Serious hypersensitivity events were observed under the alogliptin IND and NDA. As agreed, the applicant identified preferred terms in the severe cutaneous drug reactions, angioedema, and anaphylactic reaction SMQs. A summary of the narrow scope findings are shown in Table 12. The incidence of these narrow events (serious and nonserious) was similar between treatment groups.

Table 12. Summary of narrow scope hypersensitivity AEs (Controlled phase 2 and 3 studies)

	Number (%) of Subjects [Events per 100 Subject-Years]		
	All Comparators (a) N=5987	Alogliptin 25 mg N=6626	All Alogliptin (b) N=9857
All hypersensitivity events	40 (0.7) [1.1]	41 (0.6) [1.0]	67 (0.7) [1.1]
Serious hypersensitivity events	4 (<0.1) [<0.1]	2 (<0.1) [<0.1]	3 (<0.1) [<0.1]
Nonserious hypersensitivity events	36 (0.6) [1.1]	39 (0.6) [0.9]	64 (0.6) [1.0]

Source: SCS Table 2.h

When compared by treatment group, the incidence of events in the severe cutaneous adverse reactions, angioedema, and anaphylactic SMQs was similar between treatment groups. However, as described in my review of the first resubmission, there have been serious postmarketing reports of angioedema and severe cutaneous adverse reactions, including Stevens-Johnson syndrome and erythema multiforme.

Table 13. AEs in the severe cutaneous drug reactions, angioedema, and anaphylactic reaction SMQs (Controlled phase 2 and 3 study group)

SMQ	All comparators (n=5987)	Alogliptin 25 mg (n=6626)	All alogliptin (n=9857)
Severe cutaneous adverse reaction	57 (1.0)	75 (1.1)	116 (1.2)
Angioedema	183 (3.1)	216 (3.3)	320 (3.2)
Anaphylactic reaction*	24 (0.4)	22 (0.3)	30 (0.3)

*The anaphylactic reaction SMQ preferred terms are divided into four categories: A (specific MedDRA terms), B (respiratory distress), C (pruritis, generalized flushing, and urticaria), and D (vascular collapse). Subjects were considered to have experienced an anaphylactic reaction by this SMQ if they had at least one event in category A or an event from each of categories B and C or an event in category D and an event from either category B or C [i.e. A or (B and C) or (D and (B or C))].

Source: SCS Tables 2.i, 2.j, and 2.k

As described in section 2.4 Important Safety Issues With Consideration to Related Drugs, necrotizing skin lesions, which have been observed in monkeys given other DPP4 inhibitors, were not seen in alogliptin studies in mice, rats, dogs, or monkeys. Nonetheless, examination of the skin and digits was performed in all studies except 003, 303, MET-302, 305, 308, and 402. The sponsor searched the controlled phase 2 and 3 study group using the Potential Cutaneous Drug Reaction (PCDR) AE list that was agreed upon at the EOR meeting.

The incidence of PCDR events was higher in the alogliptin 25 mg and all alogliptin groups when compared to all comparators (6.9% and 7.4% versus 5.7%; see Table 14.). The most common events were rash and pruritis. Although these skin reactions are not likely related to the necrotic lesions seen with other DPP4 inhibitors, they suggest that some individuals may be hypersensitive to alogliptin. This idea is supported by nonclinical findings in dogs, as described in David Carlson's August 27, 2008 review.

Table 14. PCDR AEs reported in >0.1% of subjects in any group (Controlled phase 2 and 3 studies)

Preferred Term	Number (%) of Subjects		
	All Comparators (a) N=5987	Alogliptin 25 mg N=6626	All Alogliptin (b) N=9857
Any PCDR AE	344 (5.7)	460 (6.9)	727 (7.4)
Rash	58 (1.0)	77 (1.2)	113 (1.1)
Pruritus	31 (0.5)	66 (1.0)	101 (1.0)
Eczema	23 (0.4)	25 (0.4)	39 (0.4)
Dry skin	17 (0.3)	23 (0.3)	35 (0.4)
Dermatitis contact	17 (0.3)	21 (0.3)	34 (0.3)
Urticaria	16 (0.3)	19 (0.3)	33 (0.3)
Skin ulcer	18 (0.3)	24 (0.4)	31 (0.3)
Dermatitis	9 (0.2)	17 (0.3)	28 (0.3)
Skin lesion	14 (0.2)	17 (0.3)	28 (0.3)
Asthma	14 (0.2)	19 (0.3)	27 (0.3)
Blister	10 (0.2)	15 (0.2)	27 (0.3)
Dermatitis allergic	8 (0.1)	8 (0.1)	21 (0.2)
Rash papular	7 (0.1)	14 (0.2)	20 (0.2)
Skin exfoliation	9 (0.2)	10 (0.2)	20 (0.2)
Hypersensitivity	5 (<0.1)	8 (0.1)	17 (0.2)
Erythema	6 (0.1)	13 (0.2)	16 (0.2)
Rash macular	3 (<0.1)	11 (0.2)	16 (0.2)
Rash pruritic	8 (0.1)	7 (0.1)	12 (0.1)
Face edema	2 (<0.1)	7 (0.1)	10 (0.1)
Pruritus generalized	6 (0.1)	4 (<0.1)	9 (<0.1)
Diabetic foot	7 (0.1)	5 (<0.1)	6 (<0.1)
Bronchospasm	6 (0.1)	4 (<0.1)	5 (<0.1)
Angioedema	6 (0.1)	1 (<0.1)	2 (<0.1)

Source: SCS Table 2.I

With regard to the label, I recommend that use of alogliptin be contraindicated in subjects with a history of serious hypersensitivity reaction to alogliptin. I also recommend a warning such as the following that is consistent with other DPP-4 inhibitor labeling: *There have been postmarketing reports of serious hypersensitivity reactions in patients treated with alogliptin such as angioedema and severe cutaneous adverse reactions. In such cases, promptly discontinued alogliptin, assess for other potential causes, and institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes.* Hypersensitivity should be monitored as an AE of special interest in the controlled CV study 402, the PSURs, and an enhanced pharmacovigilance PMR.

Pancreatitis: The MedDRA SMQ for acute pancreatitis specifies narrow (category A) scope terms and an algorithm for the broad scope terms in which a subject must report an AE for both a clinically significant laboratory abnormality (category B) and a symptom associated with pancreatitis (category C). The incidence of acute pancreatitis events

was similar between treatment groups when stratified by narrow and/or broad events, serious events, and events leading to discontinuation of study drug.

Table 15. AEs in the acute pancreatitis MedDRA SMQ by criteria (Controlled phase 2 and 3 studies)

Criteria Met (a)	Number (%) of Subjects		
	All Comparators (b) N=5987	Alogliptin 25 mg N=6626	All Alogliptin (c) N=9857
AEs			
A or (B and C)	12 (0.2)	20 (0.3)	23 (0.2)
A	6 (0.1)	11 (0.2)	14 (0.1)
B and C	7 (0.1)	9 (0.1)	9 (<0.1)
Serious AEs			
A or (B and C)	6 (0.1)	6 (<0.1)	8 (<0.1)
A	6 (0.1)	6 (<0.1)	8 (<0.1)
B and C	0	0	0
Leading to discontinuation of study drug			
A or (B and C)	2 (<0.1)	4 (<0.1)	5 (<0.1)
A	2 (<0.1)	2 (<0.1)	3 (<0.1)
B and C	0	2 (<0.1)	2 (<0.1)

Source: IAS Table 4.7.1.

(a) The MedDRA v13.0 'Acute pancreatitis' SMQ includes preferred terms divided into 3 categories: A (narrow-scope terms), B (laboratory values), and C (signs and symptoms). Subjects are considered to have experienced acute pancreatitis by this SMQ if they have at least 1 event in category A or at least 1 event from each of categories B and C [A or (B and C)]. Subjects who had AEs in both categories B and C are counted in the summary of SAEs if at least 1 of the events was serious.

(b) The All Comparators grouping combines placebo and active comparator groups.

(c) The All Alogliptin grouping combines 25 mg with the 6.25, 12.5, 50, and 100 mg groups.

Source: SCS Table 2.n

Pancreatitis events have been observed in alogliptin subjects in clinical studies and postmarketing in Japan. I therefore recommend that the labeling contain an acute pancreatitis warning consistent with that for other DPP4 inhibitors. I also recommend that the applicant analyze pancreatitis events as an AE of special interest in controlled CV safety study 402 (as is planned) and summarize pancreatitis events in the PSURs.

Infections: DPP4 has many substrates other than GIP and GLP-1, including chemokines involved in immune development and function. DPP-4 is expressed on a subset of CD4+ and CD8+ T-cells and natural killer cells. Thus, there is a theoretical concern that DPP-4 inhibition may increase the risk for infections.

The applicant searched the pooled phase 2 and 3 controlled safety data for events in the infections and infestations SOC. The incidence of events in this SOC was higher in the alogliptin 25 mg and all alogliptin groups than the all comparator group (25.6% and 27.0% versus 23.6%, respectively). The incidence of nasopharyngitis and URI was greater in the alogliptin groups when compared to the all comparators group. This is consistent with the prescribing information for approved DPP-4 inhibitors which describes an increase in common infections, such as nasopharyngitis, UTI, and URI.

Table 16. AEs from the infections and infestations SOC reported by >0.1% of subjects in any group (Controlled phase 2 and 3 studies)

Preferred Term	Number (%) of Subjects		
	All Comparators (a) N=5987	Alogliptin 25 mg N=6626	All Alogliptin (b) N=9857
Any Infections and Infestations AE	1410 (23.6)	1695 (25.6)	2657 (27.0)
Nasopharyngitis	265 (4.4)	334 (5.0)	564 (5.7)
Upper respiratory tract infection	188 (3.1)	257 (3.9)	400 (4.1)
Urinary tract infection	198 (3.3)	220 (3.3)	338 (3.4)
Bronchitis	114 (1.9)	141 (2.1)	225 (2.3)
Influenza	139 (2.3)	141 (2.1)	215 (2.2)
Sinusitis	69 (1.2)	90 (1.4)	135 (1.4)
Pharyngitis	66 (1.1)	85 (1.3)	132 (1.3)
Gastroenteritis	64 (1.1)	78 (1.2)	125 (1.3)
Pneumonia	56 (0.9)	61 (0.9)	72 (0.7)
Viral infection	24 (0.4)	29 (0.4)	58 (0.6)
Cellulitis	36 (0.6)	41 (0.6)	56 (0.6)
Rhinitis	21 (0.4)	31 (0.5)	53 (0.5)
Respiratory tract infection	26 (0.4)	28 (0.4)	45 (0.5)
Tinea pedis	28 (0.5)	26 (0.4)	43 (0.4)
Cystitis	26 (0.4)	17 (0.3)	37 (0.4)
Lower respiratory tract infection	24 (0.4)	17 (0.3)	34 (0.3)
Tooth abscess	17 (0.3)	21 (0.3)	33 (0.3)
Otitis media	8 (0.1)	20 (0.3)	30 (0.3)
Fungal skin infection	9 (0.2)	20 (0.3)	29 (0.3)
Herpes zoster	18 (0.3)	21 (0.3)	29 (0.3)
Onychomycosis	14 (0.2)	17 (0.3)	29 (0.3)
Respiratory tract infection viral	29 (0.5)	21 (0.3)	29 (0.3)
Tooth infection	16 (0.3)	12 (0.2)	29 (0.3)
Ear infection	14 (0.2)	19 (0.3)	28 (0.3)
Furuncle	9 (0.2)	15 (0.2)	27 (0.3)
Gastroenteritis viral	14 (0.2)	16 (0.2)	27 (0.3)
Tonsillitis	12 (0.2)	17 (0.3)	25 (0.3)
Acute sinusitis	13 (0.2)	6 (<0.1)	22 (0.2)
Paronychia	6 (0.1)	14 (0.2)	21 (0.2)
Pharyngotonsillitis	6 (0.1)	10 (0.2)	21 (0.2)
Laryngitis	7 (0.1)	10 (0.2)	18 (0.2)
Oral herpes	12 (0.2)	7 (0.1)	16 (0.2)
Viral upper respiratory tract infection	11 (0.2)	10 (0.2)	16 (0.2)
Vulvovaginal candidiasis	4 (<0.1)	11 (0.2)	16 (0.2)
Vaginal infection	9 (0.2)	8 (0.1)	13 (0.1)
Folliculitis	12 (0.2)	7 (0.1)	12 (0.1)
Fungal infection	11 (0.2)	5 (<0.1)	10 (0.1)
Erysipelas	10 (0.2)	5 (<0.1)	5 (<0.1)
Sepsis	9 (0.2)	5 (<0.1)	5 (<0.1)

Source: SCS Table 2.p

Malignancy (including bladder, thyroid, and pancreatic cancer): The applicant searched the pooled phase 2 and 3 controlled safety database for AEs in the malignancy SMQ. The incidence of these AEs was similar in the three treatment groups (0.6-0.7%). The incidence of AEs of malignancy which lead to discontinuation was also similar between

the treatment groups (0.1-0.2%). Therefore, in the population and for the duration studied, alogliptin does not appear to increase the risk of malignancy.

Table 17. AEs in the Narrow-scope Malignancy SMQ (Controlled phase 2 and 3 studies)

Preferred Term	Number (%) of Subjects		
	All Comparators (a) N=5937	Alogliptin 25 mg N=6626	All Alogliptin (b) N=9857
Any malignancy AE	41 (0.7)	40 (0.6)	69 (0.7)
Basal cell carcinoma	5 (<0.1)	5 (<0.1)	11 (0.1)
Breast cancer	1 (<0.1)	3 (<0.1)	6 (<0.1)
Prostate cancer	1 (<0.1)	2 (<0.1)	5 (<0.1)
Squamous cell carcinoma	0	2 (<0.1)	5 (<0.1)
Gastric cancer	0	3 (<0.1)	3 (<0.1)
Lung neoplasm	3 (<0.1)	3 (<0.1)	3 (<0.1)
Lung neoplasm malignant	0	2 (<0.1)	3 (<0.1)
Squamous cell carcinoma of skin	3 (<0.1)	2 (<0.1)	3 (<0.1)
Thyroid neoplasm	3 (<0.1)	3 (<0.1)	3 (<0.1)
Bladder transitional cell carcinoma	0	2 (<0.1)	2 (<0.1)
Malignant melanoma	0	1 (<0.1)	2 (<0.1)
Meningioma	0	1 (<0.1)	2 (<0.1)
Rectal cancer metastatic	0	1 (<0.1)	2 (<0.1)
Breast cancer stage III	0	1 (<0.1)	1 (<0.1)
Cervix carcinoma	1 (<0.1)	1 (<0.1)	1 (<0.1)
Colon cancer	3 (<0.1)	1 (<0.1)	1 (<0.1)
Colon cancer stage 0	0	1 (<0.1)	1 (<0.1)
Colon polypectomy	0	0	1 (<0.1)
Endometrial cancer	2 (<0.1)	0	1 (<0.1)
Gastric neoplasm	0	0	1 (<0.1)
Head and neck cancer	0	0	1 (<0.1)
Lentigo maligna stage unspecified	0	1 (<0.1)	1 (<0.1)

Lung adenocarcinoma	0	0	1 (<0.1)
Lung squamous cell carcinoma stage unspecified	0	1 (<0.1)	1 (<0.1)
Myeloma recurrence	0	1 (<0.1)	1 (<0.1)
Neoplasm skin	1 (<0.1)	0	1 (<0.1)
Non-Hodgkin's lymphoma	0	1 (<0.1)	1 (<0.1)
Non-secretory adenoma of pituitary	0	0	1 (<0.1)
Non-small cell lung cancer stage IIIB	0	0	1 (<0.1)
Oesophageal carcinoma	0	1 (<0.1)	1 (<0.1)
Ovarian cancer	0	1 (<0.1)	1 (<0.1)
Ovarian neoplasm	0	1 (<0.1)	1 (<0.1)
Rectal cancer	0	1 (<0.1)	1 (<0.1)
Rectosigmoid cancer	2 (<0.1)	1 (<0.1)	1 (<0.1)
Skin neoplasm excision	0	0	1 (<0.1)
Small cell lung cancer stage unspecified	0	1 (<0.1)	1 (<0.1)
Tendon neoplasm	0	0	1 (<0.1)
Thyroid cancer	0	0	1 (<0.1)
Adenocarcinoma	1 (<0.1)	0	0
Bladder cancer	2 (<0.1)	0	0
Bladder neoplasm	2 (<0.1)	0	0
Breast cancer female	1 (<0.1)	0	0
Breast neoplasm	2 (<0.1)	0	0
Central nervous system lymphoma	1 (<0.1)	0	0
Colon cancer recurrent	1 (<0.1)	0	0
Colon cancer stage II	1 (<0.1)	0	0
Colon neoplasm	1 (<0.1)	0	0
Colorectal cancer	1 (<0.1)	0	0
Gallbladder cancer	1 (<0.1)	0	0
Gammopathy	1 (<0.1)	0	0
Hepatic neoplasm malignant	1 (<0.1)	0	0
Metastases to lymph nodes	1 (<0.1)	0	0
Renal neoplasm	1 (<0.1)	0	0

Source: SCS Table 2.o

Fractures: Since the 2011 resubmission, no additional studies have been conducted with alogliptin + pioglitazone. Therefore, no additional bone fracture analyses were submitted in the second CR.

Hypoglycemia: The predefined hypoglycemia criteria were the same in all studies, except MET-302, 305, and 303. Yet, results from these studies are included in the integrated data using the same criteria as the other studies. However, hypoglycemia events in 301, 402, and the Japanese CCT studies were reported as AEs and therefore not integrated into the controlled phase 2 and 3 study group.

In the controlled phase 2 and 3 study group excluding 301, 402, and the Japanese CCT studies, the incidence of hypoglycemia was greatest in the all comparators group, regardless of the severity of the hypoglycemic event. (See Table 18.)

Table 18. Hypoglycemia events (Controlled phase 2 and 3 studies, excluding 301, 402, CCT-001, CCT-003, CCT-004, CCT-005, and CCT-006)

Event Category	Number (%) of Subjects		
	All Comparators (a) N=3279	Alogliptin 25 mg N=3954	All Alogliptin (b) N=6559
Any Hypoglycemic Event	354 (10.8)	140 (3.5)	281 (4.3)
Symptomatic event and blood glucose <60 mg/dL (Mild to Moderate)	241 (7.3)	78 (2.0)	152 (2.3)
Symptomatic or asymptomatic event and blood glucose <50 mg/dL (Mild to Moderate)	149 (4.5)	47 (1.2)	93 (1.4)
Any event that requires assistance, associated with a documented blood glucose <60 mg/dL (Severe)	13 (0.4)	4 (0.1)	7 (0.1)

Source: SCS Table 3.p

The applicant proposes the following labeling warning: *Hypoglycemia: When an insulin secretagogue (e.g. sulfonylurea) or insulin is used in combination with [alogliptin], a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia.* This is acceptable.

Interstitial Lung Disease: In the April 25, 2012 CR letter, the applicant was asked to provide an updated, comprehensive analysis of interstitial lung disease in the resubmission, because a March 15, 2012 query of the clinical trial and postmarketing database using the interstitial lung disease SMQ identified 12 potential case.

When postmarketing data (cutoff May 15, 2012) was searched for cases in the interstitial lung disease SMQ, six serious cases were identified; all were under the narrow scope terms (see Table 19). All but two of the six cases had a history of tobacco use or infection.

Table 19. Postmarketing cases of serious interstitial lung disease (cutoff May 15, 2012)

Case number	Treatment	Preferred Term	Outcome	Etiology
TCI2011A06440	Nesina 25 mg	Interstitial lung disease	Resolving	Heavy smoker (4 packs per day); Drug-induced pneumonia suspected; DLST (-) for alogliptin; KL-6 (286 U/mL)
TCI2012A00335	Nesina (dose unknown)	Interstitial lung disease	Unknown	Unknown
TCI2012A00422	Nesina 25 mg	Interstitial lung disease	Unknown	Mild increase in KL-6 (532)
TCI2012A00794	Nesina 25 mg	Interstitial lung disease	Resolved	Smoker; influenza pneumonia suspected (PCR [+]); drug-induced pneumonia could not be ruled out (DLST [+] for alogliptin); KL-6 (325 [ULN=499])
TCI2012A00884	Nesina 12.5 mg	Interstitial lung disease	Resolving	Smokes 18 cigarettes/day; high KL-6 result (6,738 U/mL [ULN=499])
TCI2012A00969	Nesina 6.25 mg	Interstitial lung disease	Ongoing	Bacterial interstitial pneumonia suspected.

Note: Per the sponsor's pharmacovigilance process, preferred terms of interstitial lung disease and pulmonary fibrosis are automatically upgraded to serious adverse event status.

Note: Krebs von den Lungen-6 (KL-6) is a pulmonary epithelial mucin that is more prominently expressed on the surface membrane of alveolar type II cells when the cells are proliferating, stimulated, and/or injured.

Source: SCS Table 6.g

When the controlled phase 2 and 3 study group was searched for AEs in the interstitial lung disease SMQ, the incidence of these events in the three treatment groups was similar (~0.1%), regardless of whether any, narrow, or broad search terms were used (see Table 20).

Table 20. Interstitial lung disease AEs (Controlled phase 2 and 3 studies)

Preferred Term	Number (%) of Subjects		
	All Comparators (a) N=5987	Alogliptin 25 mg N=6626	All Alogliptin (b) N=9857
Any Interstitial Lung Disease AE	6 (0.1)	7 (0.1)	9 (<0.1)
Narrow Scope Terms	5 (<0.1)	5 (<0.1)	7 (<0.1)
Interstitial lung disease	0	3 (<0.1)	3 (<0.1)
Pneumonitis	1 (<0.1)	2 (<0.1)	3 (<0.1)
Lung infiltration	1 (<0.1)	0	1 (<0.1)
Alveolitis allergic	1 (<0.1)	0	0
Pulmonary fibrosis	2 (<0.1)	0	0
Broad Scope Terms	1 (<0.1)	2 (<0.1)	2 (<0.1)
Acute respiratory distress syndrome	1 (<0.1)	2 (<0.1)	2 (<0.1)

Source: SCS Table 2.q

A total of nine phase 2 and 3 clinical trial subjects had interstitial lung disease SAEs. Two subjects in the all comparators group discontinued study drug due to the AE.

- 5 (0.1%) in the alogliptin 25 mg group
 - 3 interstitial lung disease
 - 2 acute respiratory distress syndrome
- 4 (0.1%) in the all comparators group
 - 2 pulmonary fibrosis
 - 1 alveolitis allergic (discontinued study drug)
 - 1 acute respiratory distress syndrome (discontinued study drug)

In summary, after review of the clinical trial database which demonstrated similar incidence of AEs in the interstitial lung disease SMQ in the alogliptin and comparator groups, I am reassured that the postmarketing safety reports of interstitial lung disease do not represent a safety signal.

7.3.5 Submission Specific Primary Safety Concerns

On April 25, 2012, a second CR was issued to the alogliptin and alogliptin/pioglitazone FDC NDAs due to 1) numerical imbalances not favoring alogliptin for serum ALT

elevations >5x, >10x, and >20x the ULN compared to control and 2) five probable cases of alogliptin hepatotoxicity among the estimated 219,000 patient-years of postmarketing experience in Japan. As agreed at the EOR meeting, the sponsor submitted hepatic safety data from 20 controlled phase 2 and 3 studies and the Fourth Japanese PSUR. Although the applicant analyzed data from unplanned data cuts for ongoing studies 305 and 402, my review focused on the controlled phase 2 and 3 study group and postmarketing data.

Nonclinical Data: As stated in David Carlson's January 18, 2012 nonclinical review, *alogliptin animal data have not indicated a strong signal for liver toxicity. Signs of modest liver toxicity were seen in chronic/lifetime rat studies with alogliptin, which showed liver hepatocellular hypertrophy, periportal vacuolation, and basophilic 'focus of cell alteration' at greater than 200-times estimated clinical dose. The NOAEL for hepatotoxicity was at least 30- times MRHD in all animal species (mouse, rat, dog, monkey). Data from combination alogliptin toxicity studies (with pioglitazone or metformin coadministration) did not indicate any drug interactions leading to exacerbated liver toxicity.*

ALT Elevations in Controlled Phase 2 and 3 Studies: As agreed at the EOR meeting, the applicant conducted an updated analysis of controlled phase 2 and 3 clinical trials. At the last assessment, the percentage of alogliptin subjects with ALT elevations is similar or less than that of the all comparators group (see Table 21).

During treatment, a greater percentage of all comparator subjects had ALT >3xULN and total bilirubin >2x ULN; ALT >20x ULN; and ALT >3x ULN, but a greater percentage of alogliptin subjects had ALT elevations >10x and >5x ULN. However, when baseline measurements are reviewed, the majority of alogliptin subjects with ALT >10x ULN had elevated ALT at baseline (n = 8/12, 66.7%) and a quarter of them (n = 4/12, 25.0%) had markedly abnormal ALT elevations at baseline (see Table 23 and Table 22). When these subjects are excluded, the percentage of subjects with ALT elevations >10x ULN is similar between treatment groups during treatment.

Table 21. Number and percentage of subjects with markedly abnormal values for hepatic function parameters (Controlled phase 2 and 3 studies)

Parameter	Number (%) of Subjects With Markedly Abnormal Result					
	Baseline (a)		During Treatment (b)		Last Assessment (c)	
	All Comparators (d) N=5786	All Alogliptin (e) N=9608	All Comparators N=5786	All Alogliptin N=9608	All Comparators N=5699	All Alogliptin N=9495
ALT (>3×ULN) and total bilirubin >2×ULN	0	0	3 (0.05) [0.07]	2 (0.02) [0.03]	2 (0.04)	1 (0.01)
ALT (>20×ULN)	0	0	3 (0.05) [0.07]	3 (0.03) [0.04]	2 (0.04)	2 (0.02)
ALT (>10×ULN)	1 (0.02)	3 (0.03)	5 (0.09) [0.11]	12 (0.12) [0.17]	3 (0.05)	4 (0.04)
ALT (>5×ULN)	2 (0.03)	6 (0.06)	17 (0.29) [0.39]	34 (0.35) [0.49]	7 (0.12)	11 (0.12)
ALT (>3×ULN)	16 (0.28)	41 (0.43)	89 (1.54) [2.04]	126 (1.31) [1.82]	30 (0.53)	32 (0.34)
ALP (>3×ULN)	3 (0.05)	3 (0.03)	9 (0.16) [0.21]	18 (0.19) [0.26]	5 (0.09)	8 (0.08)
Bilirubin, total (>2.0 mg/dL)	11 (0.19)	19 (0.20)	42 (0.73) [0.96]	55 (0.57) [0.79]	22 (0.39)	24 (0.25)

Source: IAS Table 5.1.1, 5.1.2, 5.6.1, and 5.6.2.

Note: This table includes only subjects with both a baseline and a post-baseline value.

(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.

(b) The number of subjects with marked abnormalities per 100 subject-years of exposure is presented in brackets.

(c) Last assessment is the last assessment of ALT on or before the last dose of study medication.

(d) The All Comparators grouping combines placebo and active comparator dose groups.

(e) The All Alogliptin grouping combines the 6.25, 12.5, 25, 50, and 100 mg dose groups.

Source: SCS Table 3.b

I reviewed the narratives submitted on October 5, 2012 for all alogliptin cases with ALT >10x ULN. I agree with the summary of these cases as presented in Table 22 with the following minor exceptions:

- Subject 311-9003/009 (alogliptin 12.5 mg): This 49 year old male had a baseline elevated ALT of 66 mU/ml and ALP 84 mU/ml. GGT was 201 mU/ml on day 1. On day 32, ALT was 646 mU/ml and AST 585 mU/ml. Study drug was interrupted (not continued per summary below). The investigator considered the event to be due to alcohol. Aminotransferases returned to normal by day 49. The subject voluntarily withdrew from the study. His last dose was on day 91. AST and ALT values were normal at the last on-treatment assessment on day 57. *Internal Comment: On November 10, 2012, Leonard Seef concluded that alogliptin was an unlikely cause of the aminotransferase elevation.*
- 5505-016/305 (alogliptin 25 mg): This 46 year old man had normal baseline ALT. On day 274, ALT was 356 mU/ml, AST 260 mU/ml, and GGT 273 mU/ml. Study drug was interrupted. Liver enzymes returned to normal by day 282. The subject remained on alogliptin at the time of the interim data cut on April 24, 2012 (day 555). *Internal Comment: ALT exceeds AST in this case, as well. This pattern of transaminase elevation is not typical of alcoholic liver disease. No information regarding alcohol intake was provided in the narrative. However, the fact that the subject resumed alogliptin and did not experience elevated transaminases again (i.e. negative rechallenge) suggests a cause other than the study drug.*

Internal Comment: On February 22 and May 8, 2012, OSE's Dr. Leonard Seeff concluded that insufficient data was provided for case 8635-004/402.

Table 22. Alogliptin cases of ALT >10x ULN (Controlled phase 2 and 3 studies)

Subject number/ Study Treatment Age/Sex	ALT Values				Associated with SAE (Yes/No)	Plausible Alternative Etiology	Confounders
	Baseline	>10xULN Elevation	Peak Elevation	Last Assessment (a)			
8260-010/402 Alogliptin 25 mg 58-year-old female	≤1xULN	Day 92 >10xULN	Day 92 >10xULN	Day 358 ≤1xULN	Yes	Unstable angina	Recurrent angina; negative rechallenge, Concurrent use of acetylsalicylic acid, clopidogrel, simvastatin, carvedilol
8521-002/402 Alogliptin 25 mg 81-year-old female	>10xULN	Day 9 >10xULN	Day 9 >10xULN	Day 372 ≤1xULN	No	Hepatitis C	History of cholelithiasis, and chronic pancreatitis, concurrent use of carvedilol, clopidogrel, and atorvastatin
8070-002/402 Alogliptin 25 mg 60-year-old male	>3xULN	Day 42 >10xULN	Day 42 >10xULN	Day 42 >10xULN	No	Hepatitis C	Negative dechallenge; concurrent use of metoprolol, aspirin, fenofibrate, prasugrel, furosemide, and acetaminophen, temporary use of clindamycin prior to event
395-3054/OPI-001 Alogliptin 12.5 mg 67-year-old female	>1xULN	Day 112 >10xULN	Day 112 >10xULN	Day 141 >1xULN	No	Hepatic steatosis Hepatitis A	None reported
831-2508/OPI-002 Alogliptin 25 mg 49-year-old male	>1xULN	Day 86 >20xULN	Day 91 >20xULN	Day 86 >20xULN	No	Hepatitis B	Concurrent use of acetylsalicylic acid
307-9019/009 (b) Alogliptin 25 mg 47-year-old male	>10xULN	Day 1 >10xULN	Day 8 >10xULN	NA	No	Temporal implausibility (initial elevation on Study Day 1)	Hypertriglyceridemia, obesity, concurrent use of acetaminophen
311-9003/009 Alogliptin 12.5 mg 49-year-old male	>1xULN	Day 32 >20xULN	Day 32 >20xULN	Day 57 ≤1xULN	No	Alcohol	AE of triglycerides increased, concurrent use of trazodone and ezetimibe, resolved on study drug
3128-003/303 Alogliptin 25 mg 73-year-old male	>5xULN	Day 15 >10xULN	Day 15 >10xULN	Day 20 >5xULN	No	Bile duct stone	Fatty liver, concurrent use of fluconazole
5039-003/305 Alogliptin 12.5 mg 56-year-old male	>1xULN	Day 113 >10xULN	Day 113 >10xULN	Day 113 >10xULN	No	Hemochromatosis	None reported
5304-055/305 Alogliptin 12.5 mg 45-year-old male	≤1xULN	Day 45 >10xULN	Day 51 >20xULN	Day 48 >20xULN	Yes	Hepatitis E	Concurrent use of atorvastatin
5505-016/305 Alogliptin 25 mg 46-year-old male	≤1xULN	Day 274 >10xULN	Day 274 >10xULN	Day 555 ≤1xULN	No	Alcohol	Obesity
8664-005/402 (b) Alogliptin 25 mg 59-year-old male	≤1xULN	Day 263 >10xULN	Day 263 >10xULN	Day 351 ≤1xULN	No	Atorvastatin (positive dechallenge with atorvastatin)	Negative alogliptin rechallenge, concurrent use of metoprolol, acetylsalicylic acid, and clopidogrel

(a) Last assessment is the last assessment of ALT on or before the last dose of study medication

(b) This subject only had two assessments, one at baseline, and one on day 8 (which was within the seven days after last medication)

Source: SCS Table 3.c

When the number of subjects with marked ALT abnormalities per 100 subject years of exposure was compared by treatment group, values for the alogliptin 12.5 mg, alogliptin 25 mg, and all alogliptin groups were the same or slightly exceeded those of the all comparators group, which combined active and placebo comparators. However, values for the alogliptin groups were consistently lower than the active comparator group (see Table 23), suggesting that the incidence of marked ALT abnormalities with alogliptin is less than with glipizide, metformin, and pioglitazone combined.

Table 23. Markedly abnormal ALT including values observed up to seven days after last dose (Controlled phase 2 and 3 studies)*

	Placebo n=3647	Active Comparator n=2340	All Comparators n=5987	Alo 12.5 mg n=2944	Alo 25 mg n=6626	All Alo n=9857
ALT >3x						
≥1 marked abnl	45 (1.3)	54 (2.3)	99 (1.7)	47 (1.6)	106 (1.7)	153 (1.6)
Baseline	10 (0.3)	6 (0.3)	16 (0.3)	6 (0.2)	35 (0.6)	41 (0.4)
During treatment	37 (1.1)	52 (2.3)	89 (1.5)	43 (1.5)	83 (1.3)	126 (1.3)
Exact 95% CI	0.75, 1.46	1.68, 2.94	1.4, 1.89	1.07, 1.98	1.03, 1.60	1.09, 1.56
#/100 subject years	1.6	2.6	2.0	2.1	1.7	1.8
ALT >5x						
≥1 marked abnl	8 (0.3)	11 (0.5)	19 (0.3)	12 (0.4)	25 (0.4)	37 (0.4)
Baseline	2 (0.1)	0 (0)	2 (0.0)	1 (0.0)	5 (0.1)	6 (0.1)
During treatment	6 (0.2)	11 (0.5)	17 (0.3)	11 (0.4)	23 (0.4)	34 (0.4)
Exact 95% CI	0.06, 0.38	0.24, 0.85	0.17, 0.47	0.19, 0.67	0.23, 0.54	0.25, 0.49
#/100 subject years	0.3	0.6	0.4	0.5	0.5	0.5
ALT >10x						
≥1 marked abnl	1 (0.0)	5 (0.2)	6 (0.1)	4 (0.1)	9 (0.1)	13 (0.1)
Baseline	1 (0.0)	0 (0)	1 (0.0)	0	3 (0.1)	3 (0.0)
During treatment	0 (0)	5 (0.2)	5 (0.1)	4 (0.1)	8 (0.1)	12 (0.1)
Exact 95% CI	0.00, 0.11	0.07, 0.50	0.03, 0.20	0.04, 0.35	0.05, 0.25	0.06, 0.22
#/100 subject years	0	0.3	0.1	0.2	0.2	0.2
ALT >20x						
≥1 marked abnl	0 (0)	3 (0.1)	3 (0.1)	2 (0.1)	1 (0.0)	3 (0.0)
Baseline	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
During treatment	0 (0)	3 (0.1)	3 (0.1)	2 (0.1)	1 (0.0)	3 (0.0)
Exact 95% CI	0.00, 0.11	0.03, 0.38	0.01, 0.15	<0.01, 0.25	<0.01, 0.09	<0.01, 0.09
#/100 subject years	0	0.2	0.1	0.1	0.0	0.0
ALT >3x & TBili >2x						
≥1 marked abnl	1 (0.0)	3 (0.1)	4 (0.1)	1 (0.03)	1 (0.02)	2 (0.02)
Baseline	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
During treatment	1 (0.0)	3 (0.1)	4 (0.1)	1 (0.0)	1 (0.0)	2 (0.0)
Exact 95% CI	<0.01,	0.03, 0.38	0.02, 0.18	<0.01, 0.19	<0.1, 0.09	<0.01, 0.08

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	0.16					
#/100 subject years	0.0	0.2	0.1	0.1	0.0	0.0

*The incidences shown in the table were calculated on the basis of the number of observations available in the database for that calculation and were not necessarily equal to the “n” shown at the head of the column.

Source: IAS Table 5.1.1

As shown in Figure 1, the percentage of alogliptin subjects with markedly abnormal ALT including values observed up to seven days after last dose is less than with active comparator. The exact 95% CIs for ALT >5x ULN or >10xULN and biochemical Hy's law are broad and often overlap, suggesting no statistically significant difference between the groups.

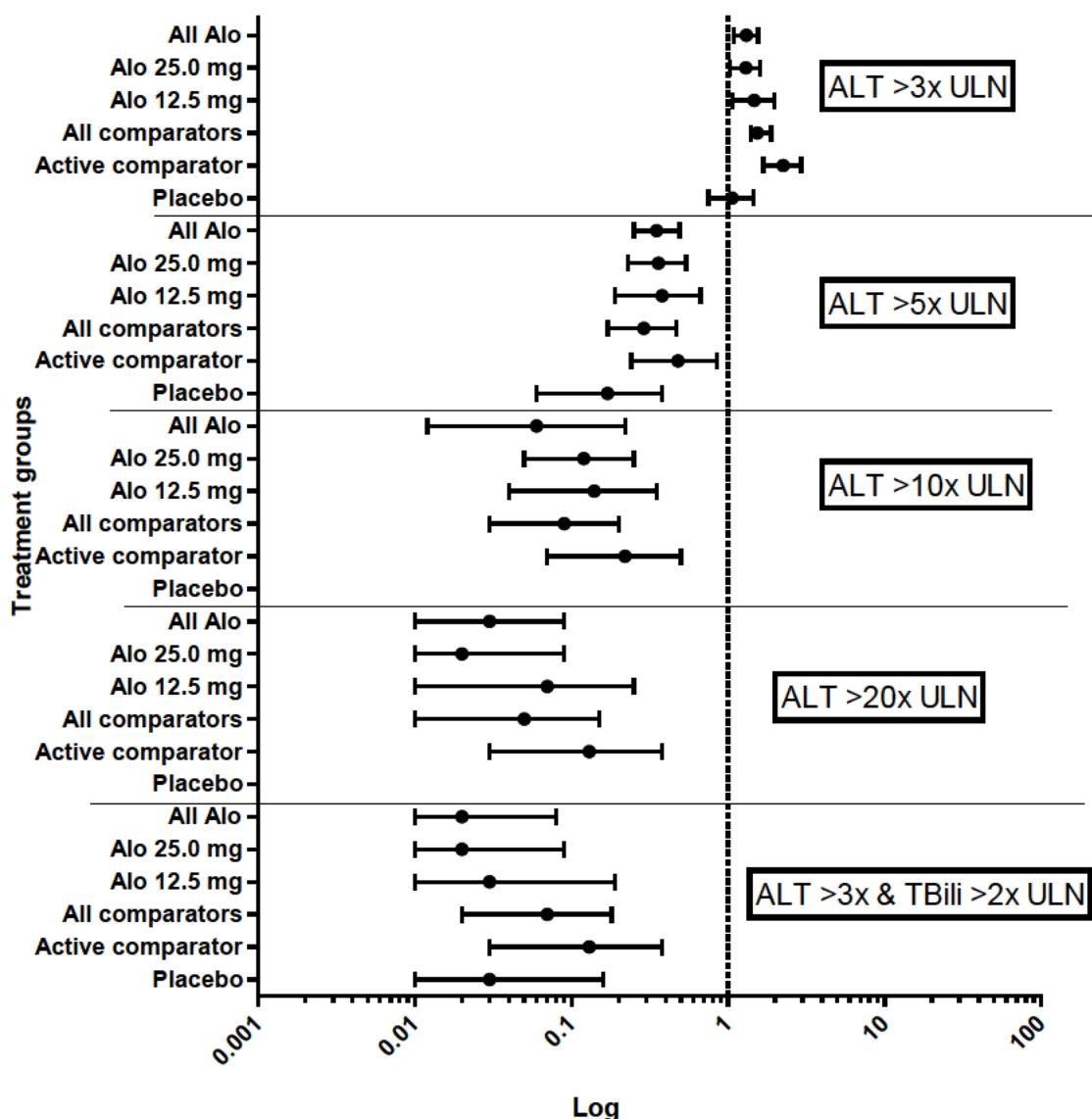


Figure 3. Percentage of subjects with markedly abnormal ALT including values observed up to seven days after last dose (Controlled phase 2 and 3 studies)

Source: Table 23.

Figure courtesy of Mary Roberts

Biochemical Hy's Law in the Clinical Program: When the entire clinical program was searched for subjects with ALT/AST >3x ULN and total bilirubin >2x ULN (i.e. "biochemical Hy's law"), 10 subjects (5 alogliptin) were identified (see Table 24). These 10 subjects include the following four alogliptin subjects who were not included in Table 22 because they took part in uncontrolled study 012 or the May 15, 2012 cutoff date exceeded that of the pooled controlled phase 2 and 3 study group (i.e. study 402 cutoff

April 18, 2012 and study 305 cutoff April 24, 2012). (Subject 5304-055/305 is listed in Table 22. Alogliptin cases of ALT >10x ULN (Controlled phase 2 and 3 studies)).

- 961-2501/012
- 961-3006/012
- 8413-006/402
- 5312-001/305

Having reviewed the narratives which were submitted on October 5, 2012, I agree with the applicant's summary of the cases in Table 24, although I wish to comment on the following two cases:

- 961-2501/012 (alogliptin 25 mg): This 66 year old female had elevated GGT at baseline and throughout study OPI-002. There were also isolated mild elevations of AST (27 mU/ml) and LDT (145 mU/ml) at week 20. On December 25, 2007, she completed study OPI-002 and rolled into study OLE-012. On June 10, 2008, ALT was 360 mU/ml, ALT 602 mU/ml, and total bilirubin 1.73 mg/dl. Transaminases were normal on June 19. The subject was asymptomatic and liver ultrasound was normal. The investigator reported the event as "lab error". On December 22, 2010, ALT was 180 mU/ml, AST 356 mU/ml, and total bilirubin 2.91 mg/dl. The subject was asymptomatic. Follow up transaminases on March 16, 2011 were normal, while the subject remained on study drug. The subject completed the study on August 25, 2011 with normal transaminase levels.
Internal Comment: I agree with the applicant's assessment that transient and recurrent elevations occurred through the study period. The findings could be due to laboratory error or recurrent congestive heart failure. The subject was asymptomatic.
- 8413-006/402 (placebo): This 57 year old man consumed 200 ml of vodka two days prior to the day 187 visit when ALT was 176 mU/ml, AST 142 mU/ml, and total bilirubin 0.82 mg/dl. The subject met the biochemical definition of Hy's law at an unscheduled visit on day 203. Hepatitis A, B, and C virus serologies were negative. *Internal Comment: The applicant originally indicated that this subject received alogliptin 25 mg. However, documents submitted in January and reviewed by OSI on January 14, 2013 indicate that the subject received placebo. See also Dr. Mary Park's review.*

Table 24. Subjects with elevations of ALT/AST >3x ULN with total bilirubin >2x ULN in the clinical program

Subject number/Study Case number (if applicable)	Treatment	Preferred Term	Outcome	Etiology	Serious
0014-407/CCT-004 TCI2008A05280	Placebo	Gallbladder cancer	Not resolved	Gallbladder cancer had been present prior to start of study drug	Yes
0313-4504/OPI-004 (a) TPA2008A01629	Pioglitazone	Hepatitis B	Ongoing	Hepatitis B, HBsAg (+) HBcAb (+)	Yes
694-3023/OPI-001 ERD2007A00172	Pioglitazone	Hepatitis	Resolved	Hepatitis E Ebstein Barr Virus (+)	Yes
3128-003/303 TPA2009A01847	Alogliptin 25 mg	Bile duct stone	Resolved	Bile duct and gall stones	Yes
5304-091/305 TPG2011A00180	Glipizide	Hepatitis viral	Resolved	Viral hepatitis	Yes
5304-055/305 ERD2010A00130	Alogliptin 12.5 mg	Hepatitis viral	Resolved	Viral hepatitis	Yes
961-2501/012 (b) Not applicable	Alogliptin 25 mg	Hepatic enzyme increased ALT increased AST increased	Resolved	Transient and recurrent elevations throughout the study period. Fatty liver.	No
961-3006/012 (b) Not applicable	Alogliptin 25 mg	ALT increased AST increased	Resolved	Chemical toxicity and/or ACE inhibitor. Enzyme elevations were transient.	No
New Case Reported After 15 May 2012 (c)					
8413-006/402 TPG2012A01058	Alogliptin 25 mg	ALT increased AST increased	Resolving	Concomitant medication (atorvastatin)	No
5312-001/305 TPG2012A01199	Alogliptin 25 mg	Cholelithiasis	Resolving	Common bile duct stone	Yes

Note: SAEs in this table are not included in the hepatic SAE table (Table 3.i).

(a) This subject only had a Day 1 (Baseline) value and no post-baseline laboratory values and therefore is not included in Table 3.b.

(b) Study 012 (long-term, open-label study) was not included in the controlled phase 2 and 3 study pool; therefore this subject is not included in Table 3.b.

(c) Cases that have occurred subsequent to the 15 May 2012 database cut-off have been submitted to the alogliptin IND 69,707 and have been reviewed and assessed by the LSEC.

Source: SCS Table 3.d (October 5, 2012 submission)

Shift Analyses for ALT Values: The shift in ALT from baseline to each visit in controlled phase 2 and 3 studies is shown in Table 26 and summarized in Table 25. The number and percentage of alogliptin subjects who had ALT ≤3x ULN at baseline and >10x ULN during treatment or at endpoint was low (<0.1), similar to placebo (0), and less than that of active comparators (0.1-0.2).

Table 25. Shifts in ALT from ≤3x at baseline to >10x ULN during treatment or at endpoint (Controlled phase 2 and 3 studies)

Time point	Placebo	Active Comparators	All Alogliptin
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During Treatment	0/3647 (0)	5/2340 (0.21)	8/9352 (0.08)
Endpoint	0/3647 (0)	3/2340 (0.12)	3/9352 (0.01)

Source: Table 26

Table 26. Shifts in ALT from baseline including values observed up to the day of last dose (Controlled phase 2 and 3 studies)

Visit Window ALT (/ULN)	Placebo (N = 3647) Baseline ALT (/ULN)						Active Comparator (N = 2340) Baseline ALT (/ULN)						All Comparators (N = 5987) Baseline ALT (/ULN)					
	<=3	>3-5	>5-8	>8-10	>10	Total	<=3	>3-5	>5-8	>8-10	>10	Total	<=3	>3-5	>5-8	>8-10	>10	Total
During Treatment																		
<=3	3381	6	1	0	1	3389	2227	2	0	0	0	2229	5608	8	1	0	1	5618
>3-5	27	0	0	0	0	27	35	2	0	0	0	37	62	2	0	0	0	64
>5-8	3	2	0	0	0	5	3	2	0	0	0	5	6	4	0	0	0	10
>8-10	1	0	0	0	0	1	1	0	0	0	0	1	2	0	0	0	0	2
>10	0	0	0	0	0	0	5	0	0	0	0	5	5	0	0	0	0	5
Total	3412	8	1	0	1	3422	2271	6	0	0	0	2277	5683	14	1	0	1	5699
Endpoint																		
<=3	3403	7	1	0	1	3412	2254	3	0	0	0	2257	5657	10	1	0	1	5669
>3-5	8	0	0	0	0	8	13	2	0	0	0	15	21	2	0	0	0	23
>5-8	1	1	0	0	0	2	1	1	0	0	0	2	2	2	0	0	0	4
>8-10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
>10	0	0	0	0	0	0	3	0	0	0	0	3	3	0	0	0	0	3
Total	3412	8	1	0	1	3422	2271	6	0	0	0	2277	5683	14	1	0	1	5699

Visit Window ALT (/ULN)	Alogliptin 12.5 mg (N = 2944) Baseline ALT (/ULN)						Alogliptin 25 mg (N = 6626) Baseline ALT (/ULN)						All Alogliptin (N = 9857) Baseline ALT (/ULN)					
	<=3	>3-5	>5-8	>8-10	>10	Total	<=3	>3-5	>5-8	>8-10	>10	Total	<=3	>3-5	>5-8	>8-10	>10	Total
During Treatment																		
<=3	2845	4	0	0	0	2849	6256	22	1	0	0	6279	9352	26	1	0	0	9379
>3-5	27	1	1	0	0	29	49	5	0	0	1	55	76	6	1	0	1	84
>5-8	5	0	0	0	0	5	10	2	0	0	0	12	15	2	0	0	0	17
>8-10	1	0	0	0	0	1	3	0	0	0	0	3	4	0	0	0	0	4
>10	4	0	0	0	0	4	4	1	1	0	1	7	8	1	1	0	1	11
Total	2882	5	1	0	0	2888	6322	30	2	0	2	6356	9455	35	3	0	2	9495
Endpoint																		
<=3	2869	5	0	0	0	2874	6309	26	1	0	2	6338	9429	31	1	0	2	9463
>3-5	8	0	1	0	0	9	10	2	0	0	0	12	18	2	1	0	0	21
>5-8	2	0	0	0	0	2	2	1	1	0	0	4	4	1	1	0	0	6
>8-10	1	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	1
>10	2	0	0	0	0	2	1	1	0	0	0	2	3	1	0	0	0	4
Total	2882	5	1	0	0	2888	6322	30	2	0	2	6356	9455	35	3	0	2	9495

Source: IAS Table 5.4.2

Time-to-Event Analyses for Markedly Abnormal ALT Values: The applicant constructed K-M curves showing the time from the day of the first dose of study drug to the first post-baseline occurrence of ALT >3x, >5x, and >10x ULN. The cumulative incidences of ALT elevations were similar between the all alogliptin and all comparators groups. However, the cumulative rate of ALT elevations >10x ULN is greater in the all alogliptin group than the all comparator group during the first 120 days of treatment (see Figure 2). Of the 11 cases of ALT >10x ULN that occurred in the first 120 days, ten were on alogliptin and one was on comparator. (See Table 22 for a summary of alogliptin cases with ALT >10x ULN in controlled phase 2 and 3 studies.) Five of the ten alogliptin cases with ALT >10x ULN showed normalization or improvement at the last assessment while still on alogliptin.

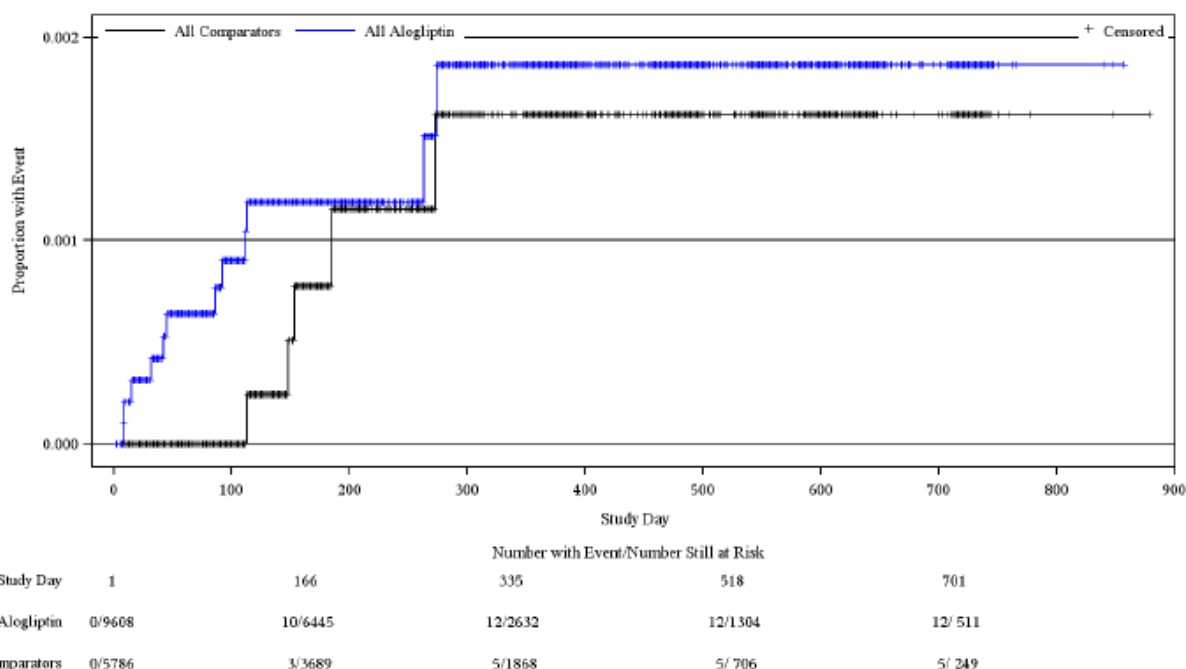


Figure 4. Time to first observed ALT >10x ULN (Controlled phase 2 and 3 studies)

Source: SCS Figure 3.c

eDISH Analysis: eDISH is a graphic tool for the Evaluation of Drug-Induced Serious Hepatotoxicity in clinical studies. ALT values are plotted on the x-axis and total bilirubin on the y-axis using log10 scales for easy visualization. The tool helps medical officers identify cases of liver injury possibly due to drug exposure.

The applicant used this tool to analyze the most extreme observation per subject on controlled phase 2 and 3 trials. As shown in Figure 3, the incidence of subjects meeting the biochemical definition of Hy's law was low and similar between the all alogliptin and all comparators treatment groups. The proportion of subjects in other quadrants was also similar between treatment groups.

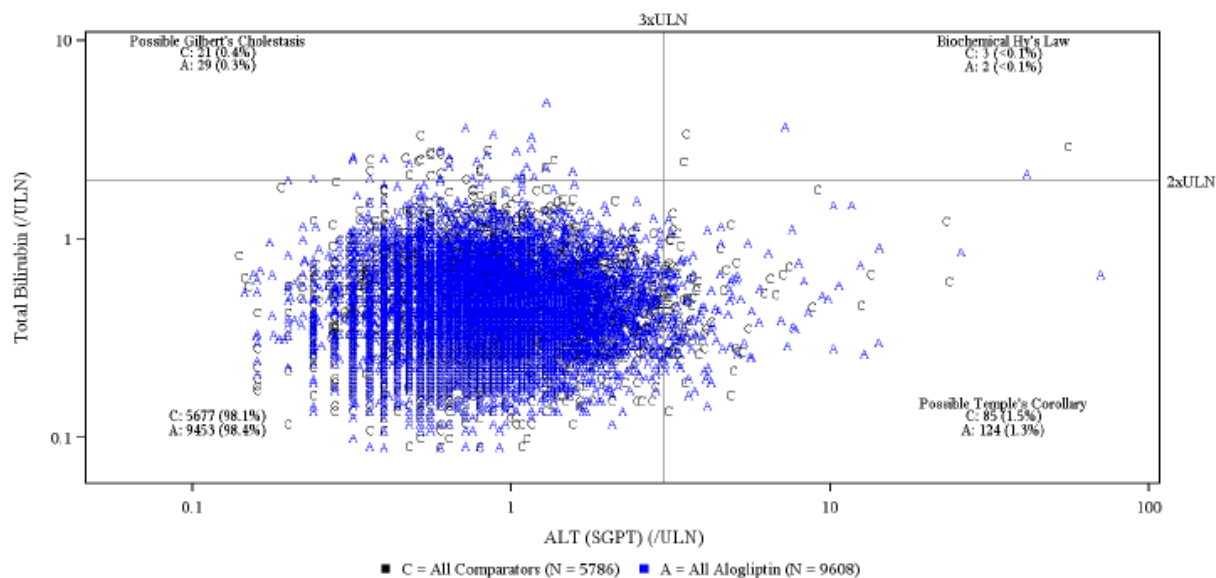


Figure 5. eDISH plot (Most extreme observation per subject) (Controlled phase 2 and 3 studies)

Source: SCS Figure 3.d

SAEs or Discontinuations due to Hepatic-Related AEs: The incidence of any hepatic AE that led to discontinuation was lower in the alogliptin 25 mg and all alogliptin groups than the all comparator group (0.2% vs. 0.3%, respectively). (See Table 27.)

Table 27. Hepatic disorders SMQ (narrow scope) that led to discontinuation of study drug (Controlled phase 2 and 3 studies)

Preferred Term	Number (%) of Subjects		
	All Comparators (a) N=5987	Alogliptin 25 mg N=6626	All Alogliptin (b) N=9857
Any hepatic AE that led to discontinuation	15 (0.3)	11 (0.2)	21 (0.2)
Liver function test abnormal	1 (<0.1)	2 (<0.1)	5 (<0.1)
Hepatic enzyme increased	2 (<0.1)	2 (<0.1)	4 (<0.1)
Alanine aminotransferase increased	1 (<0.1)	2 (<0.1)	3 (<0.1)
Hepatitis C	0	2 (<0.1)	2 (<0.1)
Hepatic steatosis	1 (<0.1)	0	1 (<0.1)
Hepatitis	0	0	1 (<0.1)
Hepatitis B	1 (<0.1)	1 (<0.1)	1 (<0.1)
Hepatitis viral	2 (<0.1)	0	1 (<0.1)
Hypertransaminasemia	0	1 (<0.1)	1 (<0.1)
Liver disorder	0	1 (<0.1)	1 (<0.1)
Transaminase increased	0	0	1 (<0.1)
Gamma-glutamyltransferase increased	1 (<0.1)	0	0
Hepatic cirrhosis	1 (<0.1)	0	0
Hepatic enzyme abnormal	1 (<0.1)	0	0
Hepatic function abnormal	3 (<0.1)	0	0
Hyperbilirubinemia	1 (<0.1)	0	0

Source: SCS Table 3.j

A total of 24 subjects had SAEs within the hepatic disorders SMQ (narrow scope) as of May 15, 2012. Eight of the 24 subjects had ALT/AST values >3x ULN with concurrent total bilirubin >2x ULN and are listed in Table 24. The remaining 16 cases (13 alogliptin) are summarized in Table 28. Case 5304-024/305 (alogliptin 12.5 mg) is a 41 year old male with normal baseline ALT who began alogliptin on October 24, 2009. ALT levels increased from January 27 to February 13, 2010, when ALT was 208 U/L (>5x ULN). The subject was asymptomatic but alogliptin was discontinued on February 17 and medical therapy begun. The event resolved on March 5, 2010. The subject had positive anti-HEV IgM antibodies, suggesting HEV infection.

Internal Comments: I do not attribute the following DILI cases to alogliptin.

- Case 666-2504/012 is a 66 year old female who was on alogliptin for 3.5 years without jaundice or hepatitis. Mechanical dysfunction was excluded and two months prior to the DILI event she had a cholecystectomy for acute cholecystitis. The event of DILI coincided with the use of clopidogrel, which is associated with postmarketing reports of acute liver failure, hepatitis (non-infectious), and abnormal liver function test.
- Case TC12012A01229 is a 70 year old male who experienced a MI on (b) (6). On (b) (6) an inpatient laboratory test showed hepatic function abnormality. On (b) (6) he consented to the study and started

alogliptin on (b) (6). In (b) (6) he experienced aggravation of chronic renal failure and CHF and hemorrhagic diverticulitis. Hospitalization was prolonged. On (b) (6) he had aggravation of hepatic function disorder. CT suggested DILI. Alogliptin was continued. As DILI was attributed to clopidogrel, it was switched to diclopidine hydrochloride, which was discontinued on (b) (6). On (b) (6) he was discharged.

Table 28. Summary of SAEs in the clinical program within the hepatic disorders SMQ (narrow scope), excluding cases of biochemical Hy's law shown in Table 24 (cutoff May 15, 2012)

Subject number/Study Case number	Treatment	Preferred Term	Onset Day	Outcome	Etiology for Liver-related AE
8503-007/402 TPG2011A00518	Placebo	Hepatic neoplasm malignant	59	Fatal	Hepatic neoplasm
490-5005/012 ERD2010A00023	Alogliptin 25 mg	Hemangioma of liver	1169	Ongoing	Hemangioma of liver
903-3017/012 ERD2010A00185	Alogliptin 12.5 mg	Hepatic neoplasm malignant	804	Fatal	Hepatic neoplasm
033-101/OCT-001 TCI2008A02169	Alogliptin 12.5 mg	Hepatitic cancer metastatic Colon cancer	196	Ongoing	Sigmoid cancer metastasis to liver
040-103/OCT-001 TCI2008A04817	Alogliptin 25 mg	Hepatic neoplasm malignant	336	Fatal	Pre-existing hepatic neoplasm, death due to intra-operative hemorrhage
282-5010/012 TPA2010A00474	Alogliptin 12.5 mg	Focal nodular hyperplasia	1101	Resolved	Unknown
381-4003/012 TPA2010A05065	Alogliptin 25 mg	Hepatitis A	1314	Resolved	Hepatitis A Gall bladder lithiasis
8349-001/402 TPG2010A00733	Alogliptin 25 mg	GGT increased Hyperglycemia	86	Resolved	Disease progression
8260-010/402 TPA2011A02627	Alogliptin 12.5 mg	Liver function test abnormal Angina unstable	92	Resolved	Concurrent with unstable angina
666-2504/012 ERD2011A00205	Alogliptin 12.5 mg	Drug-induced liver injury	~4 years	Resolved	Clopidogrel induced cholestatic hepatitis; status post cholecystectomy.
8604-008/402 TPG2011A01493	Alogliptin 25 mg	Hepatic function abnormal Cardiac arrest Acute myocardial infarction Pneumonia aspiration	309	Resolved	Concurrent with MI and cardiac arrest Hypoperfusion during cardiac arrest
5304-024/305 ERD2010A00037	Alogliptin 12.5 mg	Drug-induced liver injury	96	Resolved	None provided. Subject on rabeprazole and domperidone.

Clinical Review
Valerie S.W. Pratt, M.D.
NDAs 22-271 and 22-426
Nesina (alogliptin) and (b) (4) (alogliptin/pioglitazone FDC)

5310-063/305 TPG2011A00129	Glipizide	Hepatitis viral	185	Resolved	Viral hepatitis (Hepatitis C RNA load detected)
9023-010/402 TCI2012A01229	Alogliptin 25 mg	Hepatic function abnormal	92	Ongoing	Chronic cholecystitis, active biliary tract disease, drug-induced liver disorder suspected
8656-016/402 TPG2011A02955	Placebo	Hepatic cirrhosis Fluid overload Cutaneous lupus erythematosus Cardiac failure chronic	198	Ongoing	Disease progression
8536-007/402 TPG2012A00483	Alogliptin 25 mg	Jaundice cholestatic Pancreatitis Cholelithiasis (2 episodes) Cholecystectomy	452	Resolved	Gallstones

Source: SCS Table 3.i

Liver Safety Evaluation Committee (LSEC) and Pharmacovigilance: As described in my review of the first resubmission's EOR meeting document, the applicant has initiated a process to evaluate postmarketing hepatic cases and provide ongoing adjudication of new cases. .

Japanese Postmarketing Data: The applicant submitted the fourth alogliptin PSUR, which covered use in Japan (the only country where alogliptin is approved) from October 16, 2011 to April 15, 2012. Estimated patient exposure during this time was 169,793 patient-years. Cumulative patient exposure since approval on April 16, 2010 was 287,152 patient-years.

A total of 233 adverse event cases (255 spontaneous, 8 clinical) were received globally during the six-month reporting period and met the criteria for inclusion. During this reporting period, estimated patient exposure approximately doubled compared to the previous reporting period. The number of cases increased 36% from 171 to 233. The most common reports were in the skin and subcutaneous disorders SOC, although a total of 21 hepatic disorder events were also reported. The narratives for the six serious hepatic cases are as follows; these cases all had confounding factors.

- TCI2011A06481: A 53 year old male patient felt as if "his chest was being strangled" approximately 3.5 months after switching from sitagliptin to alogliptin 25 mg and sought treatment 2 days later. Angina was ruled out, but laboratory test findings showed elevated transaminase levels (ALT 1583 [37x ULN], AST 921 [27x ULN]) and slightly elevated ALP. Two days after the transaminase elevations were detected, alogliptin was discontinued. Tests conducted at a different hospital on the day of last dose showed that the enzymes were beginning to decrease with ALT 982 and AST 320. Hepatic serology and other factors (hepatitis virus, autoimmunity, EBV, gallstone) were ruled out; IgG for CMV was positive but the antigen was negative. The patient had a history of Hepatitis B at age 26 years-old and used alcohol socially. Concomitant

medications included: glimepiride, rabeprazole sodium, rebamipide, and mosapride citrate. Transaminase levels continued to decline after discontinuation of alogliptin; AST was <ULN and ALT was mildly elevated (<1.25x ULN) about 3 weeks after the initial rise. *Internal Comment: This case is confounded by a history of hepatitis B and social alcohol use.*

- TC12011A06837: A 66 year old male had an asymptomatic increase in liver function test results (ALT 1512 [36x ULN], AST 2188 [66x ULN], and total bilirubin 3.9 [3x ULN] about 1 month after starting alogliptin 25 mg. Prior to alogliptin he had taken sitagliptin for 6 weeks. The patient reported that he increased his alcohol consumption 1 week after starting alogliptin (from 2 drinks twice weekly to 2 drinks thrice weekly for about 2 weeks, no binge drinking reported), then decreased to 2 drinks once a week. HBV and HCV results were negative, but EBV, CMV, and HSV (HAV, HEV, or autoimmune hepatitis markers) were not examined. A substantial improvement in liver enzymes was seen 1 day after discontinuing alogliptin and returned to baseline within one week. Lymphocyte stimulation tests were negative for both sitagliptin and alogliptin. There was no history of changes in his medications or the use of herbals or supplements. Abdominal ultrasound disclosed only a “dull” liver edge. Gallstones were not detected on ultrasound. Concomitant medications included: isosorbide mononitrate, sodium guaienate, famotidine, teprenone, nifedipine, glimepiride, and pravastatin sodium. *Internal Comment: A substantial decline in transaminase levels one day after drug discontinuation is not generally consistent with DILI. This case was also confounded by rabeprazole and alcohol use.*
- TC1201106892: A 78 year-old male had increased transaminase test results (ALT 237 [5x ULN], AST 542 [13x ULN], and GGT 224 [2x ULN]) about 2 months after initiating alogliptin 12.5 mg; alogliptin was discontinued the same day. Ultrasound results did not show liver abnormalities or dilation of intrahepatic bile ducts; however, cancer of the tail of the pancreas was suspected. Mild elevations (<1.5x ULN) in ALT and AST were noted the same day alogliptin was initiated. About 5 weeks after initiating alogliptin, HBs Ab and HCV Ab testing were negative. Relevant medical history included diagnosis of gastric cancer 7 months prior to starting alogliptin, hepatic steatosis, and heavy alcohol use. He was admitted to the hospital the day after discontinuing alogliptin, and transaminase testing showed improvement (ALT 143 [4x ULN], AST 118 [3x ULN], GGT 170 [2x ULN]). The liver disorder resolved 2 days after hospital admission. On an unknown date the patient was transferred to a different hospital to seek medical attention from the same physician who treated his gastric cancer, and was found to have liver and lymph node metastases, but not cancer of the tail of the pancreas. Concomitant medications included voglibose and glimepiride. *Internal Comment: This case is confounded by liver metastases.*
- TC12011A01179: A 65 year-old male patient experienced chills, malaise, itching of his back, and orange-color urine, 20.5 weeks after starting treatment with

alogliptin 12.5 mg. The patient sought treatment at a local hospital 2 weeks later when the symptoms did not improve. Whole body jaundice was observed, total bilirubin was 8.2, ALT was 204, AST was 282. Abdominal CT scan did not show a mass-like lesion that could cause obstructive jaundice, thus acute hepatitis was diagnosed and alogliptin discontinued. Liver biopsy results were not inconsistent with drug-induced hepatitis. Over the next week, total bilirubin, ALT, and AST continued to rise to 16x ULN, 13x ULN, and 29x ULN, respectively. ALP was 4x ULN. HEV RNA and HEV IgA Ab testing were both positive. Relevant medical history included jaundice and liver disorder at ages 20 and 39 years-old, acute cholecystitis, cholecystectomy, and alcohol-use. The patient took no concomitant medications. The patient made a complete recovery.

Internal Comment: This case is likely due to hepatitis E.

- TC12012A01573: An 83 year-old diabetic female with history of Alzheimer's disease, experienced acute pancreatitis and hepatic function disorder, 7 months after initiation of alogliptin 25mg QD. One day after presenting to the hospital with fever (prescribed levofloxacin hydrate), the patient, was tested for influenza, and was given oseltamivir phosphate for likely influenza (though testing was negative). The following day, she returned to the hospital with complaints of epigastric pain, vomiting and fever. Upon examination, the patient was afebrile, however, yellow bulbar conjunctivae was noted. Blood tests showed elevated amylase 172 IU/L [ULN=160]), and hepatic function disorder: AST 357 IU/L (8x ULN), ALT 432 IU/L (12x ULN), ALP 878 IU/L (2x ULN), total bilirubin 4.3 mg/dL (ULN≤1.2), platelet count 107,000, and WBC count 7,400 (neutrophil 83%). Alogliptin was discontinued. The patient was transferred to another hospital. Laboratory testing on that same day revealed further elevations in amylase (2375 [ULN=125] and total bilirubin (6.3 mg/dL [ULN=1.2]). No bile duct stone was observed upon CT scan. Concomitant medications included: donepezil hydrochloride, limaprost, diclofenac sodium, magnesium oxide, herbal extract NOS, metformin hydrochloride. Within 10 days of hospitalization, pancreatic and hepatobiliary enzymes were within normal limits and the event resolved. *Internal Comment: This case is confounded by acute pancreatitis.*
- TC12011A02923: A 64 year-old male patient with history of chronic hepatitis C, evidence of prior hepatitis B infection, and alcohol-use, experienced asymptomatic increases in ALT (7x ULN) and AST (5x ULN) 4 weeks after starting alogliptin 12.5 mg. One week after the initial transaminase elevation, alogliptin was discontinued; however transaminases continued to rise, peaking 8-12 days after discontinuation (ALT 22x ULN, AST 9x ULN). Total bilirubin was noted to be 2x ULN and ALP just over the upper limit of normal when the transaminase levels peaked. He tested positive for HCVAb and had a high viral load (HCV-RNA=6.1 log IU/mL). HBsAB and HBcAb were also both positive. HBsAg was negative. Abdominal CT scan of the liver, gallbladder, and pancreas showed a calcified gallstone and mild hepatic steatosis or hepatitis. A liver biopsy performed 5 months after the initial transaminase elevations showed

chronic hepatitis C. Glimeperide was the only concomitant medication. *Internal Comment: This case is confounded by hepatitis C infection.*

Of the 15 nonserious hepatic AE cases, none met the criteria for biochemical Hy's law. Eight resolved, five had significant improvement, one case is unknown, and 1 case remains unresolved. Alogliptin was continued in three cases, including the one with unknown resolution.

Two additional postmarketing cases (TCI2012A05586 and TCI2012A05429) were consulted to OSE for review (see below).

Table 29. Summary of nonserious and serious AEs for the current PSUR reporting period and cumulative serious unlisted hepatic disorder AEs

	Current Period		Total Cumulative
Patient-Years of Exposure	169,793		287,152
SOC Preferred Term	Nonserious	Serious	Serious Unlisted
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
hepatic neoplasm malignant ^{*,1}	0	0	1
Hepatobiliary disorders			
drug induced liver injury [*]	2	1	2
hepatitis [*]	2	0	0
hepatitis acute [*]	0	1	2
hepatic function abnormal ^{*,2}	8	3	3
liver disorder [*]	3	1	2
Total	15	6	10

* Denotes an unlisted term in the CCSI.

¹ The one serious unlisted ADR is from a clinical study.

² One serious ADR contained follow-up information to a report initially included with the 3rd PSUR.

Source: PSUR 4 Table 19

OSE: OSE's hepatologists Leonard Seeff and John Senior were consulted to review 11 clinical cases with ALT >10x ULN and 5 clinical cases with biochemical Hy's law to provide an assessment as to whether there is a concern for severe DILI with alogliptin. Please see their November 10, 2012 review. It recommends the following:

- Review of clinical trial data suggest that most serious liver injury or dysfunction has some other causative explanation than alogliptin, but there remain cases in which no satisfactory or convincing alternative diagnosis was found or could be determined by review of the clinical information supplied
- There is inadequate investigation or reporting of patients receiving alogliptin after approval. This is a world-wide problem, which is not alogliptin-specific. The sponsor should advise prescribers to be somewhat cautious, check liver tests

(serum ALT, AST, ALP, and bili) twice before starting alogliptin, monitor ALT monthly for six months, and repeat testing for elevations above 2x ULN or 2x the average pre-treatment baseline value within a week to confirm. If still elevated or worse, temporary interruption of alogliptin, investigation for a probable cause, and case reporting should occur.

- *Internal Comment: I do not agree with OSE's recommendation to provide specific laboratory testing advice in the PI. However, I do agree with the recommendation that prescribers be advised of this risk. I recommend a hepatotoxicity warning in the label.*
- Alogliptin is approvable.
- The sponsor should be cautious and vigilant about the hepatic safety of alogliptin until more experience can be gained worldwide.

Summary: In summary,

- Nonclinical data do not indicate a strong signal for liver toxicity.
- The percentage of alogliptin subjects with markedly abnormal ALT including values observed up to seven days after last dose is less than with active comparator (i.e. glipizide, metformin, and pioglitazone).
- When the number of subjects with marked ALT abnormalities per 100 subject years of exposure was compared by treatment group, values for the alogliptin groups were consistently lower than the active comparator group.
- The number and percentage of alogliptin subjects who had ALT $\leq 3x$ ULN at baseline and shifted to $>10x$ ULN during treatment or at endpoint was low (<0.1), similar to placebo (0), and less than that of active comparators (0.1-0.2).
- The incidence of any hepatic AE that led to discontinuation was lower in the alogliptin 25 mg and all alogliptin groups than the all comparator group (0.2% vs. 0.3%, respectively).
- When treatment groups were compared using eDISH, a graphic tool for the Evaluation of Drug-Induced Serious Hepatotoxicity in clinical studies, the proportion of subjects in each quadrant was similar between the all alogliptin and all comparators groups.
- Although a greater percentage of alogliptin subjects had ALT elevations $>10x$ ULN, the majority of these subjects ($n = 8/12$, 66.7%) had elevated ALT at baseline and a quarter of them ($n = 4/12$, 25.0%) had markedly abnormal ALT elevations at baseline.

When K-M curves showing the time from the day of the first dose of study drug to the first post-baseline occurrence of ALT $>3x$, $>5x$, and $>10x$ ULN were compared, the cumulative incidences of ALT elevations were similar between the all alogliptin and all comparators groups. However, the cumulative rate of ALT elevations $>10x$ ULN is greater in the all alogliptin group than the all comparator group during the first 120 days of treatment. Five of the ten alogliptin cases with ALT $>10x$ ULN showed normalization or improvement at the last assessment while still on alogliptin.

In short, clinical data indicates that the incidence of transaminase elevation with alogliptin is low and lower than with active comparators (glipizide, metformin, and pioglitazone) and all comparators (active comparators and placebo). The number and percentage of alogliptin subjects who had ALT $\leq 3 \times$ ULN at baseline and shifted to $> 10 \times$ ULN during treatment or at endpoint was similar to placebo (< 0.1 and 0, respectively). Although 1) K-M curves indicate that cumulative rate of ALT elevations $> 10 \times$ ULN is greater in the all alogliptin group than the all comparator group during the first 120 days of treatment and 2) there are cases of probable alogliptin hepatotoxicity, these cases are infrequent and, according to Leonard Seeff's first review "trivial" once the drug is discontinued. Therefore, in my opinion, review of the current clinical database supports approval of alogliptin. The sponsor proposes including hepatic enzyme elevations in the labeling section 6.2 Postmarketing Experience. I agree with this proposal and also recommend a hepatotoxicity warning. Hepatotoxicity should be monitored as an adverse event (AE) of special interest in the controlled CV study 402, PSURs, and an enhanced pharmacovigilance PMR.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events which occurred in $\geq 3\%$ of subjects in any treatment group were analyzed in the first and second resubmissions. There was a slightly lower incidence of AEs in alogliptin 25 mg subjects in the second CR when compared to the first CR (63.8% versus 58.6%). However, the most common alogliptin AEs were similar between the resubmissions and were as follows (percentages are for the second versus first resubmission):

- Nasopharyngitis (5.0% versus 3.9%)
- Hypertension (4.0% versus 2.9%)
- Headache (3.9% versus 3.9%)
- Diarrhea (3.5% versus 2.7%)
- Urinary tract infection (3.3% versus 3.7%)
- Upper respiratory tract infection (3.9% versus 3.5%)

In the pooled controlled phase 2 and 3 database, when common AEs were compared between alogliptin and all comparator subjects in the second CR, incidence rates were similar, although more alogliptin 25 mg subjects experienced the following AEs (see Table 30:

- Nasopharyngitis (5.0% versus 4.4%)
- URI (3.9% versus 3.1%)
- Headache (3.9% versus 3.4%)

- Hypertension (4.0% versus 3.9%)

Table 30. Common AEs (≥3% of subjects in any group) in the 2011 and 2012 resubmissions

SOC Preferred Term	Number (%) of Subjects					
	2011 NDA Resubmission			2012 NDA Resubmission		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232	All Comparators N=5987	Alogliptin 25 mg N=6626	All Alogliptin N=9857
Any AE	1651 (56.3)	2052 (58.6)	3146 (60.1)	3785 (63.2)	4226 (63.8)	6315 (64.1)
Gastrointestinal disorders	336 (11.5)	436 (12.5)	664 (12.7)	867 (14.5)	988 (14.9)	1488 (15.1)
Diarrhea	105 (3.6)	94 (2.7)	138 (2.6)	233 (3.9)	233 (3.5)	345 (3.5)
Infections and infestations	656 (22.4)	833 (23.8)	1319 (25.2)	1410 (23.6)	1695 (25.6)	2657 (27.0)
Nasopharyngitis	98 (3.3)	137 (3.9)	213 (4.1)	265 (4.4)	334 (5.0)	564 (5.7)
Upper respiratory tract infection	70 (2.4)	122 (3.5)	180 (3.4)	188 (3.1)	257 (3.9)	400 (4.1)
Urinary tract infection	108 (3.7)	130 (3.7)	212 (4.1)	198 (3.3)	220 (3.3)	338 (3.4)
Nervous system disorders	277 (9.4)	368 (10.5)	587 (11.2)	599 (10.0)	729 (11.0)	1108 (11.2)
Headache	103 (3.5)	136 (3.9)	214 (4.1)	204 (3.4)	256 (3.9)	388 (3.9)
Vascular disorders	130 (4.4)	165 (4.7)	235 (4.5)	359 (6.0)	401 (6.1)	538 (5.5)
Hypertension	85 (2.9)	101 (2.9)	159 (3.0)	233 (3.9)	263 (4.0)	367 (3.7)

Source: SCS Table 2.b

7.4.2 Laboratory Findings

Overview of Laboratory Analysis in the Resubmission:

The sponsor updated the laboratory data as agreed at the EOR meeting. This included an analysis of hepatic function parameters (see section 7.3.5), hypoglycemic events (see section 7.3.4), and renal function parameters, which are discussed here.

The clinical laboratory data was updated using the controlled phase 2 and 3 data set (i.e. studies 003, 007, 008, 009, 010, 011, 303, 301, 402(b), OPI-001, OPI-002, OPI-004, CCT-001, CCT-003, CCT-004, CCT-005, CCT-006, MET-302, 308, and 305(c)). I analyze the change in renal parameters from baseline, shift analyses, markedly abnormal results, and SAEs or discontinuations due to renal AEs here.

Analyses Focused on Measures of Central Tendency:

In the controlled phase 2 and 3 study group, the mean changes from baseline to endpoint in albumin, BUN, and serum creatinine were small, similar between treatment groups, and not clinically meaningful (see Table 31).

Table 31. Mean change from baseline to endpoint for renal function parameters (Controlled phase 2 and 3 studies)

Parameter	Mean (SD) Change From Baseline to Endpoint		
	All Comparators (a) N=5987	Alogliptin 25 mg N=6626	All Alogliptin (b) N=9857
Albumin (g/dL)	n=3561 -0.02 (0.271)	n=4161 -0.03 (0.264)	n=7361 -0.02 (0.264)
BUN (mg/dL)	n=5786 0.4 (5.10)	n=6408 0.6 (5.23)	n=9608 0.5 (4.84)
Serum creatinine (mg/dL)	n=5786 0.00 (0.193)	n=6408 0.01 (0.220)	n=9608 0.01 (0.190)

Source: IAS Table 10.1.

Note: Albumin was not measured in Studies 402 and 308.

BUN=blood urea nitrogen.

(a) The All Comparators Grouping combines placebo and active comparator groups, which are not shown in the table.

(b) The All Alogliptin Grouping combines 25 mg with the 6.25, 12.5, 50, and 100 mg groups, which are not shown in the table.

Source: SCS Table 3.k

Outliers or Shifts from Normal to Abnormal:

In controlled phase 2 and 3 studies, the shifts in renal function (CG and MDRD formulas) from baseline to endpoint were similar between treatment groups. (See Table 32 and Table 33.)

Table 32. Shifts in renal function (CG) from baseline to endpoint (Controlled phase 2 and 3 studies)

Endpoint Renal Function	Number (%) of Subjects											
	All Comparators (a) N=5786				Alogliptin 25 mg N=6407				All Alogliptin (b) N=9607			
	Baseline Renal Function											
	Normal N=3262	Mild N=1919	Moderate N=567	Severe N=38	Normal N=3672	Mild N=2068	Moderate N=624	Severe N=43	Normal N=5779	Mild N=3019	Moderate N=765	Severe N=44
Normal	2979 (91.3)	354 (18.4)	3 (0.5)	0	3344 (91.1)	360 (17.4)	3 (0.5)	0	5294 (91.6)	514 (17.0)	3 (0.4)	0
Mild	278 (8.5)	1428 (74.4)	113 (19.9)	0	321 (8.7)	1548 (74.9)	134 (21.5)	0	473 (8.2)	2299 (76.2)	166 (21.7)	0
Moderate	5 (0.2)	136 (7.1)	435 (76.7)	9 (23.7)	6 (0.2)	159 (7.7)	463 (74.2)	10 (23.3)	11 (0.2)	205 (6.8)	571 (74.6)	10 (22.7)
Severe	0	1 (<0.1)	16 (2.8)	29 (76.3)	1 (<0.1)	1 (<0.1)	24 (3.8)	33 (76.7)	1 (<0.1)	1 (<0.1)	25 (3.3)	34 (77.3)

Source: IAS Table 10.4.

Note: Renal function is defined as follows: normal = estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m²; mild = eGFR ≥ 60 - <90 mL/min/1.73 m²; moderate = eGFR ≥ 30 - <60 mL/min/1.73 m²; severe = eGFR <30 mL/min/1.73 m².

(a) The All Comparators Grouping combines placebo and active comparator groups.

(b) The All Alogliptin Grouping combines 25 mg with the 6.25, 12.5, 50, and 100 mg groups.

Source: SCS Table 3.l

Table 33. Shifts in renal function (MDRD) from baseline to endpoint (Controlled phase 2 and 3 studies)

Endpoint RF	All Comparators n=5786				Alogliptin 25 mg n=6407				All Alogliptin N=9857			
	Baseline n=5786				Baseline n=6407				Baseline n=9607			
	Normal	Mild	Mod	Severe	Normal	Mild	Mod	Severe	Normal	Mild	Mod	Severe
Normal	999	460	5	0	1042	447	4	0	1677	661	5	0
Mild	358	2769	255	0	409	3191	246	0	644	4864	322	0
Moderate	4	246	605	14	8	309	656	11	10	473	864	11
Severe	0	2	26	43	0	3	29	42	0	3	30	43

Source: IAS Table 10.3

Marked outliers and dropouts for laboratory abnormalities:

In controlled phase 2 and 3 studies, the incidence of subjects with abnormal BUN, serum creatinine, and eGFR during treatment was generally similar between groups. (See Table 34.) More alogliptin 25 mg subjects (8.2%) experienced >25% decrease in eGFR from baseline (CG) than all comparator (7.0%) and all alogliptin (7.4%) subjects. The percentage of subjects who experienced >50% decrease from baseline eGFR (CG) was similar between groups (0.4 – 0.5%).

Table 34. Subjects with abnormal renal function during treatment (Controlled phase 2 and 3 studies)

Parameter (Criterion)	Number (%) of Subjects With ≥1 Markedly Abnormal Result During Treatment		
	All Comparators (a) N=5786	Alogliptin 25 mg N=6408	All Alogliptin (b) N=9608
BUN (>3×ULN)	39 (0.7)	36 (0.5)	38 (0.4)
Albumin (<2.5 g/dL)	0	0	0
Serum creatinine			
>1.5×Baseline	125 (2.2)	149 (2.3)	187 (1.9)
>1.5×Baseline and >ULN	72 (1.2)	86 (1.3)	105 (1.1)
>ULN with >0.3 mg/dL increase from Baseline	172 (3.0)	213 (3.3)	250 (2.6)
≥2× Baseline value	23 (0.4)	37 (0.6)	43 (0.4)
>2.0 mg/dL	103 (1.8)	121 (1.9)	131 (1.4)
eGFR			
>25% decrease from Baseline (C-G)	406 (7.0)	523 (8.2)	710 (7.4)
>50% decrease from Baseline (C-G)	22 (0.4)	33 (0.5)	39 (0.4)

Source: SCS Table 3.m

The percentage of subjects with renal function-related SAEs or AE that led to discontinuation was similar between treatment groups (see Table 35). The incidence of any specific renal-related SAE was low (≤0.4%) and similar between groups. The incidence of any specific renal-related AE that led to discontinuation was low (≤0.3%). More alogliptin subjects experienced renal impairment than all comparator subjects (0.2% versus <0.1%). However, more all comparator subjects experienced renal failure chronic than alogliptin subjects (0.1% versus <0.1%).

Table 35. Number and percentage of subjects with renal function-related SAEs and AEs that led to discontinuation (Controlled phase 2 and 3 studies)

	All comparators n=5987	Alogliptin 25 mg n=6626	All Alogliptin n=9857
SAEs	56 (0.9%)	62 (0.9%)	71 (0.7%)
AEs that led to discontinuation	40 (0.7%)	22 (0.9%)	90 (0.9%)

Source: SCS Tables 3.n and 3.o

In summary, there is no renal safety signal in the controlled phase 2 and 3 study data. The sponsor's proposed alogliptin dosage adjustment for RI is acceptable.

7.4.3 Vital Signs

Please refer to my previous alogliptin and alogliptin/pioglitazone FDC reviews. In summary, alogliptin does not appear to be associated with clinically meaningful changes in vital signs.

7.4.4 Electrocardiograms (ECGs)

Please refer to my previous alogliptin and alogliptin/pioglitazone FDC reviews. In summary, alogliptin does not appear to result in a clinically significant change in mean ECG parameters, the incidence of abnormal ECGs, or ECG-related SAEs or discontinuations. The interim analysis of CV study 402 demonstrated that alogliptin does not increase CV risk.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

No immunogenicity studies were completed. Alogliptin is a small molecule and is, therefore, not expected to be immunogenic. See also section 7.3.4 Significant Adverse Events for a description of hypersensitivity adverse events.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Please refer to my previous alogliptin and alogliptin/pioglitazone FDC reviews.

7.5.2 Time Dependency for Adverse Events

Please refer to my previous alogliptin and alogliptin/pioglitazone FDC reviews.

7.5.3 Drug-Demographic Interactions

Please refer to my previous alogliptin and alogliptin/pioglitazone FDC reviews.

7.5.4 Drug-Disease Interactions

Please refer to my previous alogliptin and alogliptin/pioglitazone FDC reviews.

7.5.5 Drug-Drug Interactions

Please refer to Sang Chung's and Ritesh Jain's clinical pharmacology reviews as well as my reviews of alogliptin NDA 22-271 and alogliptin/pioglitazone FDC NDA 22-426.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please refer to the malignancy subsection of 7.3.4 Significant Adverse Events, my original NDA reviews, and David Carlson's pharmacology/toxicology reviews.

7.6.2 Human Reproduction and Pregnancy Data

Please refer to my alogliptin and alogliptin/pioglitazone FDC reviews.

7.6.3 Pediatrics and Assessment of Effects on Growth

For the alogliptin/pioglitazone FDC, the applicant requested a full waiver because "the product would be ineffective or unsafe...in the pediatric age group". (b) (4)

I agree with the requested waiver. On January 11, 2012, PeRC recommended a full waiver for alogliptin/pioglitazone NDA 22-426.



On September 24, 2008, the Pediatric Review Committee (PeRC) agreed with the Division's recommendation that alogliptin studies should be deferred in T2DM subjects 10-16 years old and waived in T2DM subjects 0-9 years old. The applicant requested a waiver of alogliptin studies in T2DM subjects 0-9 years old, stating "studies are

impossible or highly impractical because there are too few subjects under 10 years of age diagnosed with T2DM who required pharmacologic intervention". I agree.

On January 20 and November 7, 2012, the applicant revised its alogliptin pediatric plan for deferred studies in T2DM subjects 10-17 years (inclusive). It proposed the following three studies:

- SYR-322_104 (104): *A comparative, randomized, open-label, multicenter, single dose, pharmacokinetic, pharmacodynamic and safety study of alogliptin (12.5 mg and 25 mg) between children, adolescents, and adults with type 2 (non-insulin dependent) diabetes mellitus.* According to protocol amendment 8, the purpose of this study is to confirm that the PK and PD profiles are similar between children and adults, and that the dose selection (12.5 or 25 mg) is appropriate. Subjects will have a fasting plasma glucose level ≥ 126 mg/dl, 2-hour plasma glucose level ≥ 200 mg/dl during an oral glucose tolerance test, random plasma glucose level ≥ 200 mg/dl, or HbA1c $\geq 6.5\%$. If taken, the metformin dose must be stable for ≥ 30 days prior to Day 1. Subjects will be enrolled as follows:
 - Group 1: 6 T2DM subjects aged 10 to <14 years
 - Group 2: 18 T2DM subjects aged 14 to <18 years
 - Group 3: 24 T2DM adults, aged 18-65 years

The applicant proposes the following timelines for study 104:

- Study start date: November 11, 2009.
- Study completion date: September 30, 2013
- Report submission date: March 31, 2014
- SYR-322_307 (307): *A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of alogliptin compared with placebo as monotherapy (with a metformin control arm) in pediatric subjects with T2DM.* (b) (4)

 - Protocol submission: October 31, 2014
 - Study completion date: May 31, 2019
 - Report submission date: January 31, 2020
- SYR-322_309 (309): *A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of alogliptin compared with placebo when added on to metformin in pediatric subjects with type 2 diabetes.* (b) (4)


(b) (4)

- Protocol submission: October 31, 2014
- Study completion date: October 31, 2018
- Report submission date: May 31, 2019

The CR contained the following responses to the April 25, 2012 CR letter's pediatric information request. The applicant's responses are acceptable unless otherwise noted.

(b) (4)

- *Comment: As discussed with statistic's Janice Derr, the proposed sample sizes and power calculations for studies 307 and 309 will need to be reviewed after the complete protocols have been submitted.*

Statistic's Janice Derr reviewed protocol synopsis 309 on September 20, 2012. On September 21, 2012, her comments were conveyed regarding the proposed number of randomized subjects, primary analysis set imputation method, and data standards were conveyed to the applicant. The applicant responded with the following on October 11, 2012:

(b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Please refer to my original reviews of alogliptin NDA 22-271 and alogliptin/pioglitazone FDC NDA 22-426.

7.7 Additional Submissions / Safety Issues

The applicant's enhanced pharmacovigilance monitoring plan, LSEC charter, and June 26, 2012 LSEC consensus statement were previously reviewed in the EOR meeting package. The applicant also submitted the following case consensus assessments:

- TC12012A03395: Case cannot be assessed for DILI due to insufficient information
- TPG2012A01199: DILI is excluded. Event was due to choledocolithiasis
- TPG2012A01058: DILI with adaptation due to study medication is possible.

See also section 7.3.5 Submission Specific Primary Safety Concerns.

8 Postmarket Experience

Alogliptin was approved for use in Japan on April 16, 2010. Alogliptin/pioglitazone FDC was approved for use in Japan on July 1, 2011. I reviewed the third Japanese alogliptin PSUR (April 16, 2011 – October 15, 2011; 117,359 cumulative patient-years exposure) in the first resubmission. Dr. Hylton Joffe's April 20, 2012 Cross-Discipline Team Leader review discussed the liver safety findings up to 219,000 patient-years exposure.

As agreed, the sponsor submitted the fourth Japanese PSUR (October 16, 2011 – April 15, 2012) in the second resubmission. Patient exposure during the reporting period was 169,793 patient-years. Cumulative patient exposure is 287,152 patient-years. During the six-month reporting period, 233 cases of adverse drug reactions (50 serious) were received globally and met criteria for inclusion. This included 225 cases for the marketed product in Japan and 8 cases received from ongoing studies worldwide. Reports of skin and subcutaneous tissue disorders were most common (9 serious, 77 non-serious), including one case of Stevens-Johnson Syndrome and five cases of erythema multiforme. Five serious cases of pancreatitis were reported. A total of 21 cases (6 serious) met the SMQ criteria for hepatic disorders, although the majority had confounding factors. See also section 7.4.2 Laboratory Findings for a discussion of the pertinent findings from these postmarketing reports. In summary, the PSUR data supports the safety findings previously identified (i.e., hypersensitivity [particularly, skin and subcutaneous tissue disorders], liver disorders, and pancreatitis).

9 Appendices

9.1 Literature Review/References

Not applicable.

9.2 Labeling Recommendations

Please refer to my review of the original NDA submission and the following sections of this review for my proposed changes and the rationale underlying those changes.

- Under each of the trials in the Clinical Studies section, the applicant proposes, (b) (4) and includes specific HbA1c data. As proportional HbA1c improvement is not unique to alogliptin treatment and language describing this effect has not been permitted in other recently approved labels, the applicant should be asked again to remove this language.
- 1.2 Risk Benefit Assessment
- 2.4 Important Safety Issues With Consideration to Related Drugs
- 2.5 Summary of Presubmission Regulatory Activity Related to Submission
- 3.2 Compliance with Good Clinical Practices
- 7.3.4 Significant Adverse Events
- 7.3.5 Submission Specific Primary Safety Concerns

Chinese study 308 is not included in the Adverse Reactions or Clinical Studies sections of the label. It is cited as part of a group to support general “no clinically meaningful” vital sign and laboratory statements, which is acceptable.

See also the following consults:

- DMEPA’s review of the carton and container labels and trade name
- OPDP’s labeling review
- DMPP’s patient labeling review

9.3 Advisory Committee Meeting

Not applicable.

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/s/

VALERIE S PRATT
01/17/2013

MARY H PARKS
01/21/2013

**Medical Officer Safety Review
Division of Metabolism and Endocrinology Products (DMEP)**

NDA: Alogliptin NDA 22-271 and alogliptin/pioglitazone FDC NDA 22-426

Submissions: SDNs 86 and 69, respectively

Contents: End of Review (EOR) meeting document

Relevant INDs: Alogliptin IND 69,707 and alogliptin/pioglitazone FDC IND 73,193

Sponsor: Takeda

Indication: Type 2 diabetes mellitus (T2DM)

Medical Reviewer: Valerie Pratt, M.D.

Division Director: Mary Parks, M.D.

Background: On April 25, 2012, a second complete response (CR) was issued to alogliptin and alogliptin/pioglitazone FDC NDAs 22-271 and 22-426, respectively. Although the deficiencies communicated in the first CR letters were adequately addressed, a concerning signal for drug-induced liver injury (DILI) was identified in the complete response submissions. Specifically, in the controlled phase 2/3 database, there were numerical imbalances not favoring alogliptin for serum alanine aminotransferase (ALT) elevations >5x, >10x, and >20x the upper limit of normal (ULN) compared to control. In addition, five probable cases of alogliptin hepatotoxicity were identified among ~219,000 patient-years of postmarketing experience in Japan. (Cases were TCI2011A04573, TCI2011A06837, TCI2011A03640, TCI2010A05612, and TCI2011A06481.)

The CR letter recommended the following be included in the resubmission:

- Additional postmarketing data from countries where alogliptin is approved as well as additional clinical trial data to provide reassurance that alogliptin hepatotoxicity is of limited clinical significance. The additional clinical trial data may come from the ongoing EXAMINE trial as well as other available clinical trials, such as Study 305. If the imbalances in serum ALT elevations in the controlled clinical trial database become less apparent with additional patient exposures and a true Hy's Law case is still not seen, we may have sufficient reassurance that alogliptin has an acceptable hepatic profile, particularly if additional postmarketing data do not identify further reports of severe drug-induced liver injury (e.g., leading to death or liver transplantation).

- We strongly encourage you to perform enhanced pharmacovigilance (e.g., real-time follow-up to rule out alternative etiologies) for all potential cases of drug-induced liver injury reported with alogliptin to ensure that as much information as possible is obtained for these cases.
- When presenting serum ALT elevations >3X, >5X, >10X and >20X ULN for the controlled phase 2/3 database in the resubmission, show baseline data only for those patients who received at least one dose of study medication and who have at least one post-baseline serum ALT value.
- The extent of additional clinical trial and postmarketing data needed for the resubmission can be discussed at the End-of-Review meeting.
- In addition, you could consider [REDACTED] (b) (4)
[REDACTED] (b) (4)
[REDACTED] and the concerns for hepatotoxicity with alogliptin are confirmed.

Comments on the proposed pediatric plan were also conveyed in the CR letter.

The purpose of the EOR meeting document is 1) to provide updated clinical trial liver safety information along with the Liver Safety Evaluation Committee (LSEC) assessment of clinical and postmarketing liver safety data and 2) to summarize the proposed content of the NDA resubmission.

The main objective of the meeting will be to confirm and gain agreement from the Agency that the following approach will fully address all items listed in the CR letter, including:

- Additional currently available clinical hepatic safety data from the ongoing clinical program.
- Additional postmarketing data from Japan as provided in the 4th Periodic Safety Update Report (PSUR) (16th October 2011 through 15 April 2012).
- Overall content of the proposed NDA resubmissions.
- Process for monitoring, reviewing, and reporting spontaneous clinical and postmarketing liver-related cases.

The sponsor plans to provide NDA resubmissions to address the April 2012 CR letter to the alogliptin and SYR-322-4833 NDAs in July 2012 assuming agreement is reached at the Type B End of Review meeting scheduled with the Agency on June 29, 2012.

Submission: The July 2011 NDA resubmission included safety data from 5232 alogliptin subjects in 11 phase 2/3 completed, controlled trials and ongoing CV trial 402. (See Table 1.) After the Agency's October 24, 2011 global hepatic safety information request, the sponsor analyzed data from 18 clinical studies (including five conducted in Japan). To address the April 2012 CR, the sponsor has updated the analysis (i.e. the Integrated Analysis of Safety [IAS]) to include completed controlled study 308 and

interim data from ongoing controlled studies 402 and 305 (cutoff dates of April 18 and 24, 2012, respectively). This analysis of 20 completed or ongoing controlled studies includes 9857 subjects exposed to alogliptin. Exposure duration also increased to 3823 subjects exposed for ≥ 6 months to ≤ 1 year, 1270 subjects exposed for ≥ 1 year to ≤ 18 months, and 1500 subjects exposed for ≥ 18 months. (See Table 2.) The demographics of this population are generally similar between the all comparators (n=5987) and all alogliptin (n=9857) groups. The global distribution of alogliptin subjects is US and Canada (25.9%); Mexico and Central/South America (20.9%); Western Europe, Australia, New Zealand, and Middle East (8.4%); and Rest of World (e.g. Asia or Africa) (44.7%).

Table 1. Studies included integrated analysis

Submission	Studies Included	All Comparator	All Alogliptin
July 2011 Resubmission	003, 007, 008, 009, 010, 011, 301, 303, 402 (interim data as of 29APR2011), 322OPI-001, 322OPI-002, and 322OPI-004	N=2934	N=5232
October 2011 Information Request	003, 007, 008, 009, 010, 011, 301, 303, 322OPI-001, 322OPI-002, 322OPI-004, CCT-001, CCT-003, CCT-004, CCT-005, CCT-006, MET-302, and 402 (data as of 11 September 2011[1])	N=4074	N=7011
Planned Resubmission (April 2012 IAS Update)	003, 007, 008, 009, 010, 011, 301, 303, 322OPI-001, 322OPI-002, 322OPI-004, CCT-001, CCT-003, CCT-004, CCT-005, CCT-006, MET-302, 308, 305 (data as of 24 April 2012[2]), and 402 (data as of 18 April 2012[1])	N=5987	N=9857

Note: Updates to the integrated dataset with regard to hepatic safety are shown in bold.

[1] Updated for safety analyses only, excluding major adverse cardiovascular event (MACE).

[2] Updated for safety analyses only.

Source: EOR meeting document Table 1

Note: CCT-studies were conducted in Japan. Study 308 was conducted in China. See the Appendix 1 for study details.

Table 2. Exposure by dose and duration (Controlled phase 2/3 studies)

Exposure	July 2011 Resubmission		April 2012 IAS Update	
	All Comparators (a) N=2934	All Alogliptin (b) N=5232	All Comparators N=5987	All Alogliptin N=9857
Duration in days (c)				
Mean (SD)	179.4 (107.68)	174.4 (88.27)	266.7 (202.74)	256.9 (203.15)
Median (min, max)	181.0 (1-533)	182.0 (1-550)	183.0 (1-888)	182.0 (1-942)
Cumulative exposure (subjects-years) (d)	1441.16	2497.89	4372.11	6933.77
Number (%) of subjects exposed for (c)				
1 day	5 (0.2)	7 (0.1)	12 (0.2)	14 (0.1)
>1 to <7 days	26 (0.9)	22 (0.4)	30 (0.5)	32 (0.3)
≥7 to <30 days	162 (5.5)	247 (4.7)	213 (3.6)	315 (3.2)
≥30 to <6 months	1044 (35.6)	1378 (26.3)	1899 (31.7)	2903 (29.5)
≥6 months to <12 months	1225 (41.8)	3052 (58.3)	1831 (30.6)	3823 (38.8)
≥12 months to <18 months	469 (16.0)	522 (10.0)	1091 (18.2)	1270 (12.9)
≥18 months	3 (0.1)	4 (0.1)	911 (15.2)	1500 (15.2)

Source: IAS Table 8.1.1.1Ra and 8.1.2.1Ra (July 2011 resubmission) and Appendix J, Tables 1.1 and 1.2.

Note: For exposure, 6 months is defined as 166 days, 12 months is defined as 335 days, and 18 months is defined as 518 days.

(a) The All Comparators Grouping combines placebo and active comparator groups, which are not shown in the table.

(b) The All Alogliptin Grouping combines the 6.25, 12.5, 25, 50, and 100 mg groups, which are not shown in the table.

(c) Duration of exposure in days is calculated as date of last dose - date of first dose + 1. Last dose date is estimated for subjects ongoing in Study 402 using the earlier of the interim data cut date and the last study drug dispensing date plus the number of days in the dosing interval.

(d) Cumulative exposure in subject-years is defined as the sum of days for all subjects within a grouping divided by 365.25.

Source: EOR meeting document Table 2

In the reanalysis, the imbalance in ALT elevations is no longer apparent. (See Table 3 and Table 4.) The rate of ALT elevation >10x ULN is 0.1% for the all alogliptin group and 0.1% for the all comparators group with an upper limit of the 95% confidence interval (CI) of 0.2% and 0.2%.

Table 3. Number (%) subjects with markedly abnormal ALT values (Controlled phase 2/3 studies of April 2012 IAS Update)

Parameter	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline (a)		During Treatment (b)		Last Assessment (c)	
	All Comparators(d) N=5786	All Alogliptin (e) N=9608	All Comparators N=5786	All Alogliptin N=9608	All Comparators N=5699	All Alogliptin N=9495
ALT	0	0	3 (0.1) [0.1]	3 (<0.1) [<0.1]	2 (<0.1)	2 (<0.1)
>20×ULN						
ALT	1 (<0.1)	3 (<0.1)	5 (0.1) [0.1]	12 (0.1) [0.2]	3 (0.1)	4 (<0.1)
>10×ULN						
ALT >5×ULN	2 (<0.1)	6 (0.1)	17 (0.3) [0.4]	34 (0.4) [0.5]	7 (0.1)	11 (0.1)
ALT >3×ULN	16 (0.3)	41 (0.4)	89 (1.5) [2.0]	126 (1.3) [1.8]	30 (0.5)	32 (0.3)

Source: Appendix J, Tables 3.1 and 3.2.

Note: This table includes only subjects with both a baseline and a post-baseline value.

(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.

(b) The number of subjects with marked abnormalities per 100 subject-years of exposure is presented in square brackets.

(c) Last assessment is the last assessment of ALT on or before the last dose of study medication.

(d) The All Comparators Grouping combines placebo and active comparator dose groups.

(e) The All Alogliptin Grouping combines the 6.25, 12.5, 25, 50, and 100 mg dose groups.

Source: EOR meeting document Table 4

See Appendix 2 for a summary of new clinical cases with ALT >10xULN identified in the April 2012 IAS Update.

Table 4. Subjects with at least one markedly abnormal value (Phase 2/3 controlled studies)

	Placebo N=3647	Active Comparator N=2340	All Comparators N=5987	Alo 12.5 N=2944	Alo 25 N=6626	Alo N=9857
ALT >3xULN and Total Bili >2 mg/dl	1 (0.03%)	3 (0.09%)	4 (0.05%)	1 (0.03%)	1 (0.02%)	2 (0.02%)
ALT >3xULN and Total Bili >2ULN	1 (0.03%)	2 (0.09%)	3 (0.05%)	1 (0.03%)	1 (0.02%)	2 (0.02%)

Source: EOR meeting document, Appendix J, Table 3.1

The available Japanese postmarketing data has also increased. As of April 15, 2012, there is 287,153 (up from 219,000) patient-years exposure to alogliptin (Nesina) and 13,832 patient-years exposure to alogliptin/pioglitazone FDC (Liovel).

The sponsor submitted a letter from (b) (4) (a consultant expert in epidemiology and safety surveillance) which concluded that the comparative AERS data presented in the CR letter is relatively unreliable. The sponsor believes that there should be an absence of confounding factors prior to attributing the event as severe DILI (e.g. leading to death or liver transplantation). The sponsor believes that case TCI2011A04573 is attributable to other factors (e.g. possible autoimmune hepatitis with death due to pneumonia after steroid use).

Nonetheless, the sponsor has taken steps to assure that potential liver events are closely evaluated. It has initiated a process to evaluate postmarketing hepatic cases and provide ongoing adjudication of new cases. All available information for clinical and postmarketing hepatic cases has and will be sent to the Liver Safety Evaluation Committee (LSEC). LSEC members are as follows:

(b) (4)

After reviewing the available data, the LSEC concluded the following:

- Controlled trials: *We conclude that there is no significant hepatic signal in the clinical trials database.*
- Postmarketing Experience: *In the context of the reassuring hepatic safety database obtained in the extensive controlled clinical trials, and the lack of a 'signature' presentation among alogliptin-associated liver events, we believe that*

the rate of serious hepatic event reports received in Japan in association with alogliptin treatment does not reach a threshold of concern regarding black box warnings, restrictions on usage, or monitoring requirements.

- **Summary Consensus Statement:** *We have reviewed the five Japanese post-marketing cases of concern and the extensive clinical trial experienced with alogliptin. Although it is never possible to accurately assess the risk of rare and serious liver events at the time of NDA submission, we find no compelling evidence for a clinically important hepatic safety risk for alogliptin.*

The LSEC's overall assessment of the five postmarketing cases of probable alogliptin hepatotoxicity identified in the CR letter is shown in Table 5.

Table 5. Summary of the LSEC's assessment of the five probable alogliptin hepatotoxicity cases identified in the CR letter

Case number/ (CIOMS Date Received by Manufacturer)	Treatment	Preferred Term	Sponsor Description	LSEC Assessment
TCI2011A03640 (15 Sep 2011)	Nesina 6.25 mg	Liver disorder	Symptoms did not improve after discontinuation of Nesina. Association with concomitant medication (allopurinol) is suspected.	Possible
TCI2011A04573 (26 Apr 2012)	Nesina 25 mg	Liver disorder	Likely autoimmune acute hepatitis. A case of newly diagnosed Hashimoto's Disease, 1 month prior to starting Nesina. Clinical course, response to steroids and relapse after steroid dose tapering while off Nesina are consistent with etiology of autoimmune hepatitis.	Probable
TCI2011A06837 (22 Mar 2012)	Nesina 25 mg	Liver Disorder	Rapid increase and decrease of liver enzymes over the holiday week. DLST (-) for both alogliptin and sitagliptin, autoimmune antibody (-), HAV, HBV, HCV, HEV all negative.	Probable
TCI2011A06481 (05 Apr 2012)	Nesina 25 mg	Hepatic function abnormal	HAV, HCV, EBV, HSV HBV serologies indicate these etiologies as unlikely; CMV IgM and IgG were elevated but a non-specified CMV antigenemia test was negative. Autoimmune serologies were negative.	Possible
TCI2010A05612 (09 Mar 2012)	Nesina 25 mg	Hepatic function abnormal	ALT and AST elevations occurred after approximately 2 months of alogliptin use. The subject was found to be HCV and HAV antibody negative. HBsAg was negative	Probable

Source: EOR meeting document Appendix E

Pharmacovigilance: Hepatic AEs/SAEs and liver function test (LFT) abnormalities are closely monitored and prioritized for rapid review and follow-up for additional information. The Liver Function Test Abnormality Form (LFTA) is completed for hepatic enzyme abnormalities or hepatic AEs as defined in protocols and includes:

- ALT or aspartate aminotransferase (AST) $>8 \times \text{ULN}$
- ALT or AST $\geq 3 \times \text{ULN}$ in conjunction with a bilirubin $>2 \times \text{ULN}$
- ALT or AST $>5 \times \text{ULN}$ for more than 2 weeks

- ALT or AST $\geq 3 \times$ ULN with the appearance of fatigue, nausea, vomiting, upper right-quadrant tenderness, fever, rash or eosinophilia

Protocols also provide clear guidance on repeat labs, further evaluations and discontinuation of study drug based on changes in LFTs consistent with the DILI guidance.

Additionally, the sponsor has established an enhanced pharmacovigilance process that ensures rapid follow-up of postmarketing cases of potential DILI to gather relevant information in order to fully evaluate each case. Hepatic postmarketing reports of AEs and SAEs are prioritized for global monitoring, review, and rapid follow-up, and the MedDRA SMQ Hepatic Disorders will be used to assist in this prioritization for rapid identification and follow-up of potentially concerning cases. Similar to the LFTA, a global standardized Follow-up Form will be used to guide a standardized approach to gather relevant information to assess alternative etiologies. The standardized Follow-up Form includes a comprehensive history of risk factors, concurrent conditions, laboratory tests including a detailed serology workup and imaging assessments of the causes of liver injury. This standardized approach will enable the rapid evaluation of all cases with a similarly rigorous process for both clinical and postmarketing reports and reduce the likelihood of missing important data.

The sponsor will determine the need for enhanced pharmacovigilance activities, including the LSEC, on an ongoing basis and may discontinue them at any time following consultation with the Agency.

Sponsor's Questions (in regular font) with the Agency's Answers (in bold):

Question 1: Provided that the Agency's review of the new clinical and postmarketing data are consistent with Takeda's interpretation of the data summarized in this briefing document, does the Agency agree that the information planned for submission can provide the additional reassurance the FDA is seeking on the hepatic safety profile of alogliptin in order to complete the review and approve the applications?

Response: Whether or not the information planned for submission can provide the additional reassurance necessary for approval is a review issue. However, the April 2012 IAS exposure sufficiently exceeds that of the July 2011 submission, so as to justify submission of the data for a complete review.

Question 2: Takeda's understanding per the CRL is that the resubmission must be supported by the absence of any postmarketing reports of severe drug-induced liver injury events that are convincingly linked to alogliptin therapy (eg, leading to death or liver transplantation). Takeda would like to clarify that any such case would need to be devoid of confounding factors prior to the Agency attributing the event to alogliptin (or any drug) therapy. This should especially be the case in light of the current lack of liver case imbalance in the clinical database. Does the Agency agree?

Response: A case need not be devoid of all confounding factors prior to attributing the event to alogliptin therapy. Although the assessment of potential drug-induced

liver injury is grounded in the scientific grading system developed by the National Institutes of Health Drug-Induced Liver Injury Network (DILIN) Study Group, the Agency recognizes that, at times, the final classification of a particular case may be a matter of opinion. Consistent with the DILIN Study Group grading system, an attempt will be made to assess the effect of potential confounders before attributing causality to drug therapy.

Question 3: Does the Agency agree with the proposed structure and contents of the NDA resubmission?

Response: The Agency generally agrees with the proposed structure and contents of the NDA resubmission. However, the Summary of Clinical Safety in Module 2 should also contain the following:

- **Summary of deaths**
- **Updated summary tables for cardiovascular safety, renal safety, hypersensitivity, skin lesions, pancreatitis, infections, malignancy, fractures, and hypoglycemia. Please include a summary of the changes from the previous submission.**

Question 4: Does the Agency agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable?

Response: Yes, we agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable.

Question 5: Does the Agency agree with Takeda's plan to summarize safety data within Module 2.7.4 of both NDA resubmissions and therefore not submit a separate summary report of the integrated analyses within Module 5.3.5.3?

Response: Yes, we agree with the plan to summarize safety data within Module 2.7.4 of both NDA resubmissions and therefore not to submit a separate summary report of the integrated analyses within Module 5.3.5.3.

Question 6: Since Studies 402 and 305 are still ongoing, Case Report Forms for these studies will not be included in the NDA resubmissions as agreed upon for the July 2011 resubmission with regard to Study 402. Is this proposal acceptable?

Response: Yes, your proposal is acceptable. However, additional information may be requested if it is needed.

Question 7: Takeda does not plan to summarize data from the recently completed, 4-year, open-label extension study (012) within 2.7.4. However, the final clinical study report will be provided in the resubmission. Is this approach acceptable to the Agency?

Response: Yes, we agree with your plan to not summarize data from uncontrolled, open-label extension study (012) within 2.7.4.

Question 8: Takeda plans to update the efficacy section of the alogliptin package insert based on data from Studies MET-302 (b) (4). Since the efficacy information is not integrated, Takeda does not plan to include a Clinical Summary of Efficacy (2.7.3) in the NDA resubmission but will rely on the data included in the individual clinical study reports. Is the Agency agreeable to this approach?

Response: (b) (4)
However, we agree with your plan to update the efficacy section of the alogliptin package insert with data from completed study MET-302. Since the efficacy information is not integrated, we agree with your plan to not include a Clinical Summary of Efficacy (2.7.3) in the resubmission.

Question 9: Due to the fact that labeling negotiations had initiated under the previous review cycle and there are still some aspects other than safety that need to be discussed, Takeda proposes not to include Structured Product Labeling (SPL) in the NDA resubmissions. Takeda will provide the package insert information in SPL format once labeling language has been agreed upon by both Takeda and the Agency. Is this acceptable?

Response: Yes, your proposal is acceptable.

Question 10: Does the Agency agree with the process for enhanced monitoring of postmarketing liver-related cases?

Response: Yes, we agree with the process for enhanced monitoring of postmarketing liver-related cases.

Question 11: During the course of the review of the NDA resubmissions, spontaneous reports related to hepatic safety may be received. Takeda will continue to expedite these reports to the INDs and NDAs, as previously agreed. However, in an effort to provide a meaningful adjudication of these cases, Takeda often needs adequate time to gather relevant information for an individual postmarketing case. Therefore, the LSEC will review new cases on a monthly basis, and their assessments will be subsequently submitted to the Agency. Is this approach reasonable to the Agency?

Response: Yes, your approach is reasonable. However, additional information may be requested as needed.

Question 12: If during the course of the review of the NDA resubmissions, there is striking disagreement between the Agency and the LSEC on a particular liver safety case(s), would the Agency consider discussing the case(s) with the LSEC (and Takeda)?

Response: Yes, we may consider discussing case(s) with you and the LSEC. However, the purpose of such discussion would be to share information to ensure that both you and the Agency have all currently available data to aid decision –

making. The objective of the meeting would not be to obtain a consensus of opinion on liver cases(s) or to discuss upcoming regulatory decision(s).

Question 13: Is the Agency agreeable to discussing how to move forward with the SYR-322MET NDA at a meeting/teleconference to be held shortly after this End of Review meeting?

Response: Yes, we may discuss how to move forward with the SYR-322MET NDA at a meeting/teleconference to be held shortly after this EOR meeting.

Question 14: In the 25 April 2012 Complete Response Letter, there are questions related to the alogliptin pediatric program. Takeda is currently planning on initiating the phase 3 program in early 2013 due to Pediatric Committee requirements. In order to incorporate the Agency's feedback into the studies before they are started, Takeda plans to submit responses to the pediatric questions in an IND Amendment. Is this proposal acceptable?

Response: You may submit responses to the pediatric questions in an IND amendment. However, please note that a pediatric study requirement cannot be issued until after an NDA is approved. Please also submit relevant information the NDA.

Additional Comment: Please explain whether or not you plan to (b) (4)

(b) (4)
possibly offset the potential liver liability.

Appendix 1. Summary of the 20 Phase 2/3 Clinical Studies Included in the IAS

Study	Design, Key Inclusion Criteria, and Primary Endpoint	N	Treatment
July 2011 Resubmission			
003 Dose-ranging	Phase 2, 12-week, multicenter, randomized, double-blind, placebo-controlled study in T2DM subjects on diet and exercise alone, or monotherapy with SU/MET, or a combination of SU and MET. Age: 18 to 75 years; HbA1c: 6.8% to 11.0%. Change from Baseline in HbA1c at Week 12.	265	A6.25, A12.5, A25, A50, A100 r Placebo once daily Randomization ratio: 1:1:1:1:1
010 Monotherapy	26-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, in T2DM subjects on diet and exercise alone. Age: 18 to 80 years; HbA1c: 7.0% to 10.0%. Change from Baseline in HbA1c at Week 26.	329	A12.5 once daily or A25 once daily or Placebo once daily Randomization ratio: 2:2:1
007 Add-on to SU	26-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, in T2DM subjects on SU monotherapy (≥ 10 mg or MTD of glyburide). Age: 18 to 80 years; HbA1c: 7.0% to 10.0%. Change from Baseline in HbA1c at Week 26.	500	A12.5 once daily or A25 once daily or Placebo once daily Randomization ratio: 2:2:1
008 Add-on to MET	26-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, in T2DM subjects on MET monotherapy (≥ 1500 mg or MTD). Age: 18 to 80 years; HbA1c: 7.0% to 10.0%. Change from Baseline in HbA1c at Week 26.	527	A12.5 once daily or A25 once daily or Placebo once daily Randomization ratio: 2:2:1
009 Add-on to TZD, with or without MET or SU	26-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, in T2DM subjects on TZD (pioglitazone or rosiglitazone), with or without MET or SU. Age: 18 to 80 years; HbA1c: 7.0% to 10.0%. Change from Baseline in HbA1c at Week 26.	493	A12.5 once daily or A25 once daily or Placebo once daily Randomization ratio: 2:2:1
011 Add-on to insulin, with or without MET	26-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, in T2DM subjects on insulin with or without MET. Age: 18 to 80 years; HbA1c: $\geq 8.0\%$. Change from Baseline in HbA1c at Week 26.	390	A12.5 once daily or A25 once daily or Placebo once daily Randomization ratio: 1:1:1
322OPI-004 Add-on to PIO/MET	52-week, multicenter, randomized, double-blind, active-comparator (A25 vs titrating pioglitazone from 30 to 45 mg) study in T2DM subjects on combination pioglitazone 30 mg and MET ≥ 1500 mg (or MTD). Age: 18 to 80 years; HbA1c: 7.0% to 10.0%. Change from Baseline in HbA1c at Weeks 26 and 52.	803	A25+P30 once daily or P45 once daily (titrated from P30) Randomization ratio: 1:1

322OPI-001 Combination ALO/PIO add-on to MET	26-week, multicenter, randomized, double-blind, placebo-controlled, 12-arm, factorial study evaluating alogliptin alone, pioglitazone alone and alogliptin/pioglitazone in combination, in T2DM subjects on MET monotherapy ≥ 1500 mg (or MTD). Age: 18 to 80 years; HbA1c: 7.5% to 10.0%. Change from Baseline in HbA1c at Week 26.	1554	Placebo+placebo once daily or A12.5+placebo once daily or A25+placebo once daily or P15+placebo once daily or P30+placebo once daily or P45+placebo once daily or A12.5+P15 once daily or A12.5+P30 once daily or A12.5+P45 once daily or A25+P15 once daily or A25+P30 once daily or A25+P45 once daily Randomization ratio: 1:1:1:1:1:1:1:1:1:1:1:1
322OPI-002 Initial combination ALO/PIO	26-week, multicenter, randomized, double-blind, placebo-controlled, 4-arm, study evaluating alogliptin alone, pioglitazone alone and alogliptin/pioglitazone in combination, in T2DM subjects on diet and exercise alone. Age: 18 to 80 years; HbA1c: 7.5% to 11.0%. Change from Baseline in HbA1c at Week 26.	655	A12.5+P30 once daily or A25+P30 once daily or A25+placebo once daily or P30+placebo once daily Randomization ratio: 1:1:1:1
303 Elderly	52-week, multicenter, randomized, double-blind, active-comparator (alogliptin vs SU) study in elderly T2DM subjects. Age: 65 to 90 years. HbA1c: 6.5% to 9.0% if on diet and exercise Alone; 6.5% to 8.0% if on oral monotherapy. Change from Baseline in HbA1c at Week 52.	441	A25 once daily or Glipizide 5 mg once daily (titrated to 10 mg for inadequate control) Randomization ratio: 1:1
301 Postprandial lipids	16-week, multicenter, randomized, double-blind, active- and placebo-controlled study in T2DM subjects on diet and exercise or treatment with MET, SU, nateglinide, or repaglinide. Age: 18 to 70 years; HbA1c: 6.5% to 9.0%. Change from Baseline in postprandial incremental area under the plasma concentration-time curve changes for triglycerides at Week 16.	71	A25 once daily A25+P30 once daily Placebo once daily Randomization ratio: 1:1:1
402 (a) CV outcomes (interim data as of 29 April 2011)	~4.75-year, multicenter, randomized, double-blind, placebo-controlled, CV outcomes study in subjects with T2DM and recent ACS (within 15–90 days). Age: ≥ 18 years of age; HbA1c: 6.5% to 11.0% if antidiabetic regimen includes oral monotherapy or oral combination therapy; 7.0% to 11.0% if antidiabetic regimen includes insulin. MACE composite (CV death, nonfatal MI, nonfatal stroke).	2149	In addition to Standard of Care antidiabetic medications: A25 once daily (6.25 and 12.5 mg dose available for severe and moderate renal impairment) or Placebo once daily Randomization ratio: 1:1

302 Initial combination ALO/MET	26-week, multicenter, randomized, double-blind, placebo-controlled, 7-arm, factorial study evaluating alogliptin alone, MET alone or alogliptin/MET in combination, in T2DM subjects on diet and exercise alone. Age: 18 to 80 years; HbA1c: 7.5% to 10.0%. Change from Baseline in HbA1c at Week 26.	784	Placebo BID or A25 once daily or A12.5 BID or M500 BID or M1000 BID or A12.5+MET500, BID or A12.5+MET1000 mg, BID Randomization ratio: 1:1:1:1:1:1:1
CCT-001 Monotherapy	Phase 2, 12-week, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of alogliptin (6.25, 12.5, 25, and 50 mg) in T2DM subjects on diet and exercise alone. Age: ≥20 years; HbA1c: 6.5% to 9.9%. Change from Baseline in HbA1c at Week 12.	480	A6.25 once daily or A12.5 once daily or A25 once daily or A50 once daily or Placebo once daily or Voglibose 0.2 mg TID Randomization ratio: 1:1:1:1:1:1
CCT-003 Add-on to voglibose	Phase 2/3, 12-week, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of alogliptin (12.5 and 25 mg) when used in combination with an α-glucosidase inhibitor (voglibose 0.2 mg TID). Age: ≥20 years; HbA1c: 6.5% to 9.9%. Change from Baseline in HbA1c at Week 12.	230	A12.5 once daily or A25 once daily or Placebo Randomization ratio: 1:1:1
CCT-004 Add-on to PIO	Phase 2/3, 12-week, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of alogliptin (12.5 and 25 mg) in T2DM subjects on TZD (pioglitazone 15 or 30 mg). Age: ≥20 years; HbA1c: 6.5% to 9.9%. Change from Baseline in HbA1c at Week 12.	339	A12.5 once daily or A25 once daily or Placebo once daily Randomization ratio: 1:1:1
CCT-005 Add-on to SU	Phase 2/3, 12-week, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of alogliptin (12.5 and 25 mg) in T2DM subjects on SU (glimepiride 1-4 mg once daily or BID). Age: ≥20 years; HbA1c: 7.0% to 9.9%. Change from Baseline in HbA1c at Week 12.	312	A12.5 once daily or A25 once daily or Placebo once daily Randomization ratio: 1:1:1
CCT-006 Add-on to MET	Phase 2/3, 12-week, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of alogliptin (12.5 and 25 mg) in T2DM subjects on MET (500 mg/day or 750 mg/day). Age: 20-64 years; HbA1c: 6.5% to 9.9%. Change from Baseline in HbA1c at Week 12.	288	A12.5 once daily or A25 once daily or Placebo once daily Randomization ratio: 1:1:1
305 Add-on to MET; ongoing (Interim data as of 24 April 2012)	2-year, multicenter, randomized, double-blind, Active Comparator (alogliptin vs SU) study in T2DM subjects on MET ≥1500 mg (or MTD) alone. Age: 18 to 80 years; HbA1c: 7.0% to 9.0%. Change from Baseline in HbA1c at Weeks 52 and 104.	2638	A12.5 once daily or A25 once daily or Glipizide 5-20 mg (titrated) Randomization ratio: 1:1:1
308 Monotherapy, Add-on to MET, Add-on to PIO (with or without MET)	Phase 3, 16-week, double-blind, placebo-controlled, parallel group study to determine the efficacy and safety of alogliptin 25 mg in T2DM subjects on diet and exercise alone, in subjects on MET ≥1000 mg (or MTD), or in subjects on PIO (with or without MET). Age: 18 to 75 years; HbA1c: 7.0% to 10.0%. Change from Baseline in HbA1c at Week 16.	506	A25 once daily or Placebo once daily Randomization ratio: 1:1

ACS=acute coronary syndrome, BID=twice daily, HbA1c=glycosylated hemoglobin, MI=myocardial infarction, MTD=maximum tolerated dose, SU= sulfonylurea, TID=3 times daily, TZD= thiazolidinedione.
(a) Interim data as of 11 September 2011 included in the Response to October 2011 FDA Request and interim data as of 18 April 2012 included in the April 2012 IAS Update.

Source: EOR meeting document Appendix A

Appendix 2. Sponsor's assessment of cases of ALT >10xULN in clinical database

Subject number/Study/Dose	Highlight	Alternative Etiologies
Cases Previously Submitted in Response to 24 October 2011 Information Request		
8260-010/402 Alogliptin 25 mg	Elevations occurred during acute episode of unstable angina; negative rechallenge	58 year old male with history of recurrent angina had transient enzyme elevations associated with an acute event of unstable angina on study day 91 which normalized on day 102. Study drug was interrupted between days 91 and 103. The subject resumed alogliptin without any elevations in liver enzymes.
8521-002/402* Alogliptin 25 mg	ALT 10x ULN at baseline; hepatitis C; chronic pancreatitis	81 year old female with history of cholelithiasis had LFTs 10 x ULN at baseline. Serological diagnosis of hepatitis C was made and alogliptin was discontinued on Day 31. The liver enzyme elevations did not worsen on alogliptin treatment. Two months after alogliptin was stopped, the subject was hospitalized for exacerbation of chronic pancreatitis.
8070-002/402** Alogliptin 25 mg	hepatitis C history; negative dechallenge	60 year old male Subject with diagnosis of hepatitis C at screening. The LFTs were elevated at screening and continued to be high throughout the study (day 292). Alogliptin was discontinued on day 47 due to AE of increase in liver enzymes, but subject continued to have elevated enzymes after stopping alogliptin. Negative dechallenge.
395-3054/OPI-001 Alogliptin 12.5 mg No Pio/Met 1700mg	Single transient elevation; resolved while remaining on drug	67 year old female with hepatic steatosis and normal LFTs at baseline. Transient single episode of elevation of LFTs observed on study day 112, which resolved on study day 119. The subject continued on alogliptin until day 182 with enzymes within normal limits.
831-2508/OPI-002 Alogliptin 25 mg No Pio	Elevation coincided with hepatitis B diagnosis	49 year old male was diagnosed with hepatitis B by serology associated with elevated enzymes on study day 86 which peaked on study day 91. Subject continued alogliptin until day 107. Approximately one month later hepatology consult showed subject was clinically well with normal LFTs.
307-9019/009* Alogliptin 25 mg	Elevations occurred on Day 1 of study drug	47 year old obese male reported elevated enzymes on study day 1, and was discontinued alogliptin on day 5.
311-9003/009 Alogliptin 12.5 mg	Single transient elevation; resolved while remaining on drug	49 year old male with normal LFTs at baseline had single transient elevation of LFTs on study day 32, with normalization while on alogliptin by day 49.
3128-003/303** Alogliptin 25 mg	Elevations associated with bile duct stone	73 year old male with history of cholelithiasis had elevated LFTs at baseline. On study day 8, had upper abdominal pain diagnosed as bile duct stone, associated with acute increase in LFTs on day 15 which normalized by study day 35. Alogliptin was discontinued on day 20.
New Cases Based on April 2012 IAS		
5039-003/305 Alogliptin 12.5 mg	Nonserious AEs of ALT increased and AST increased; hemochromatosis	56 year old with mild elevations of ALT prior to study drug and elevated ALT on study day 113. The AE of hemochromatosis was reported on study day 107. Subject voluntarily withdrew due to study schedule. ALT/AST were normal at time of termination.
5304-055/305 Alogliptin 12.5 mg	hepatitis E; concurrent ALT and total bilirubin elevations	45 year old male with mild elevations of ALT prior to study drug and diagnosed with viral hepatitis on study day 79. Concurrent elevation of ALT and Total Bili on study day 51. The etiology was determined to be acute hepatitis E by serological detection of IgM.

Subject number/Study/Dose	Highlight	Alternative Etiologies
New Cases in April 2012 IAS (continued)		
5505-016/305 Alogliptin 25 mg	Nonserious AEs; single transient elevation; excessive alcohol use; resolved while remaining on drug	46 year old male with ALT and AST elevations on study day 274. Documented excessive alcohol use a day before blood draw. ALT and AST 8 days later were normal.
8664-005/402** Alogliptin 25 mg	Nonserious AE of ALT increased; transient elevation; negative rechallenge; statin is a confounder	59 year old with ALT elevation > 3xULN prior to study drug and ALT elevation on study day 263. ALT < 2x ULN on study day 277 and resolved on study day 277. Study drug was interrupted and resumed. Subject also on atorvastatin at the time of the event. Atorvastatin was discontinued on study day 267.
5090-016/305 Active Comparator Glip 5mg/ Met 2000mg	Statin is a confounder	79 year old male with history of cholecystectomy experienced ALT/AST elevation on study day 113. The lab normalized after discontinuing from the SD and subject withdrew from the study. Subject also on pravastatin at the time of the event.
5304-091/305 Active Comparator Glip 5mg/ Met 2000mg	hepatitis E; concurrent ALT and total bilirubin elevations	51 year old male with history of hepatomegaly, hypertriglyceridemia, and an ex-alcoholic with SAE report of viral hepatitis on study day 271. Anti-HEV IgM was consistent with acute hepatitis E infection. Concurrent elevation of ALT and total bilirubin on study day 273. Liver enzymes including ALT, AST, total bilirubin normalized on study day 323.
5310-063/305 Active Comparator Glip 5mg/ Met 2000mg	Acute viral hepatitis; HCV RNA (+)	48 year old male with SAE report of acute viral hepatitis on study day 185. Serology results included: HCV Ab(+), and HCV RNA (+).
5359-015/305 Active Comparator Glip 5mg/ Met 1500mg	Nonserious; acute cholelithiasis	55 year old female with mild elevation of ALT prior to study drug. AE report of acute cholelithiasis on study day 128 and ALT elevation on study day 148. Ultrasound confirmed the diagnosis of acute cholelithiasis.
5476-003/305 Active Comparator Glip 5mg/ Met 1700mg	Nonserious AEs of transaminases increased; hepatic steatosis	42 year old female with history of hepatic steatosis and elevation of ALT >2x ULN prior to study drug. Multiple AEs of transaminases increased reported on study days 98 (ALT > 5xULN) and 153 (ALT >10xULN).

IGM= immunoglobulin M.

*ALT at baseline was greater than 10xULN.

**ALT at baseline was greater than 3x ULN.

Source: EOR meeting document Appendix C

Appendix 3. Proposed Structure of the NDA Resubmission

Module 1: The following documents will be provided.

- 1.3.1.4 Transfer of Obligations for Studies 302, 012, 402 (interim data as of 18 April 2012) and 305 (interim data as of 24 April 2012)
- 1.3.3 Debarment Certification
- 1.3.4 Financial Disclosure for 302, 402 (interim data as of 18 April 2012) and 305 (interim data as of 24 April 2012)
- 1.3.5 Patent Information and Patent Certification (revised)
- 1.9 Deferral of Pediatric Studies (updated for alogliptin only)
- 1.11 Response to the SYR-322MET NDA Information Request dated 16 May 2012
- 1.13.12 Status of Postmarketing Commitments (revised)
- 1.14 Labeling
 - Draft Labeling
 - Revised Draft Carton and Container Labels (SYR-322-4833 Only)
 - Revised Package Inserts
 - Foreign Labeling
 - NESINA and Liovel Package Inserts from Japan (updated)
- 1.16 Risk Management Plan
 - Request to Remove REMS (SYR-322-4833 only)

Module 2: The following documents will be provided.

- A new Section 2.2 (Introduction)
- A new Section 2.7.4 (Summary of Clinical Safety) based on the April 2012 IAS update will be provided. A detailed Table of Contents for 2.7.4 is provided in [Appendix G](#). As previously noted, the updated IAS includes a total of 20 studies (003, 007, 008, 009, 010, 011, 301, 303, 308, CCT-001, CCT-003, CCT-004, CCT-005, CCT-006, 322OPI-001, 322OPI-002, 322OPI-004, and MET-302), 402 (interim data as of 18 April 2012), and 305 (interim data as of 24 April 2012). Section 2.7.4 will focus only on the information required to satisfy the requests of the Agency as noted in the April 2012 Complete Response Letter. The proposed content of 2.7.4 is outlined below.

- Overview of clinical program and summary study designs for studies included in the integrated dataset.
- Disposition, demographic, and exposure data based on the April 2012 IAS update.
- Summary of common adverse events (AEs), serious adverse events (SAEs), and AEs that led to study drug discontinuation based on the April 2012 IAS update. The frequency of these events will be compared to that provided in the July 2011 NDA resubmission.
- Summary of interstitial lung disease based on updated clinical and postmarketing data will be provided as requested by the Agency.
- Any other relevant safety data needed to support the updated product label (such as hypersensitivity and pancreatitis).
- Clinical laboratory evaluation including only an analysis of hepatic parameters based on the April 2012 IAS update for the integrated dataset and by study for Studies 402 and 305.
- Summary of liver-related postmarketing cases from Japan.

Module 5: The following documents will be provided.

- Final clinical study reports for Studies MET-302, 308, 012 (open-label extension study).
- Clinical study report for 1-year interim data from Study 305 (data as of 10 November 2011). Please note that the 1-year interim data may differ from the data contained in the April 2012 IAS due to different cut-off dates.
- Council for International Organization of Medical Sciences (CIOMS) for all deaths.
- Narratives for AEs that led to study drug discontinuation that have not been previously provided (ie, events reported after 31 May 2011 for 402 and 10 November 2011 for Study 305).
- CIOMS for SAEs that have not been previously provided (ie, events reported after 31 May 2011 for 402 and 10 November 2011 for Study 305)
- CIOMS for all hepatic SAEs and narratives for all hepatic AEs that led to study drug discontinuation.
- Program assisted or written narratives for all subjects with ALT >5×ULN.
- Supporting statistical tables. (A Table of Contents for the proposed tables is provided in [Appendix H](#).)
- Supporting datasets in the same format as prior alogliptin submissions.
 - Takeda plans to provide SAS Version 5 transport integrated data sets for the phase 2/3 controlled studies used to generate the set of tables supporting the resubmission. The data set format and structure will be identical to the IAS data previously submitted to the FDA, but will only include variables used for analysis presented. The following domains

will be provided: exposure, disposition, demographic and other baseline characteristics, AEs, and liver enzyme clinical laboratory evaluations. The integrated data set files will contain treatment assignments, variables used in the integrated analyses, variables used in the calculations of the analysis variables, variables indicating whether an observation is used in a particular analysis, and other variables as appropriate. The SAS Version 5 transport files will not have a maximum file size limit. Each data set will be accompanied by a data definition table (define.pdf), which will include metadata information, such as variable name, a description of the variable, the type of the variable (numeric, character, date, time) and codes (and decodes). The data definition table will also include a comments field that will provide the method for calculating the derived variables, and the location of raw variables on the respective annotated case report form.

- 4th alogliptin PSUR (data as of 15 April 2012).
- Charter for the Liver Safety Evaluation Committee (see Appendix F).
- Assessment of hepatic safety provided by the Liver Safety Evaluation Committee.

Case report forms for Studies 402 and 305 will not be included in the resubmission but will be included in the final clinical study reports once the studies are completed.

Source: EOR meeting document section 3.2

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/s/

VALERIE S PRATT
06/28/2012

MARY H PARKS
07/03/2012

Summary Basis for Regulatory Action

Date	April 25, 2012
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA #	NDA 22-271 (alogliptin)
Supp #	NDA 22-426 (alogliptin/pioglitazone)
Applicant Name	Takeda Pharmaceuticals
Proprietary / Established (USAN) Names	Nesina alogliptin
Dosage Forms / Strength	Tablets 6.25 mg, 12.5 mg, 25 mg
Proposed Indication(s)	Adjunct to diet and exercise for the treatment of hyperglycemia in adults with T2DM
Action:	<i>Complete Response</i>

Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding alogliptin and the reader should refer to the reviews in the action package for a more detailed discussion. Alogliptin is an inhibitor of the serine protease enzyme - dipeptidyl peptidase IV (DPP-4). It is thought that the mechanism of action for this class of drugs is that they enhance the availability of the incretin hormone, glucagon-like peptide-1 (GLP-1). GLP-1, along with glucose-dependent insulintropic polypeptide (GIP), are short-lived intestinal peptides released in response to food ingestion that have an inhibitory effect on glucagon (which would result in inhibiting hepatic glucose synthesis) and an enhancing effect on insulin secretion when serum glucose is elevated. DPP-4 inhibitors therefore enhance the effect of the incretins by inhibiting their metabolism by the enzyme DPP-4.

There are currently three approved and marketed drugs considered DPP-4 inhibitors used for the indication above: Januvia (sitagliptin) approved 2006, Onglyza (saxagliptin) approved 2009 and Tradjenta (linagliptin) approved 2011.

The original application for alogliptin was submitted in December 2007. The original application was filed before a public meeting (July, 2008) and subsequent publication of guidance to industry regarding cardiovascular evaluation (December, 2008)¹ of new antidiabetic therapy to treat type 2 diabetes (T2DM) to demonstrate that there is not an unacceptable increase in cardiovascular risk attributable to the drug. All antidiabetic drug applications submitted to treat T2DM that were under review at the time of this policy enactment underwent evaluation in the spirit of this guidance, and alogliptin was found to lack suitable evaluation to rule out unacceptable cardiovascular risk. Therefore, a Complete

¹ Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, December 2008.

Response (CR) action letter was sent to the sponsor on June 26, 2009 for NDA 22-271, which was for alogliptin, identifying this deficiency. All issues identified for NDA 22-271 were also applicable to NDA 22-426, which was an application for the alogliptin/pioglitazone combination product. While the lack of evidence of cardiovascular safety has been resolved with this submission, a new potential safety signal of hepatotoxicity has been identified. I will focus on this issue for this review.

Efficacy

In the original NDA, the range of effect of alogliptin on HbA1c reduction was 0.4 to 0.6% relative to placebo, depending on the design of the trial. It was agreed by all reviewers that alogliptin demonstrated efficacy in treatment of hyperglycemia in adults with T2DM. There is some new efficacy data in this application which is discussed by Drs. Derr and Joffe. The new trial results do not alter the original conclusion regarding efficacy.

Safety

There are two issues upon which the approvability of this application rests; 1) recent findings of potential liver toxicity, and 2) the response to the deficiency identified in the first action letter regarding the lack of evidence ruling out an unacceptable increase in cardiovascular risk. I will focus on these two issues

Liver safety

With the original application, a potential liver toxicity signal was not identified although there were two subjects exposed to alogliptin with ALT elevations > 10x normal, compared to none in the placebo/comparator group. At the time, this finding was felt to probably a chance finding which could reasonably occur because of the 4:1 (alogliptin:placebo/comparator) disproportionate randomization making it so that there was not enough exposure in the placebo/comparator group due to projected baseline rates to expect even one event. When there is a small number of events, like in the case with the original application where the disproportionate randomization ratio exceeds the number of events it can be difficult, depending upon the adverse event of interest, to ascribe the finding to drug exposure. As such, this finding was not identified in the CR letter.

This resubmission contained a greatly expanded database where it is noted that a greater number of alogliptin-treated subjects experienced marked ALT elevations over comparators, probably more than should be ascribed to simply a chance finding. Even more concerning was the finding of two subjects that had ALT elevations > 20x normal. This is demonstrated in the following table from Dr. Parks' review (Page 9).

Table 8.3 ALT Elevations in Original NDA and Resubmission (Phase 2/3 Clinical Trials)

	Placebo/Comparator	All Alogliptin
Original NDA	N=534	N=1961

ALT > 3 xULN	6 (1.1%)	23 (1.2%)
ALT > 5x ULN	1 (0.2%)	7 (0.4%)
ALT > 10x ULN	0	2 (0.1%)
Resubmission	N=4074	N=7011
ALT > 3 xULN	39 (1%)	71 (1%)
ALT > 5x ULN	6 (0.1%)	21 (0.3%)
ALT > 10x ULN	0	8 (0.1%)
ALT > 20x ULN	0	2 (<0.1%)

Interim analysis of a large CV outcome trial (Study 402-included in the overall results above) also demonstrated similar findings.

Study 402: Number (%) Subjects with ≥1 Marked Abnormal Result				
	Baseline		Post-Baseline	
Parameter	Placebo N=1466	Alogliptin N=1467	Placebo N=1372	Alogliptin N=1387
ALT >20x ULN	0	0	0	0
ALT>10x ULN	1 (0.1%)	2 (0.1%)	0	5 (0.4%)
ALT>8x ULN	1 (0.1%)	2 (0.1%)	0	6 (0.4%)
ALT>5x ULN	2 (0.1%)	5 (0.3%)	1 (0.1%)	10 (0.7%)
ALT>3x ULN	13 (0.9%)	18 (1.2%)	5 (0.4%)	17 (1.2%)

Additionally, postmarketing reports from Japan, the only country where alogliptin is approved and marketed, have been received and include cases that may represent Hy's law in that they fulfill the biochemical definition, although in some cases alternative explanations may exist.

Although the expanded database also has disproportionate randomization between the alogliptin and placebo/comparator groups, it is important to note that there are not ANY cases of ALT elevation > than 10x ULN in the placebo/comparator group. As Dr. Parks' details in her review, each case of ALT>10x ULN was reviewed and adjudicated by our internal hepatologists as well as the sponsor's external hepatologists. Please refer to her and Dr. Joffe's reviews for details of this evaluation. None of these cases were definitively identified as drug-induced injury. However, when an imbalance of an adverse event is demonstrated between groups, and it is an infrequent event, some consideration must be given to what the ramifications are to reviewing each case, if in the case of the sponsor it is with the purpose of explaining away the finding. To elaborate on this point, while each individual case can be looked at for alternative reasons (confounders) to explain the subjects with marked ALT elevations receiving alogliptin, in reality, the confounders should have been matched in the placebo/comparator group. If we believe that randomization should have matched possible confounders, the placebo/comparator group for this application should have demonstrated ~five cases of ALT elevations greater than 10-fold. If we believe that we should have observed approximately five cases in the placebo/comparator subjects, the probability of observing zero cases is 1.0%. While it is always difficult to know what to do when confronted

with a limited number of events of a safety issue, trying to explain away cases not matched to some extent in the placebo/comparator group may not be appropriate depending upon the circumstances. (b) (4)

(b) (4)

(b) (4)

With

the original application, because there was an almost four-fold difference in the randomization, having two cases in the alogliptin group (1961 subjects exposed) with ALT elevations greater than 10-fold may not be matched by the placebo/comparator group (534 exposures) as even one subject with ALT elevations in that group would have not been expected if the true baseline rate of non-drug associated ALT elevation was 1:980 (1961÷2). Now, with 10 cases of ALT elevation greater than 10-fold, giving a rate of 1:700, and more data in the placebo/comparator group (N=4074) we can speculate that there should have been five or six cases of ALT elevation greater than 10-fold in the placebo/comparator group. Yet, we have NO cases, which is concerning that alogliptin may be exerting some toxic effect.

Dr. Parks also discusses this concept and uses the example from one subject (Case 402/8260-010) from the CV outcomes trial (Study 402). This subject had ALT elevations (11.7x ULN) that occurred and were attributed by the sponsor's hepatologists as caused by unstable angina. No cases of ALT elevation to this extent occurred in the placebo group. One would expect that unstable angina occurred in the comparator/placebo group as well as this trial was conducted in subjects with a high rate of cardiovascular events. So if indeed unstable angina was the cause of this subject's ALT elevations >10x ULN (and not drug exposure), there should also have been cases in both groups.

There have been several cases of liver toxicity that are concerning in the post-marketing experience from Japan, despite the recent marketing starting in April 2010 and somewhat limited exposure which was estimated at 120,000 patient-years through October 2011, although the sponsor continues to submit further updates which are summarized by Dr. Parks and Joffe. The most concerning of these cases is summarized in the table below from Dr. Parks' review (page 10).

Table 8.5 Concerning Cases of Liver Injury Associated with Alogliptin Use in Japan

	Biochemical Hy's Law	Onset from Drug Initiation	Liver Tests	Outcome	Expert Assessment		
					(b) (4)	(b) (4)	Seeff

TCI2011A03640	no	immediate N/V, darkening or urine about 4 days, abnl labs 3wks	mixed hepatocellular/cholestatic injury w/ cholestatic pattern predominating ALT869,AST625, AP1169 bilirubin normal no viral hepatitis reports	not life- threatening	possible	possible	probable
TCI2010A05612	no	2 months	mixed hepatocellular/cholestatic pattern ALT230, AST108, AP1260, bili 0.9 u/s shows steatosis Hep A/B/C negative	recovering	possible	possible	probable
TCI2011A04039	no	3 days	ALT106,AST125, AP336, bili0.3	recovering	possible	possible	possible/probable
TCI2011A04573	yes	13 days-1 month	@ 1month ALT 1178, AST1070, AP905, bili 6.3 increase ammonia and coags, febrile	death	unlikely	possible	probable to highly likely
TCI2011A06837	yes	1 month	ALT 1512,AST 2188,bili3.9,AP313	recovered	probable	probable	probable to highly likely

I agree with Dr. Parks and other internal reviewers that the two most concerning cases are the ones highlighted in red above. While a case may be made that these are not clearly drug-related, they are highly suspicious and a reasonable person could come to a conclusion that this is the result of alogliptin therapy. Please refer to Dr. Parks and Joffe's reviews for the details of these two cases consisting of the narratives as provided by Dr. Seeff, our hepatology expert.

To summarize, we received additional clinical trial data in response to a deficiency regarding cardiac safety assessment. This additional randomized, blinded, data became sufficient in amount to demonstrate heretofore undiscovered transaminitis shift associated with alogliptin use compared to placebo/comparator. These shifts included higher, concerning levels of ALT elevation not demonstrated by placebo/comparator. There have been no cases of Hy's law in the controlled phase 2/3 clinical trial data with 5232 patients (2498 patient-year) exposed to any dose and 3,500 (1773 patient-year) exposed to alogliptin 25 mg. Further data for evaluation is approximately 120,000 patient-years of postmarketing experience in Japan where cases of liver injury have been identified that were internally evaluated as being probably to highly likely as drug-induced liver injury. The sponsor has two hepatologists also reviewing these cases, one in an unblinded fashion (as was our internal consultant), and they seem to rank the association of drug-induced liver injury categorically lower for most cases than our internal reviewers.

In order to try to make some informed conclusions upon the post-marketing data, we have tried to get a sense of what the Japanese post-marketing experience has been with the other

DPP4-inhibitors. It should be recognized that these types of comparisons are always fraught with peril and any conclusions are at best speculative. This particular exercise has been difficult in part due to a language barrier. However, for the most part it seems that there have been fewer global reports for the degree of marketing with the other agents. As an example, while sitagliptin does have a number of reports, it seems that the level of concerning cases, such as those above, while similar in number come with magnitudes higher (133-fold worldwide based on the alogliptin October 2011 cut-off) marketing exposures. Also, when examining the Japanese marketing experience for comparisons of sitagliptin vs. alogliptin reports, there seems to be less with sitagliptin. This is a difficult comparison however, and the sponsor has provided data that they feel signifies that the reporting rates for alogliptin and sitagliptin are similar. This comparison however suffers from very broad search terms that could include a lot of 'noise' such that any significant event with which we are really concerned is lost. As such, any conclusions based upon the sponsor's comparisons is fragile at best, and as discussed above it has been difficult to understand if we are comparing 'apples to apples' particularly with the Japanese data due to a language barrier. It should also be recognized that either transaminitis shifts alone, or some post-marketing reports alone, may not cause the level of concern (suspicion) that the combination together causes. In that regard, none of the other DPP4-inhibitors have demonstrated transaminitis imbalances in the NDA application and therefore post-marketing reports may be viewed with less suspicion. The sponsor has also articulated that saxagliptin also had ALT elevation imbalances greater than 10x at the time of approval of 4 vs 0 to placebo/comparator. This is ignoring that there was also an approximate 3:1 randomization difference, so that one would expect to have only at most one case in the placebo/comparator arm. This cannot be considered an imbalance as there was not sufficient exposure in the placebo group to experience any cases. In this case we did examine each of the four cases to further explore drug-induced causation (much like we did with the original alogliptin application), and did not find any concerns. That along with the lack of transaminitis shifts allowed us to comfortably recommend approval.

We have also had our OSE colleagues review the AERS database for potential liver signals with the marketed agents. Using their criteria, they identified 45 initial AERS cases that were subsequently narrowed to eight by specific case definitions, all in sitagliptin. Using their same search criteria, they would have identified the two cases in the Japanese database that we are most concerned about. The reports for sitagliptin and are confounded or lack adequate information. Considering the difference in marketing exposure between sitagliptin and alogliptin, this is another, while imprecise, indication of a potential (at least relative) drug-induced liver adverse event signal. One would expect most or all reports would be in sitagliptin as it has been marketed substantially longer than any of the other agents. While as discussed earlier, trying to make decisions based on post-marketing experience is tenuous at best, it does seem that even if we considered a worse case scenario, the post-marketing experience of reports associated with liver abnormalities with alogliptin use in Japan is an outlier from what we have experienced for the other DPP4-inhibitors. Dr. Parks has undergone this exercise which I have copied below in italics from her review (page 17-18).

Merck has recently submitted a response to our information request to search its database using the OSE search strategy. The information is currently being reviewed by OSE and Dr. Seeff but Dr. Joffe has provided a table summarizing Merck's findings. He points out that

review of these cases may eliminate some as associated with sitagliptin use; however, the worst-case scenario illustrated by the yellow highlighted rows in the table below in which we consider all reports to be related to sitagliptin is still a magnitude lower than what has been observed with alogliptin if we consider only the two probably to highly likely cases identified in table 8.5. Such a comparison would yield the most conservative assessment of 1 in (b) (4) pt-yrs for sitagliptin versus 1 in 110,000 pt-yrs for alogliptin.

Table 10 (provided by Dr. Joffe). Postmarketing liver reports with sitagliptin products (from Merck, using our requested search strategy)				
Preferred Term	Worldwide		Japan	
	All	Serious Only	All	Serious Only
<i>Acute hepatic failure</i>	3	3	0	0
<i>Chronic hepatic failure</i>	1	1	0	0
<i>Hepatic encephalopathy</i>	4	4	0	0
<i>Hepatic failure</i>	12	12	0	0
<i>Bilirubin conjugated increased</i>	3	1	0	0
<i>Blood bilirubin increased</i>	18	9	1	1
<i>Hepatitis fulminant</i>	1	1	1	1
<i>Hyperbilirubinemia</i>	2	0		
<i>Jaundice</i>	35	17	6	5
TOTAL¹	70	42	7	6
Total patient-years (PY)²	(b) (4)		(b) (4)	
Reporting rates	1 per (b) (4) PY	1 per (b) (4) PY	1 per (b) (4) PY	1 per (b) (4) PY
¹ Totals are less than the sum of the annual preferred terms because some reports included more than one preferred term				
² Estimated by dividing distributed tablets by 365 for sitagliptin (which is dosed once-daily) and by 730 for Janumet (which is dosed twice-daily). Excludes sitagliptin/simvastatin, which has (b) (4) patient-years of global exposure.				

In summary of all the available data, clinical trial data have revealed transaminitis shifts that are concerning. Postmarketing experience in Japan has identified several concerning liver injury cases that provide evidence that the transaminitis shifts may be harbingers of an ominous, albeit rare, toxicity for alogliptin. We do not have a Hy's law case in the clinical trial database, which may indicate that if alogliptin does have adverse liver toxicity, it occurs at a low rate (less than 1:17,000 to 1:50,000 depending upon the exposure criteria used). However, the post-marketing comparisons that we have performed indicate that alogliptin does seem to have an adverse effect upon the liver that is not seen with the other agents. This sets alogliptin apart and needs to be carefully considered in any risk:benefit assessment.

Cardiovascular safety

To fulfill this deficiency, Takeda is conducting Study SRY-322-402 (Study 402) a non-inferiority, event-driven, cardiovascular safety study in patients with T2DM who had recent

acute coronary syndrome (ACS). Interim data from Study 402 was submitted independently and as part of a meta-analysis including 12 clinical trials. A total of 106 major adverse cardiovascular events (MACE) events were reported of which Study 402 contributed 83. Regardless of the database explored, alogliptin excluded the 1.8 margin of 95% CI for the risk ratio of MACE that would allow marketing. These results are provided in the table below from Dr. Parks' review (page 7).

Table 8.2 Analysis of MACE and MACE+ Endpoints in Study 402

	Alogliptin N=1058	Placebo N=1076
Incidence of MACE	37/1058 (3.5%)	46/1076 (4.3%)
Hazard ratio (repeated 95% CI)	0.81 (0.44, 1.50)	
Incidence of MACE+	41/1058 (3.9%)	55/1076 (5.1%)
Hazard ratio (repeated 95% CI)	0.74 (0.42, 1.32)	

Considering the point estimate above, should this trend continue the sponsor may be able to demonstrate CV benefit. Since no agent used in the treatment of T2DM has demonstrated convincing evidence of CV benefit, such a demonstration could potentially be an important consideration to offset concern over liver toxicity concerns (unless some of the other drugs used in the treatment of T2DM that are currently undergoing CV evaluation demonstrate benefit).

Advisory committee meeting

An advisory committee was not held for this NME as this drug is not a first in its class and at this point outside expertise is not necessary.

Conclusions and Recommendations

Alogliptin is a DPP4-Inhibitor that has demonstrated efficacy by placebo-corrected reductions in HbA1c of 0.4 to 0.6% in a range of different populations. There are currently three other approved DPP4-Inhibitors, all have approximately the same effect on HbA1c (by cross-study comparisons). Alogliptin at present does not seem to have any advantage over these agents, although CV outcome trials are pending for all.

All deficiencies identified in the original CR letter have been successfully remediated in this resubmission. However, in generating the additional data necessary for the remediation, a new

signal of potential drug-induced liver injury has been identified that does not seem to be present with the other DPP4-Inhibitors.

The evidence of this potential adverse event is in way of the combination of transaminitis imbalances (ALT>10x ULN) between alogliptin compared to placebo/comparator and concerning post-marketing case reports from Japan. Neither of these findings by themselves may have caused us enough concern to take a CR action, but the combination is unique for alogliptin compared to the other DPP4 inhibitors. There are not any Hy's law cases in the NDA database, which may give some indication that DILI associated with alogliptin use, if real, is rare. While there does not seem to be a 'clean' case that clearly implicates alogliptin, there is strong circumstantial evidence with the combination of the database transaminitis imbalances and the post-marketing experience. This is equivalent to 'a lot of smoke, but no fire'. So is the smoke that is being expressed just 'steam' from some innocuous source, or a small fire that could cause tremendous damage, if even rarely? It is difficult to tell based on the data (incomplete in some cases) that we have to date. Yet, a decision must be made based on the totality of what we presently have to review. Such are the complexities of trying to make decisions with incomplete data on what are possibly rare events. I believe that the reports that we have from Japan and the transaminitis shifts that are in the clinical database stand alogliptin texturally apart from the other DPP4 inhibitors, and that we should take a Complete Response action until further data become available to assuage our concern.

The question will then become what data are necessary to either allow marketing or confirm our suspicion? This is a difficult question as we have very imprecise measures of what the true event rate may be should alogliptin really cause liver injury. As I have stated above, the rate may be less than 1:17,000 or less than 1:50,000 based on extrapolations from the lack of Hy's law cases in the trial database. One approach may be to collect further data from Study 402 which will add anywhere from 5400 to 7400 patient-years of exposure to the existing trial database. This could provide anywhere from 7100 patient-years to 9900 patient-years depending upon when another evaluation is taken and what limitations we use for the evaluation (further interim data from Study 402, all data from the NDA or only data from the 25 mg dose etc.). If a Hy's Law or DILI case does not occur, we should feel comfortable that the risk of liver induced injury with alogliptin use may not be real, or at least that the rate would be so low as to not be detectable. This may allow marketing as this data would be from clinical trials and provide a more secure estimate than the post-marketing data.

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/s/

CURTIS J ROSEBRAUGH
04/25/2012

Summary Review for Regulatory Action

Date	April 25, 2012
From	Mary H. Parks, M.D.
Subject	Division Director Summary Review
NDA/BLA #	22271 (alogliptin)
Supplement #	22426 (alogliptin/pioglitazone FDC)
Applicant Name	Takeda
Date of Submission	July 25, 2011
PDUFA Goal Date	April 25, 2012
Proprietary Name / Established (USAN) Name	Nesina® (alogliptin)
Dosage Forms / Strength	6.25, 12.5 and 25 mg tablets 6.25 mg recommended for severe renal impairment 12.5 mg recommended for moderate renal impairment
Proposed Indication(s)	Adjunct to diet and exercise for the treatment of hyperglycemia in adults with T2DM
Action/Recommended Action for NME:	<i>Complete Response</i>

1. Introduction

Alogliptin is a dipeptidyl peptidase-4 enzyme inhibitor (DPP4-inhibitor) developed for the management of hyperglycemia in patients with Type 2 diabetes mellitus (T2DM). There are currently three other approved and marketed DPP4-inhibitors: Januvia (sitagliptin) approved in 2006; Onglyza (saxagliptin) approved in 2010; and Tradjenta (linagliptin) approved in 2011.

The original NDA for alogliptin was submitted to FDA in December 2007. An NDA for the fixed-dosed combination (FDC) of alogliptin and pioglitazone was submitted on September 2008. In July 2008, FDA convened a public advisory committee meeting to discuss the role of CV assessment for new anti-diabetic therapies and in December 2008, FDA issued a Guidance to Industry titled, *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (hereafter referred to as the 2008 Guidance). FDA applied the expectations laid out in this Guidance to both NDAs 22271 and 22426 and found them inadequate to fully evaluate for CV safety.

On June 26, 2009, a *Complete Response* action letter was sent to the applicant with deficiencies listed under Clinical and Nonclinical disciplines. A *Complete Response* letter was sent to NDA 22426 on September 2, 2009, which in addition to the clinical items identified in the June 2009 letter, two other deficiencies were cited related to dosage strength availability and field inspection deficiencies.

Resubmission to both NDAs was received on July 25, 2011. This memo will discuss the applicant's resubmission with respect to the response to deficiencies in the alogliptin NDA since determining approvability of the FDC hinges on resolution of the NDA for the NME, alogliptin. The deficiencies specific to the FDC NDA have been resolved and documented in discipline specific memos and will not be touched on in this memo. In addition, I will also discuss new findings of liver injury not identified in the original application as a result of additional data provided to FDA in this resubmission. My memo will not discuss areas in the NDA review in which there was agreement in conclusions within FDA and between FDA and the applicant. Instead, my memo will only focus on controversial scientific areas and problematic findings contributing to the division's recommendation to not approve this application.

The reader is referred to Dr. Hylton Joffe's excellent cross-discipline team leader (CDTL) memo which provides a complete summary of all discipline findings and recommendations. The reader is also referred to individual discipline reviews for details of the data submitted and evaluated by FDA. Under specific sections of this review, I will point the reader to the discipline review document and date of completion for ease of reference.

2. Background

The clinical development for alogliptin at the time of the original NDA submission reflected the regulatory landscape for diabetes drug development prior to the public and political scrutiny of its approval process arising from the rosiglitazone controversy in 2007. The typical trials considered for approval of diabetes drugs at that time were placebo-controlled monotherapy or add-on trials with the controlled phase for safety evaluation limited to 6 months. Longer-term exposure came from open-label extensions in which patients initially exposed to placebo were switched over to the investigational drug to bolster exposures. Unless a very rare and serious adverse event occurred in this portion of the studies, these uncontrolled extensions were severely limited for evaluating serious but common safety signals.

The 2008 Guidance required, as a condition of approval, an applicant to compare the incidence of CV events between its investigational agent to a control group and to show that the upper bound of the 2-sided 95% CI for the estimated risk ratio was less than 1.8. Upon meeting this threshold, an applicant would be required to provide more definitive evidence of cardiovascular safety through the conduct of a postmarketing trial which would rule out a 30% excess CV risk over comparators. The objectives of the Guidance were to improve the quality of clinical trial data and enable a thorough assessment of cardiovascular safety of new diabetes therapies, but in a staged approach to not seriously impact the availability of new and promising treatments.

Since its *Complete Response* letter, Takeda has provided additional data to meet the expectations of the 2008 Guidance. FDA's review of these data is summarized under Section 8.1 of this memo.

3. CMC/Device

The final recommendation from CMC is approval without any postmarketing required studies. Please see the following reviews (authored by/date) for complete review history from the Office of New Drug Quality Assurance (ONDQA) for this NDA:

- Drs. John Hill and Ali Al Hakim: January 4, 2012
- Drs. Suong Tran and Ali Al Hakim: March 30, 2009
- Drs. Chien-Hua Niu and Ali Al Hakim: August 20, September 10, and November 6, 2008
- Dr. Blair Fraser: September 10, 2008

4. Nonclinical Pharmacology/Toxicology

The final recommendation from the Pharmacology/Toxicology discipline is approval without additional postmarketing required studies. In the 2009 *Complete Response* letter for NDA 22-271, the FDA noted the following:

4. There is a signal for potential teratogenicity in an embryofetal development study testing the combination of another dipeptidyl-peptidase (DPP)-4 inhibitor and metformin. If approved, alogliptin will frequently be used in combination with metformin. Therefore, you should conduct an embryofetal development study in rats that includes separate alogliptin and metformin arms in addition to the combination groups. Include the complete study report from this embryofetal development study in the Complete Response.

With this resubmission the applicant provided the results of an embryofetal rat study which included alogliptin and metformin control arms and the combined therapy of these two drugs (low and high dose arms). No treatment-related fetal findings were observed in the control arms or low dose combination group. Adverse findings noted in 4 fetuses from 2 dams receiving high dose combination treatment were considered related to maternal toxicity. Pharm/tox reviewers considered the results of this study as adequately addressing the nonclinical deficiency in the 2009 *Complete Response* letter.

Please see the following reviews (authors/date) for details of the pharmtox findings and recommendations:

- Drs. David Carlson and Todd Bourcier: August 27, 2008 and January 18, 2012
- Dr. Todd Bourcier: January 18, 2012

5. Clinical Pharmacology/Biopharmaceutics

In the 2009 *Complete Response* letter for NDA 22-271, the FDA noted the following:

3. In the renal pharmacokinetic study, mean exposure to alogliptin, as assessed by the area under the time-concentration curve (AUC), was increased by approximately 70% in patients with mild renal impairment compared to patients with normal renal function. This finding suggests there may be a need to adjust dosage of alogliptin in patients with mild renal impairment. In your complete response, you should include analyses of the controlled phase 2/3 program comparing safety and tolerability in patients with normal renal function to those with mild renal impairment. Present the data in two ways; one using the Cockcroft-Gault formula to categorize renal function and another using the Modification of Diet in Renal Disease (MDRD) equation to categorize renal function.

The applicant provided an explanation for the increased exposure in patients with mild renal impairment in this resubmission. It appears that the mean increase was driven primarily by a single patient outlier whose estimated creatinine clearance was 53 mL/min and more likely a patient with moderate renal impairment. Re-analysis excluding the outlier data resulted in a lesser increase in exposure, not necessitating dose adjustments in the mild renal impairment population.

Please see reviews by Drs. Sang Chung and Jayabharathi Vaidyanathan entered into DARRTS on August 28, 2008 (original review, January 18 (resubmission review) and 24, 2012, and March 7, 2012. The final recommendation from Clinical Pharmacology and Biopharmaceutics is approval with no postmarketing requirements.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Please see the following reviews authored by Drs. Janice Derr and Todd Sahlroot from the Division of Biometrics:

- January 18, 2011 (resubmission)
- September 3, 2008 (original)

In the original NDA, 5 Phase 3 trials were reviewed and supported a conclusion that alogliptin 12.5 and 25 mg significantly lowered HbA1c relative to placebo. The range of effect relative to placebo was 0.4 to 0.6% reduction across the five studies which included a monotherapy study (010), three add-on studies to SU (007), metformin (008) or pioglitazone (009), and an add-on to insulin study (011).

Although the *Complete Response* letter did not identify the need for additional glycemic efficacy studies, the applicant was required to submit additional studies to provide longer duration of controlled data to better assess safety, as stated in the following:

2. The alogliptin NDA contains only uncontrolled data beyond week 26, substantially limiting interpretability. Your complete response should contain controlled data for at least 500 patients with at least 1-year total exposure to alogliptin to supplement the ~2,000 patients with uncontrolled 1-year exposure to alogliptin included in the 120-day safety update and to provide additional assurance regarding safety for this therapy that will be used chronically, if approved. These data can be derived from the cardiovascular safety trial and/or from other appropriate trials, such as the one-year trial comparing alogliptin to titration of pioglitazone in patients on background metformin plus pioglitazone therapy and the one-year trial comparing alogliptin to sulfonylurea in elderly patients.

Consequently, this resubmission includes additional glycemic efficacy data from Studies 004 and 303, both 52-week trials. In addition to these two studies, the applicant provided results from a 12-week Phase 2 trial and a 16-week trial evaluating the effect of alogliptin, alogliptin plus pioglitazone, and placebo on postprandial triglycerides.

Drs. Derr and Joffe have thoroughly discussed the limitations and findings from these trials. Overall, these new studies do not alter the original efficacy conclusion of alogliptin. Alogliptin provides effective but modest reductions in HbA1c in a variety of patient populations, and the degree of HbA1c reduction appears on par with other approved DPP4-inhibitors. Alogliptin has a neutral effect on weight, lipids and blood pressure.

8. Safety

For this section I will only present the safety findings for the CV risk assessment to meet the FDA's 2008 Guidance and the recent findings of liver toxicity. Please see the reviews by Drs. Pratt and Joffe for other safety findings. I would note that other adverse events related with this class of drugs, namely hypersensitivity reactions and pancreatitis, were observed in this NDA and I concur with the review team that it does not appear that alogliptin has a safer profile to other DPP4-inhibitors in this regard. On the contrary, Section 8.2 discusses the liver safety concern that might place alogliptin at a disadvantage over these other available therapies.

8.1 Cardiovascular Safety

Please see the review prepared by Dr. Eugenio Andraca-Carrera dated January 5, 2012, from the Division of Biometrics VII.

The June 29, 2009 *Complete Response* letter stated that the applicant had not ruled out an unacceptable increase in CV risk with alogliptin. To resolve the deficiency, the applicant was told to conduct a CV safety trial that satisfies the 1.8 bound criterion incorporating design features as described in the FDA's December 2008 Guidance.

Prior to this resubmission Takeda met with the FDA at an End-of-Review meeting and also had several teleconferences to gain agreement on what data would be acceptable to address the above-mentioned deficiency. Study SYR-322-402 (Study 402) is a multicenter, randomized, double-blind, placebo-controlled study evaluating alogliptin with standard of care in patients with T2DM who had a recent acute coronary syndrome (ACS) that was designed and initiated specifically to address this deficiency. In conjunction with the Division of CardioRenal Products, agreement was reached on the trial design, study endpoints, and statistical analysis plan. For the resubmission, data from an interim analysis of Study 402 was submitted both on its own and as part of a meta-analysis of 12 clinical trials. The objective in both cases was to demonstrate that alogliptin compared to placebo or comparators excluded the 1.8 margin of the 95% CI for the risk ratio of major adverse cardiovascular events (MACE).

The majority of the trials were 26 weeks in duration (7), with the shortest duration being one 12-week, Phase 2 trial. However, the meta-analysis also included data from two 52-week trials. The interim analysis of the CVOT took place after a mean duration of 5.4 months but as will be discussed later, a large proportion of CV events were derived from this one trial. In all, data from 8162 patients were included in this meta-analysis (5226 alogliptin and 2936 comparator) with approximately 2500 pt-yrs of exposure to alogliptin. The resubmission provides more than twice the number of patients exposed to alogliptin in the original NDA, which had 3,490 alogliptin-treated patients.

The 2008 Guidance recommended that Phase 2 and 3 programs enroll patients at high risk of CV events including those with relatively advanced disease, elderly, and some degree of renal impairment. The following table summarizes some of the characteristics of patients from all 12 trials and Study 402 alone.

Table 8.1 Patient Characteristics of Controlled Phase 2/3 Trials (including Study 402) and Study 402 only

	All Controlled P2/3 Trials		Study 402	
	Comparator	Alogliptin	Comparator	Alogliptin
Mean age, yrs	58.3	56.6	60.9	60.9
Mean BMI, kg/m ²	30.5	30.9	29.3	29.6
Mean duration of DM, yrs	7.5	6.9	9.2	9.1
Renal function, MDRD	17.2%	18.9%	11.9%	10.7%
Normal	62.5%	65.5%	52.6%	58.0%
Mild	18.3%	14.4%	28.4%	26.5%
Moderate	1.0%	0.6%	2.9%	2.6%
Severe				
Concurrent CVD	10.8%	7.4%	100%	100%
Dyslipidemia	19.3%	17.9%	22.9%	22.2%

Source: Applicant's Submission 2.7.4 Summary of Clinical Safety

As noted in Table 8.1, Study 402 enrolled a higher CV risk patient population as eligibility criteria included a diagnosis of T2DM and an ACS event within 15 to 90 days prior to randomization.

All CV events were adjudicated by an independent cardiovascular endpoints committee (CED) using accepted FDA definitions. Events were (and are still being) adjudicated prospectively in Study 402 whereas events in the remainder of the studies in the pooled analysis were adjudicated retrospectively. A total of (b) (4) MACE were reported: (b) (4) in the alogliptin-treated group versus (b) (4) in the comparator group, which was comprised of placebo, glipizide, and pioglitazone. The number of MACE in this resubmission is in stark contrast to what was gleaned from the original NDA submission which identified (b) (4) 'custom MACE' events after post-hoc assessment using expanded standard MedDRA query terms were applied in the search strategy.

Drs. Joffe and Andraca-Carrera have presented the CV risk assessments from both the pooled Phase 2/3 trials and Study 402 alone. For this memo I will only discuss the interim results from Study 402. Since Study 402 enrolled a higher risk population, is prospectively designed to evaluate CV risk, and contributed (b) (4) out of the total (b) (4) MACE in all Phase 2/3 trial results combined, I believe the interim results should be given greater weight alone than the results of the combined 12 trials. However, it should be noted that both analyses support a conclusion that alogliptin did not increase CV risk for MACE exceeding 80% over that of comparators.

Study 402 is an ongoing trial in patients with T2DM and a recent ACS. It is an event-driven trial designed to exclude a hazard ratio of 1.8 and 1.3 with appropriate analyses for control of type 1 error from multiple interim looks. The first interim analysis was planned for after 80 events. If a HR of 1.8 can be ruled out after 80 events, the next interim analysis is planned for after 550 events to exclude a HR of 1.3. If exclusion of 1.3 cannot be achieved at this point, the trial will continue and another interim analysis will take place after 600 events occur. Again, if 1.3 is not excluded, the trial will continue to its final analysis after 650 events have occurred. This trial is event-driven for evaluating CV safety not benefit. Upon excluding a HR of 1.3, (b) (4)

(b) (4) The primary endpoint in Study 402 was MACE and the secondary endpoint included urgent revascularization due to unstable angina or MACE+.

As of April 29, 2011, 2,134 patients have been enrolled in Study 402 with approximately 169 mean days of follow-up and only 73 patients exposed to drug for at least one year. Despite the shorter duration of follow-up than some of the completed Phase 2/3 trials, Study 402 provided the majority of events for assessment of CV risk for alogliptin, underscoring the value of conducting a study in an enriched population.

The current event rates in Study 402 are (b) (4) for placebo and (b) (4) for alogliptin. The primary and secondary CV endpoint findings for Study 402 are summarized below.

Table 8.2 Analysis of MACE and MACE+ Endpoints in Study 402

(b) (4)

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(b) (4)

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In conclusion, the interim results of Study 402 alone addressed the deficiency in the 2009 *Complete Response* letter requiring additional data to rule-out an unacceptable CV risk associated with alogliptin use. The interim results are further supported by the meta-analysis of 12 controlled trials including two studies which increased the number of patients exposed to aloglitpin in a controlled duration out to one year.

Clearly, Study 402 must continue to provide more conclusive data on CV safety; however, the question to consider here is whether this trial

(b) (4)

8.2 Liver Safety

8.2.1. Clinical Trial Experience

A signal of liver toxicity was not identified in the original NDA application although Dr. Joffe's CDTL memo dated June 3, 2009, summarizes isolated cases of ALT increases. There were 7 patients in the alogliptin group versus one in the placebo group with ALT values > 5x ULN. The numerical imbalance may reflect both the 4:1 (alo:pbo) randomization scheme and the open-label extension period wherein all patients were treated with alogliptin providing greater pt-yr exposures to alogliptin over comparators. Narratives of these cases did not review any serious outcome, and the ALT elevations resolved or improved while on therapy or had other explanations which might account for the ALT elevations.

Near the end of 6 month review cycle for this resubmission, a postmarketing case of Hy's law from Japan was received prompting a request for more information from the applicant. The larger database also revealed a greater number of alogliptin-treated patients with marked ALT elevations over comparators. In fact, in the original NDA review there were no reports of ALT

> 10x ULN post-baseline for placebo/comparator group vs 2 in the alogliptin group. With the resubmission containing a greater number of patients exposed to both treatment groups, the number of patients with ALT > 10x ULN still remained at zero for comparators but increased to 8 in the alogliptin group. Some of the marked ALT elevations exceeded 20x ULN. The ratio of exposure was no longer 4:1 but 2:1 for alogliptin vs placebo; hence, an argument that differential exposures favoring alogliptin could not explain the numeric imbalance of 8:0 in the resubmission.

Table 8.3 ALT Elevations in Original NDA and Resubmission (Phase 2/3 Clinical Trials)

	Placebo/Comparator	All Alogliptin
Original NDA	N=534	N=1961
ALT > 3 xULN	6 (1.1%)	23 (1.2%)
ALT > 5x ULN	1 (0.2%)	7 (0.4%)
ALT > 10x ULN	0	2 (0.1%)
Resubmission	N=4074	N=7011
ALT > 3 xULN	39 (1%)	71 (1%)
ALT > 5x ULN	6 (0.1%)	21 (0.3%)
ALT > 10x ULN	0	8 (0.1%)
ALT > 20x ULN	0	2 (<0.1%)

Both the applicant and FDA had hepatologists review cases of abnormal ALT elevations, biochemical Hy's law, and serious liver injury. Dr. Leonard Seeff from the Office of Surveillance and Epidemiology (OSE) was consulted by DMEP. All hepatologists made their final assessment based on the same grading system as summarized in Drs. Seeff's and Joffe's reviews and displayed below for reference.

Table 8.4 Likelihood of Drug-Induced Liver Injury

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Fontana RJ, Seeff LB, Andrade RJ, et al. Hepatology 2010; 52: 73-742

The 8 cases of ALT > 10x ULN (including two that were > 20x ULN) listed in Table 8.3 were reviewed and adjudicated by the hepatologists. The narratives of these cases and the hepatologists' assessments are summarized in Dr. Joffe's memo. Not one of these 8 cases was definitively identified by any of the hepatologists as drug-induced liver injury (DILI). Confounders were noted in all; some cases showed resolution while on drug; and no cases resulted in a serious outcome. However, I would expect that for each of the confounders identified in the narratives, one should have a similar proportion of confounders (e.g., hepatitis infection or alcohol consumption) in the control arm such that if these etiologies contributed to the ALT elevations, there should have at least been some observed in the control group. For

example, Case 402/8260-010 was of a 48 year-old woman with normal baseline liver tests whose ALT rose to 11.7x ULN and total bilirubin to 1.5x ULN on Day 92. The narrative attributed this event to some other cause, possibly the SAE of unstable angina on Day 91. This event was reported in Study 402, the CV outcomes trial in patients with recent ACS in which the interim analysis has already shown numerically higher number of patients with unstable angina yet no cases of ALT elevations of this degree are noted in the placebo arm. My conclusion from these cases is that while an explanation can be provided for each of them, there remains an imbalance of marked ALT elevations not favoring alogliptin that may portend a more serious clinical outcome of hepatotoxicity when the drug is used more widely.

Four cases of biochemical Hy's law in the alogliptin group and four in comparator were identified in the clinical trial database. These were also reviewed by the consulting hepatologists and summarized in Dr. Joffe's memo. Like the cases of marked ALT elevations > 10x ULN, none of these cases was identified as DILI due to identification of another etiology. Hy's law, defined as ALT > 3x ULN accompanied by bilirubin > 2x ULN and for which no other etiology can be identified, is considered an ominous indicator of the potential for drug-induced liver injury. As discussed in FDA's Guidance for Industry titled, *Drug-induced Liver Injury: Premarketing Clinical Evaluation*,¹ "a finding of ALT elevation, usually substantial, seen concurrently with bilirubin >2x ULN, identifies a drug likely to cause severe DILI (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases". Although an actual Hy's law case was not identified in the clinical trial database, the postmarketing experience of alogliptin in Japan has identified several very concerning cases of potential drug-induced liver injury by alogliptin.

8.2.2. Postmarketing Experience for Alogliptin

Alogliptin has only been approved in Japan. Since marketing in April 2010 until October 15, 2011, the last Periodic Safety Update Report (PSUR), the estimated exposure for alogliptin as monotherapy and in the fixed-dosed combination with pioglitazone is ~ 120,000 patient-years. Recently, the applicant provided FDA with updated postmarketing exposure data covering the marketing period out to February 2012. The estimated exposure has nearly doubled to approximately 219,000 patient-years. Out of this postmarketing experience, several cases of hepatic injury or biochemical Hy's law were adjudicated by hepatologists for Takeda and FDA. Dr. Joffe has summarized the cases and the reader is referred to Dr. Seeff's consult dated February 22, 2012, for a complete summary of his assessment. The following table hones in on the most concerning cases, two (highlighted in red) of which were considered probable to highly likely alogliptin-induced liver injury by Dr. Seeff. I have included the narratives from Dr. Seeff's consult for these two cases after Table 8.5.

Table 8.5 Concerning Cases of Liver Injury Associated with Alogliptin Use in Japan

	Biochemical Hy's Law	Onset from Drug Initiation	Liver Tests	Outcome	Expert Assessment		
					(b) (4)	(b) (4)	Seeff
TCI2011A03640	no	immediate N/V, darkening	mixed hepatocellular/cholestatic injury w/ cholestatic	not life-threatening	possible	possible	probable

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

		or urine about 4 days, abnl labs 3wks	pattern predominating ALT869,AST625, AP1169 bilirubin normal no viral hepatitis reports				
TCI2010A05612	no	2 months	mixed hepatocellular/cholestatic pattern ALT230, AST108, AP1260, bili 0.9 u/s shows steatosis Hep A/B/C negative	recovering	possible	possible	probable
TCI2011A04039	no	3 days	ALT106,AST125, AP336, bili0.3	recovering	possible	possible	possible/probable
TCI2011A04573	yes	13 days-1 month	@ 1month ALT 1178, AST1070, AP905, bili 6.3 increase ammonia and coags, febrile	death	unlikely	possible	probable to highly likely
TCI2011A06837	yes	1 month	ALT 1512,AST 2188,bili3.9,AP313	recovered	probable	probable	probable to highly likely

TCI2011A4573 – Narrative as provided by Dr. Seeff

Case TCI2011A04573 is the most concerning case of all the postmarketing reports as it is the only fatal case.

This is a 77 year old Japanese female patient with a history of spinal stenosis that had required lumbar surgery, Hashimoto' s thyroiditis, and diabetes mellitus. Her diabetes had been treated with voglibose and glimepiride but she had a high HbA1c and peripheral neuropathy. On June 1, 2011, she was started on treatment with levothyroxine for her hypothyroidism, the dose being increased on June 17. On (b) (6), she was started on treatment with alogliptin. Baseline values for the ALT, AST, and serum bilirubin were normal (ALT 22 IU/L, AST 27 IU/L, bilirubin 0.4 mg/dL); her baseline ALP value was 290 IU/L. On (b) (6) 13 days after starting alogliptin, she was found to have mild increases in liver-related tests (ALT 57 IU/L, AST 56 IU/L), followed by a dramatic increase in the levels about one month later (ALT 1178 IU/L, AST 1070 IU/L, ALP 905

IU/L, serum bilirubin 6.3 mg/dl). She was also found to have increases in serum ammonia levels and coagulation parameters and she was febrile. On (b) (6) because of the continued high elevation in all the liver chemistries, alogliptin treatment was discontinued. She was begun on treatment with menatetranone, ascorbic acid, and glycyrrhizin/glycine/cysteine, followed 4 days later by treatment with ursodeoxycholic acid. At this time, levothyroxine treatment was discontinued. She appeared to be moving toward fulminant hepatitis and she was transferred to another hospital, presumably an academic institution. Although her serum enzymes began to fall, her coagulation parameters worsened, as did her serum bilirubin that peaked at 33.5 mg/dL on (b) (6)

She was treated for encephalopathy with kanamycin and lactulose. She was then started on treatment with corticosteroids, first given intravenously and then switched to oral prednisilone. The serum aminotransferases and bilirubin began to decline, and she was then transferred back to her original hospital. In (b) (6), she developed a fever and what was diagnosed as pneumonia, and she was started on treatment with a number of antibiotics. Her pneumonia worsened and she died on (b) (6) at which time her ALT was 30 IU/L, her AST 61 IU/L, her ALP 480 IU/L, and her serum bilirubin 3.8 mg/dL. Work-up had identified negative serology for hepatitis A, B, and C, for EBV and CMV, and negative tests for ANA, ASMA, LKM-1 antibody and AMA. Thus her death, clearly a result of fulminant liver disease or its complications, was not caused by infection with hepatitis viruses, and did not seem related to autoimmune hepatitis as defined by negative tests for all autoimmune hepatitis markers.

Comment: This 77 year old woman with diabetes mellitus, Hashimoto's thyroiditis and hypertension, who was admitted to hospital for treatment of her hypothyroidism with levothyroxine, developed mild elevations in aminotransferase levels 13 days after starting treatment of her diabetes with alogliptin. The liver dysfunction slowly worsened and she developed jaundice and evidence of impending fulminant hepatitis. Treatment with alogliptin was discontinued after 39 days, followed by discontinuation of the levothyroxine. She was transferred to another hospital presumably because of greater expertise at that hospital, and she was managed there for her advancing hepatic failure. Eventually she was started on treatment with corticosteroids on the assumption that the liver disease was of autoimmune origin in view of her background of diabetes and thyroiditis. This diagnosis was not, however, confirmed by identifying markers of autoimmune liver disease, all of which were negative. The liver disease appeared to improve as defined by a reduction in the liver chemistries, and the patient was transferred back to the original hospital. There she developed a fever and evidence of pneumonia, and despite treatment with a number of antibiotics, she died.

That this patient developed severe liver disease and died as a consequence seems quite clear. What is to be determined is what the cause was for the liver disease. Viral hepatitis as the cause for the liver injury is ruled out by the negative serology for all the hepatitis viruses but hepatitis E. Autoimmune hepatitis, particularly in an elderly female, needs to be excluded. This diagnosis is based generally on identifying autoimmune markers, but the test results of all markers in this patient were negative that ordinarily would exclude the diagnosis. However, given this patient's background, namely the existence of other autoimmune disorders such as the diabetes and thyroiditis, autoimmune hepatitis must be considered despite the negativity of all the autoimmune hepatitis. This presumably was the basis for treating this patient with corticosteroids that appeared to lead to the improvement of the liver dysfunction thus supporting the possibility of this diagnosis. However, the apparent rapid response to steroids seems much quicker than is normally the case for autoimmune hepatitis, and corticosteroids can "wipe out the yellow" even in instances of non-autoimmune acute hepatocellular injury. In my opinion, the absence of positive tests for autoimmune markers is compelling evidence that this patient did not spontaneously develop idiopathic autoimmune hepatitis. Rather, in view of the temporal relationship between starting treatment with alogliptin and developing acute hepatocellular injury two weeks later makes it probable to highly likely that alogliptin was indeed responsible for the fatal liver disease.

Noteworthy is that the hepatology experts assigned by the company to review the cases disagree with my conclusion, Dr. (b) (4) assessing the case as unlikely and instead due to autoimmune hepatitis (AIH), while Dr. (b) (4) assessed the case as being possibly attributable to alogliptin. The concerning issue is whether the diagnosis was actually "idiopathic" AIH rather than dili from alogliptin. The major issue responsible for the disagreement is that the usual markers of AIH were negative in this patient. In favor of a diagnosis of AIH hepatitis was the fact that the patient is a female, that she had another diagnosis with autoimmune overtones, thyroiditis, and that she appeared to respond to treatment with corticosteroids. In my view, while this diagnosis can certainly not be ruled out, there are features that suggest to me that dili represents a greater

likelihood as causation. Clearly, AIH can present for the first time in an elderly female and to occur in the absence of positive immunological tests. However, she is a little older than is usual for a first time onset of AIH and I am compelled by the fact that if she did have an underlying immunological diathesis, all of her markers for AIH were completely negative. That her liver chemistries improved with corticosteroid treatment is clear, but this can also occur with other causes of acute hepatocellular injury. Most of all, however, is that the injury occurred coincidental with use of alogliptin. Is this purely coincidental? I am left with the view that the drug played a role in the induction of the liver disease, either through a direct "idiosyncratic" mechanism or through precipitating liver injury in a patient primed for it because of a so-called autoimmune diathesis. I feel quite strongly that it is not appropriate to assign a score of unlikely to this case; on the other hand, I recognize the validity of the counter argument and therefore I am willing to downgrade my assessment from highly likely to probable.

TC12011A06837 – Narrative as provided by Dr. Seeff

This 66 year old Japanese male who had been treated with pioglitazone and glimepiride

for type 2 diabetes, was switched from pioglitazone to sitagliptin on October 13, 2011.

However, sitagliptin appeared to be ineffective, and on (b) (6), was itself

replaced by alogliptin. His baseline liver chemistries were normal (ALT 27 IU/L, AST 36

IU/L). His ALP and serum bilirubin levels are not recorded. On a routine visit

approximately 1 month later (b) (6) he is found to have an ALT value of

1512 IU/L, an AST of 2188 IU/L, a serum bilirubin of 3.9 mg/dL, and an ALP value of

313 IU/L. Initially reported to have had no symptoms at this time, he later admitted to

actually having had some malaise. He was immediately hospitalized and alogliptin

treatment was discontinued, and the dose of glimepiride was increased. The serum

aminotransferase values declined rapidly over the course of the following week, reaching

near normal values within 10 to 14 days, as shown in the last test result provided.

Work up focused on testing for the viruses of hepatitis B and C, both of which were

serologically excluded. No imaging procedures were performed. Markers for

autoimmune hepatitis were apparently not performed but the issue of potential autoimmune hepatitis was considered by his physician, and the likelihood dismissed based on the evidence of normal values for gamma globulin and the return of the abnormal values to near normal within a relatively short time and without corticosteroid treatment. Other drugs received by the patient included isosorbide, sodium gualenate, famotidine, teprenone, nifedipine, and pravastatin, but they were continued despite which the liver tests improved following withdrawal of the alogliptin. Alcoholic liver disease as a potential diagnosis is excluded by the fact that he was only an occasional drinker and the pattern of liver dysfunction was completely different from that seen in alcoholic hepatitis.

Comment: This 66 year old man developed acute hepatocellular liver injury associated with hyperbilirubinemia approximately one month after starting treatment with alogliptin. With identification of the liver injury, alogliptin was discontinued whereas all other drugs he was receiving continued to be administered. In seeking an etiology, infection with the hepatitis B and C viruses was ruled out (but, of course, not hepatitis E virus infection), as was autoimmune hepatitis based on the absence of hyperglobulinemia and the rapid recovery without immunosuppressive treatment. Although imaging was not done to exclude the possibility of obstructive causes for the liver dysfunction, there were no clinical or biochemical indicators to support the diagnosis. Accordingly, it is my opinion that a diagnosis of alogliptin hepatotoxicity is probable to highly likely causing a liver disease of moderate severity.

The liver experts employed by the company have both reached a different conclusion, Dr. (b) (4) indicating that data were insufficient to reach a reasonable conclusion whereas Dr. (b) (4) awarded this a case of barely possible alogliptin hepatotoxicity. (Note: Additional data provided on this case resulted in an upgrade to probably by both Drs. (b) (4)) Both express concern of the rapid improvement in the serum aminotransferases in the face of a drug with a long half-life, a concern with which I agree. Undoubtedly, rapid improvement such as occurred in this case from strikingly increased aminotransferase levels to near normal levels within 10 to 14 days is unusual for the common causes of acute hepatocellular injury other than acute congestion or shock. However, unless not reported, the narrative does not provide any information that even suggests the presence of cardiac disease or the occurrence of dramatic hypotension. The other issue raised to dismiss dili is that the lymphocyte stimulation test was negative. Since this test is not approved for this purpose in the U.S., and since its validity is uncertain, I cannot hang

my hat on the results reported here as an indicator that dili was excluded. Clearly missing is the lack of test results for hepatitis A and E. One or other of these viruses might well have been responsible although hepatitis A is relatively uncommon in a 66 year old man (potential risk factors not reported) and hepatitis E is not known to be endemic in Japan (at least to my knowledge). I will therefore remain with my view that alogliptin dili is the probable cause for the liver injury although I will agree that there are some conflicting data that could require assigning a score of probable rather than highly likely.

Near the end of this review, the FDA received additional postmarketing cases which has made it very difficult to complete an assessment within the regulatory timeline with continued submissions and updates to exposures. Below I only highlight some of these new cases:

TC12012A01179

On April 22, 2012, FDA received another postmarketing case of a 65 year-old man who was initiated on alogliptin 12.5 mg on September 20, 2011. On February 10, 2012 he experienced chills, malaise, itching of the back, and orange-colored urine. We specifically inquired if the patient had fever or abdominal pain and the company did not find evidence of these clinical presentations in the medical record. The patient reported to a hospital on (b) (6) where it was reported that he had whole body jaundice. Below is a summary of the hepatic panel from prior to initiation of alogliptin to last date of tests provided.

Table 8.6 Relevant Laboratory Results for TC12012A01179

	ALT nl:7-42 IU/L	AST nl:11-31 IU/L	total bili nl:0.2-1.2mg/dl	direct bili nl:0-0.2 mg/dl	alk phos nl: 133-312 IU/L	Comments
May 23, 2011	9	18	--	--	--	normal prior to drug treatment
Oct 18, 2011	7	18	--	--	--	
Alogliptin 12.5 mg daily initiated on September 20, 2011						
Oct 18, 2011	7	18	--	--	--	normal 1 month after drug treatment
Feb 10, 2012	204	282	8.2	--	--	symptoms of malaise, chills, itching and orange-colored urine reported
Last dose of Alogliptin on February 27, 2012						
Feb 27, 2012	481	778	14.4	4.8	1288	went to hospital, clinically jaundiced, ursodeoxycholic started, u/s, CT scan, MRI, and liver biopsy performed
Feb 28, 2012	535	914	14.1	11.4	1110	
Mar 5, 2012	552	701	19.4	14.9	792	
Mar 7, 2012	428	464	19.0	14.3	691	
Mar 19, 2012	65	71	4.4	1.4	336	

Abdominal ultrasound revealed no mass-like lesion which could cause obstructive jaundice. Other imaging studies included abdominal CT (b) (6) and MRI (b) (6) which did not identify any lesions to support a diagnosis of obstructive jaundice. He was diagnosed with acute hepatitis and hospitalized. Coagulation profile and ammonia levels were not increased.

On (b) (6) a liver biopsy was performed and the results were read as ‘not inconsistent with drug-induced hepatitis’ but that possibilities of viral hepatitis and autoimmune hepatitis could not be ruled out. A diagnosis of drug-induced hepatitis due to alogliptin was made.

[Histopathological diagnosis]

(b) (6)

Examined specimen: Specimen obtained from the right liver lobe by needle biopsy

Histopathological diagnosis: Hepatitis

Histopathological findings:

Fibrous dilatation (+) of the portal region was noted, but fibrous bridging formation, fibrosis with lobular distortion, and destruction of hepatic lobular architecture were not present. Inflammation in the hepatic lobules was moderate. Regarding hepatocellular degeneration, single cell necrosis (+), focal necrosis (+), and interface hepatitis (+) were noted, but there was no submassive or massive necrosis. In the area around the limiting plate, plasma cells were scatteringly seen. There was no evidence of biliary stasis. Chronic non-suppurative destructive cholangitis was not present, and there were no specific inflammatory findings

The findings were not inconsistent with drug-induced hepatitis (hepatitis type), but a possibility of chronic viral active hepatitis or autoimmune hepatitis could not be ruled out.

A drug lymphocyte stimulation test was negative (predictive value unknown and not established as biomarker in U.S.). The report specifically stated that there was no past history of intake of health foods, Chinese herbal medicines, or supplements. The patient was negative for hepatitis B and C and on additional FDA inquiry was noted to be positive for Hepatitis E RNA. Additional information requests (e.g., HEV IgM antibodies) to determine if this was acute hepatitis E infection were made and it was noted that the patient tested positive for IgA antibodies to hepatitis E reducing the likelihood of alogliptin-induced liver injury.

TC12011A06481

This case was of a 53 year-old man who presented with chest pain after 3 months of alogliptin treatment. His laboratory findings included ALT 1583 U/L, alk phos 447 U/L and total bilirubin of 0.8 mg/dL. Alogliptin was discontinued two days later but ALT levels had already started to decline to 982 U/L and declined even further after 2 weeks to 52 U/L. Hepatitis A, B, and C tests were negative but hepatitis E tests were not performed. The assessments for this case by the 3 hepatologists ranged from possible to probable.

8.2.3. Summary of Liver Safety Findings for Alogliptin and Comparison to Other DPP4-Inhibitors

In summary, the clinical trial database for alogliptin has an imbalance in marked ALT elevations (> 10x ULN) in 8 patients treated with alogliptin versus none in comparator. There were no cases of Hy's Law in the clinical trials. There are several concerning cases arising from approximately 219,000 patient-years of postmarketing experience in Japan deemed by FDA hepatologist, Dr. Leonard Seeff, as probable to highly likely. Expert hepatologists consulted by Takeda have differing and downgraded assessments with Dr. (b) (4) being the more dismissive of alogliptin causality in most cases, including one patient who had fulminant hepatic failure and subsequently died from pneumonia. In some respects, the absence of unanimity in adjudication may reflect incomplete information or confounders for each of the cases which opens up the final assessment to subjectivity and personal biases.

Left with a handful of concerning postmarketing cases for alogliptin led us to also scrutinize the liver safety profile of each of the approved DPP4-inhibitors (sitagliptin, saxagliptin, and linagliptin) to determine if their pre-marketing and post-marketing experiences had similar signals not noted by us previously. None of these three DPP4-inhibitors exhibited an imbalance in severe ALT elevations (>10x ULN) in their pre-marketing application. Hence,

much of the comparative safety assessment is based on the postmarketing experience for each of these drugs. It should be noted that such a comparison is imperfect, particularly since FDA can not do a direct search of alogliptin since it is unapproved. However, Merck (which has the market lead of all the DPP4 inhibitors) was asked to search their worldwide databases for cases using the following search terms:

- Hepatic Failure and Associated Disorders (HLT)
- bilirubin conjugated increased (PT)
- blood bilirubin increased (PT)
- hepatic necrosis (PT)
- hepatitis fulminant (PT)
- hyperbilirubinemia (PT)
- jaundice (PT)
- liver transplant (PT)

These terms have been used by OSE in their review of postmarketing liver safety for other FDA-approved diabetes drugs (e.g., TZDs). It should be noted that the two cases highlighted in red in Table 8.5 have been identified by OSE. In other words, had the postmarketing reports of alogliptin in Japan been subjected to the same search strategy as these 3 approved DPP4-inhibitors, the two probably to highly likely cases would have been captured by FDA.

No cases meeting the above search strategy have been identified for saxagliptin and linagliptin but several cases have been identified for sitagliptin. The worldwide experience for sitagliptin and saxagliptin exceeds alogliptin's experience in Japan by approximately 133-fold and 4.75-fold, respectively.

Table 8.7. Comparison of Worldwide Exposures for Sitagliptin, Saxagliptin, Linagliptin, and Alogliptin.

	Cumulative Pt-Yrs Exposure from International Birthdate
Sitagliptin-containing products Worldwide Japan	16 million pt-yrs 2 million pt-yrs
Saxagliptin-containing products Worldwide Japan	570,000 pt-yrs not marketed in Japan
Linagliptin-containing products Worldwide Japan	41,000 pt-yrs 7000 pt-yrs
Alogliptin-containing products Marketed only in Japan	219,000 pt-yrs

As described by Dr. Joffe, FDA held a teleconference with Japan's regulatory agency, the Pharmaceuticals and Medical Devices Agency (PMDA). PMDA identified 8 serious

postmarketing cases for alogliptin, 70 for sitagliptin and none for linagliptin. Their search strategy differs from the one used by OSE and appears to capture more non-specific cases and the reader is referred to his memo for the details of that teleconference.

(b) (4)



8.3.4. Conclusions on Liver Safety

In summary, alogliptin's postmarketing experience in Japan has identified several concerning liver injury cases that may support the notion that the imbalance in marked ALT elevations in its controlled clinical trial database is an ominous signal not to be ignored. A review of premarket and postmarket experience with other FDA-approved DPP4-inhibitors has not identified a signal of liver safety or at least of the same magnitude as alogliptin. These

observations set alogliptin apart from the other DPP4 inhibitors leading me to suspect a less favorable benefit-risk profile that should preclude its approval at present.

9. Advisory Committee Meeting

This application was not discussed at an advisory committee meeting. Although it is a new molecular entity, it is 4th in class and the development program evaluating efficacy and safety is not notably different from other anti-diabetic therapies to require expert opinion of an advisory panel.

10. Pediatrics

Please see Dr. Joffe's CDTL memo.

11. Other Relevant Regulatory Issues

Please see Dr. Joffe's CDTL memo

12. Labeling

Deferred as I am not recommending approval at this time.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete response

- Risk Benefit Assessment

In its original NDA submission and subsequent trials provided with this resubmission, the applicant has provided sufficient evidence that alogliptin is an effective anti-diabetic agent with glycemic efficacy comparable to others in the DPP4-inhibitor class.

I concur with Dr. Joffe that all the deficiency items identified in the 2009 *Complete Response* letter have been addressed in this resubmission. Specifically, the interim analysis of MACE from their ongoing CV outcomes trial, EXAMINE, has excluded an upper margin of 1.8. This trial is ongoing to further address the upper margin of 1.3. I also agree with him and Dr. Pratt that the additional data identified similar safety concerns

observed in this class, including hypersensitivity and pancreatitis, which can be managed through similar product labeling. However, the resubmission also provided new safety data from a larger clinical trial database and the postmarketing experience of alogliptin in Japan which raises concern for liver toxicity with this drug. Review of multiple sources of data for all the currently approved DPP4-inhibitors does not identify a signal or one of the same magnitude. Consequently, this new finding of liver safety has now tipped the balance such that I can no longer conclude that the risks of alogliptin outweigh its benefit or that it provides a unique benefit over other available therapies.

According to FDA's Guidance for Industry, "a finding of ALT elevation, usually substantial, seen concurrently with bilirubin > 2x ULN, identifies a drug likely to cause severe DILI (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases." The Guidance further defines Hy's Law cases as having the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

The above excerpts from the Guidance refer to biochemical findings in the clinical trial database which are relied upon as criteria for identifying the potential for a drug to cause serious liver injury once the drug becomes widely used in the market. The situation we have before us in this NDA is the converse. We did not identify Hy's Law cases in the pre-marketing application (i.e., cases with ALT > 3x ULN and total bilirubin > 2x ULN without another etiology identified) but we have post-marketing cases from Japan that may be alogliptin-induced liver injury. Our ability to detect risk in the pre-market decision is now augmented by greater exposure of the drug in the general population of Japan and these concerning cases, albeit fraught with limitations and differences in opinion by 3 hepatologists, provide us reason for eyeing the pre-market application with suspicion, if not caution. The suspicion relates to the imbalances in marked ALT elevations (> 10x ULN) in alogliptin-treated patients. And the totality of current information heeds caution if the signal is real for a 4th in class DPP4-inhibitor with comparable glycemic efficacy to the three currently marketed products which do not carry the same signal of liver safety concern from current controlled clinical trial databases and postmarketing experience.

But how will Takeda provide evidence to assuage our concerns? Dr. Joffe has described the current ongoing CVOT (EXAMINE) and the possibility that modification to the

(b) (4)

concerns of liver toxicity, especially if ongoing postmarketing surveillance in Japan does not identify any additional cases of concern. Based on current enrollment, discontinuation

and event rates in EXAMINE, Takeda estimates achieving 550 adjudicated MACE events in June 2014, with an interim analysis to occur in August 2014. However, as stated in the protocol, additional analyses may be conducted up to 650 events, therefore the estimated timeframe to achieve approximately 650 adjudicated MACE events for study completion is May 2015, with a final analysis planned for July 2015. The earliest expected date for submission of the completed trial results would be December 2015, which may be further delayed if the protocol is modified (b) (4)

And as pointed out by Dr. Joffe, should the accumulated evidence in 3+ years support our concern of hepatotoxicity, (b) (4)

However, I do not rule out the possibility that it may eventually come down to this. Among the reasons for my hesitancy for austerity at this point is the difficulty in establishing drug causality in all the concerning postmarketing cases, as has already been extensively described in Drs. Joffe's and Seeff's review. (b) (4)

At present I would recommend that the *Complete Response* letter inform Takeda that additional exposure and liver findings from the ongoing EXAMINE trial and any other controlled trials and continued postmarketing experience from countries marketing alogliptin and alogliptin-containing products will be necessary to address our concerns of liver toxicity and that the threshold of risk to exclude will be discussed at an End-of-Review meeting.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None at this point as I am recommending a complete response.

- Recommendation for other Postmarketing Requirements and Commitments

None at this point as I am recommending a complete response.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
04/25/2012

Cross-Discipline Team Leader Review

Date	April 20, 2012
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 22271 and NDA 22426
Supplement#	
Applicant	Takeda
Date of Submission	July 25, 2011
PDUFA Goal Date	April 25, 2012
Proprietary Name / Established (USAN) names	Nesina (alogliptin) Oseni (alogliptin/pioglitazone fixed-dose combination tablet)
Dosage forms / Strength	Nesina: 6.25 mg, 12.5 mg, 25 mg tablets Oseni: 12.5 mg/15 mg, 12.5 mg/30 mg, 12.5 mg/45 mg, 25 mg/15 mg, 25 mg/30 mg, 25 mg/45 mg
Proposed Indication(s)	Alogliptin: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Oseni: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both alogliptin and metformin is appropriate
Recommended:	<i>Complete Response</i>

Cross Discipline Team Leader Review Template

1. Introduction

Alogliptin is a dipeptidyl-peptidase 4 (DPP-4) inhibitor developed by Takeda as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. A few years ago, Takeda submitted New Drug Applications (NDAs) for alogliptin and for a fixed-dose combination (FDC) of alogliptin and pioglitazone. For reasons explained below, we issued Complete Response letters for both NDAs in 2009. We have now received Takeda's Complete Response submissions for these NDAs, which are the focus of this memorandum.

As explained in the Safety section of this memorandum, we identified a potential signal for hepatotoxicity with alogliptin that prompted a request for more comprehensive liver analyses. This information was submitted to both NDAs within three months of the action goal date. We determined that these analyses were a major amendment to the NDAs and extended the action goal date from January 25, 2012 to April 25, 2012. If these NDAs are approved, alogliptin will be the fourth DPP-4 inhibitor to market and the first FDC of a DPP-4 inhibitor and thiazolidinedione to market.

Currently, alogliptin and the alogliptin/pioglitazone FDC are only marketed in Japan. Alogliptin was approved there on April 16, 2010, and the FDC was approved there on July 1, 2011. The estimated cumulative exposure to alogliptin in Japan is 219,000 patient-years through February 2012.

2. Background

We communicated the following deficiencies and information needed to resolve the deficiencies in our June 26, 2009, Complete Response letter for the alogliptin NDA:

1. We noted that Takeda had not excluded an unacceptable increase in cardiovascular risk for alogliptin. The upper bounds of the 95% confidence intervals for the risk ratios comparing the incidence of major adverse cardiovascular events with alogliptin to placebo exceeded the 1.8 criterion as recommended in the Guidance for Industry, entitled *Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. To resolve this deficiency, we requested that Takeda conduct a cardiovascular safety trial that satisfies the 1.8 upper bound criterion.
2. We noted that all clinical data for alogliptin beyond six months were uncontrolled, limiting interpretability. We requested that the Complete Response submission contain controlled data for at least 500 patients with ≥ 1 year exposure to alogliptin.
3. We noted increased alogliptin pharmacokinetic exposures (area under the time-concentration curve or AUC) of ~70% in patients with mild renal impairment, suggesting the need for a dosage adjustment in this population. We requested that the Complete Response submission contain analyses of the controlled phase 2/3 program comparing

safety and tolerability in patients with normal renal function to those with mild renal impairment.

4. We noted a signal for potential teratogenicity in an embryofetal development study testing the combination of another DPP-4 inhibitor and metformin. We requested that the Complete Response submission include an embryofetal development study in rats with separate alogliptin and metformin arms as well as a combination arm.

Our September 2, 2009, Complete Response letter for the alogliptin/pioglitazone FDC NDA contained deficiencies 1-3 listed above, as well as the following additional deficiencies:

- We noted a greater incidence in elevations of serum creatinine, blood urea nitrogen, and urinary albumin/creatinine ratios in the combination alogliptin/pioglitazone treatment group compared to the alogliptin and pioglitazone monotherapy groups. We also noted that more patients in the combination group experienced a shift from normal to mild or moderate renal impairment compared to the individual treatment groups. We stated that these findings raise concern about the lack of an FDC containing alogliptin 6.25 mg, which is the recommended alogliptin dose for patients with severe renal impairment or end-stage renal disease.
- The field inspector noted deficiencies at the (b) (4) manufacturing facility. We requested satisfactory compliance with Current Good Manufacturing Practices for all manufacturing and testing facilities to support approval.

At the End-of-Review meeting, we agreed that the sponsor no longer needs to manufacture an FDC tablet containing 6.25 mg of alogliptin. This decision was based on the fact that this dosage strength would account for less than 2% of the expected use of the FDC tablet taking into account the prevalence of end-stage renal disease in patients with type 2 diabetes. Nonetheless, this memorandum will still address the imbalances noted above pertaining to some of the renal laboratories.

3. CMC

The Chemistry/Manufacturing/Controls (CMC) reviewers recommend approval of the alogliptin and alogliptin/pioglitazone FDC NDAs. The deficiency in the Complete Response letter pertaining to the manufacturing facility for the FDC has been adequately addressed. See the review by Dr. John Hill for details.

With regard to the FDC, the biopharmaceutics reviewers agree with Takeda's postmarketing commitment pertaining to the pioglitazone dissolution specification and recommend approval. See the review by Dr. Tapash Ghosh for details. During this review cycle, no biopharmaceutics review was needed for the alogliptin NDA.

Note that the chemical structure of alogliptin is distinct from that of vildagliptin, another DPP-4 inhibitor. This is relevant because potential hepatotoxicity has been identified with vildagliptin and, based on the data in the current submissions, with alogliptin as well (see the Safety section).

4. Nonclinical Pharmacology/Toxicology

The non-clinical pharmacology/toxicology reviewers recommend approval of the alogliptin and alogliptin/pioglitazone FDC NDAs. See the reviews by Drs. David Carlson and Todd Bourcier for details.

Takeda submitted the rat embryofetal study that we requested in the alogliptin Complete Response letter. Dr. Bourcier concludes that the results from this study do not identify drug-related fetal abnormalities that are relevant to humans. Two dams from the high-dose combination group produced four fetuses with abnormalities, but he notes that this finding was associated with evidence of toxicity in the dams. Safety margins for these findings are 23-fold for alogliptin and 6-fold for metformin relative to the recommended clinical doses. In addition, Dr. Bourcier notes that the teratogenicity finding (craniofacial malformations) with saxagliptin (which prompted our request for this study with alogliptin) was subsequently resolved with additional studies and that no further evidence of augmented teratogenicity has been observed with the combination of DPP-4 inhibitors and metformin.

Takeda's Complete Response also included results from several other non-clinical studies. Dr. Carlson has reviewed these data and did not identify new non-clinical safety issues for alogliptin. He states that there are large exposure margins to toxic animal doses with no unique toxicity concern for alogliptin compared to other DPP-4 inhibitors.

Other findings of note from Dr. Carlson's review of the original NDA and Complete Response submissions include:

- Alogliptin did not cause skin lesions in the non-clinical program
- Dogs developed facial edema at ≥ 32 times the maximum recommended clinical alogliptin dose of 25 mg, which Dr. Carlson notes may predict hypersensitivity in susceptible humans.
- There is no signal for pancreas toxicity in rodents and non-rodent animal studies.
- There are signs of modest liver toxicity in chronic/lifetime rat studies with alogliptin (liver hepatocellular hypertrophy, periportal vacuolation, and basophilic 'focus of cell alteration') with a No Observed Adverse Effect Level in all animal species of ≥ 30 -times the maximum recommended clinical dose of 25 mg.
- There were no additive or synergistic effects of alogliptin co-treatment on pioglitazone-mediated toxicity.

5. Clinical Pharmacology/Biopharmaceutics

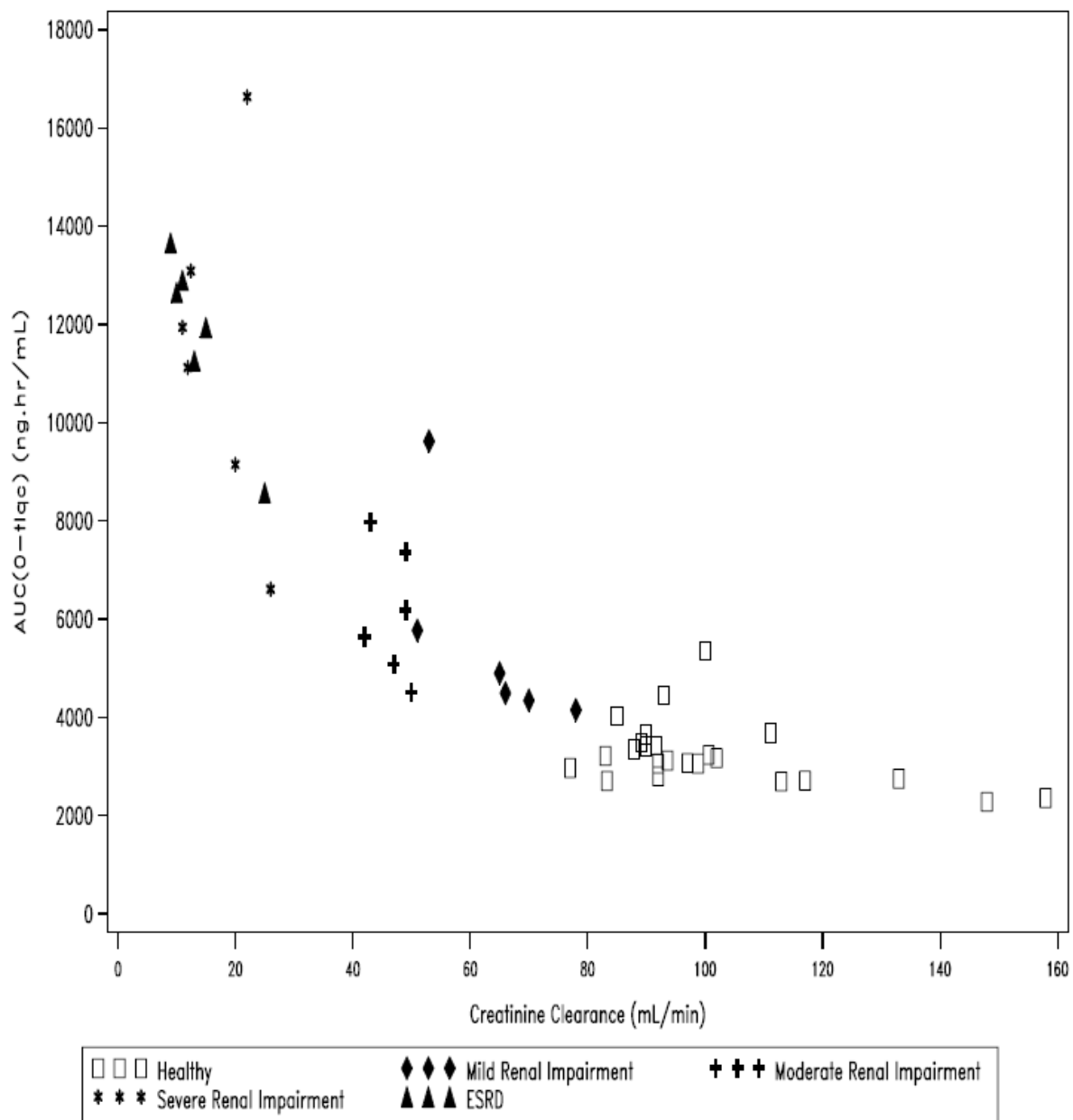
The clinical pharmacology reviewers recommend approval. See the reviews by Drs. Sang Chung and Ritesh Jain for details.

The Complete Response submissions contain the following new clinical pharmacology data:

- Study 101 showing that alogliptin 12.5 mg twice daily and alogliptin 25 mg once daily have comparable pharmacokinetics and pharmacodynamics (as assessed by DPP-4 inhibition). These results are not being incorporated into the alogliptin or alogliptin/pioglitazone label (both products are dosed once daily) but will be relevant for the alogliptin/metformin FDC, which will be administered twice daily (this NDA was recently submitted and will be covered under a separate CDTL memorandum).
- Study 103 showing that the absolute bioavailability of alogliptin is ~100%
- Study CPH-004 showing no significant effect of voglibose (an alpha-glucosidase inhibitor) on alogliptin exposure in Japanese subjects. I agree with Dr. Chung that the voglibose drug-drug interaction data should not be labeled given that voglibose is not approved in the United States.

The sponsor is proposing a daily alogliptin dose of 25 mg for patients with normal renal function or mild renal impairment, 12.5 mg for patients with moderate renal impairment and 6.25 mg for patients with severe renal impairment. As noted above, one deficiency in our Complete Response letters pertains to whether there should be a dosage adjustment for patients with mild renal impairment based on the increased alogliptin AUC_{0-t} of 76% in this population compared to subjects with normal renal function. In the resubmissions, the sponsor clarified that this AUC_{0-t} increase of 76% for the mild renal impairment group is driven by one patient and that the mean AUC_{0-t} for the remaining five patients (4739 ng/mL*min) is closer (45% increase) to the mean AUC_{0-t} (3258 ng*hr/mL) for the group of 24 subjects with normal renal function. The outlier patient had an estimated creatinine clearance of 53 mL/min (which is close to the moderate renal impairment range) and had an AUC_{0-t} of 9630 ng*hr/mL. The overall relationship between creatinine clearance and AUC is shown in Figure 1. Based on these considerations, Dr. Chung agrees that no dosage adjustment is needed for patients with mild renal impairment provided that the phase 3 data support the safety of the 25 mg dose for patients with mild renal impairment (in the phase 3 program patients randomized to alogliptin received 25 mg daily regardless of whether renal function was normal or mildly impaired). These safety data are discussed in the Safety section of my memorandum.

Figure 1. Overall alogliptin pharmacokinetic exposure (AUC_{0-t}) according to creatinine clearance.



6. Clinical Microbiology

These submissions do not contain new clinical microbiology data.

7. Clinical/Statistical- Efficacy

The efficacy of alogliptin was established in the original NDA. The Complete Response submissions contain data from two newly completed 52-week phase 3 trials that were not included in the original alogliptin or alogliptin/pioglitazone FDC NDAs. These data were provided to help satisfy the deficiency in our Complete Response letter pertaining to the lack of controlled clinical data beyond six months of treatment in the original NDAs. This section summarizes the designs of these trials and their efficacy results. Please see the clinical review by Dr. Valerie Pratt and the statistical review by Dr. Janice Derr for further details.

The sponsor also includes study reports for the phase 2/3 trials conducted exclusively in Japan to support registration there. I do not address the study design or efficacy results from those supportive trials in this memorandum but do comment on the safety findings from those trials in the Safety section.

The sponsor also includes data from a 16-week trial that randomized only 71 patients to one of three treatment groups with a primary efficacy endpoint of change from baseline in postprandial triglycerides. Although the sponsor classified this as a phase 3 trial, the scope is more consistent with a phase 2 trial. Therefore, I will comment only briefly on this trial but will cover pertinent results that the sponsor is proposing to incorporate into the Pharmacodynamics section of the labels.

Study 402, the ongoing cardiovascular outcomes trial, is covered under the Safety section of this memorandum.

Study 303: This is a non-inferiority trial that randomized patients aged 65-90 years old with type 2 diabetes and inadequate glycemic control (HbA1c 6.5%-9.0%) to 52 weeks of double-blind therapy with either alogliptin 25 mg once daily or glipizide (5-10 mg) once daily.

Inclusion criteria at screening included a HbA1c of 6.5%-9.0% (if treatment naïve) or 6.5%-8.0% (if on oral antidiabetic monotherapy). Patients only on diet and exercise were randomized directly into the 52-week treatment period after the screening period, whereas those on oral antidiabetic monotherapy underwent a 4- to 6-week washout period and were required to have a HbA1c of 6.5%-9.0% prior to entering the 52-week treatment period. As noted under Demographics, the mean baseline HbA1c was only 7.5%. To more convincingly show non-inferiority, patients with a higher baseline HbA1c should have been enrolled.

Exclusion criteria included serum alanine aminotransferase (ALT) $\geq 3 \times$ ULN, calculated creatinine clearance ≤ 50 mL/min, New York Heart Association Class III or IV heart failure, or a major cardiovascular event within the preceding 6 months (e.g., myocardial infarction, percutaneous coronary intervention).

Doses of glipizide (or matching placebo) were to be increased from 5 mg to 10 mg for patients with fasting plasma glucose ≥ 250 mg/dL between weeks 1 and 12. Patients who remained persistently hyperglycemic on the 10 mg dose (confirmed fasting plasma glucose ≥ 250 mg/dL until Week 12 or confirmed HbA1c $\geq 8.0\%$ from Week 12 through Week 52) were to be withdrawn. The glipizide dose could be reduced due to hypoglycemia but such patients were not permitted to again undergo uptitration of the glipizide.

In addition to the low baseline HbA1c discussed above, the glipizide dose was not optimized in this study. These features limit interpretability of non-inferiority. For example, glipizide was only to be uptitrated for significant hyperglycemia (fasting plasma glucose ≥ 250 mg/dL) when it would ordinarily be appropriate to titrate the glipizide for less extreme hyperglycemia. In addition, the maximum permitted dose of 10 mg is considerably less than the maximal or near-maximal efficacious dose. The maximum permitted dose should have at least been 20 mg (the maximum labeled total daily dose is 40 mg) although this may have introduced some complexity because the glipizide label recommends divided daily doses when the daily glipizide dose is ≥ 15 mg. Even though this trial was conducted in the elderly (the label recommends conservative initial and maintenance dosing to avoid hypoglycemia), slow upward titration of glipizide would still have been appropriate for those patients who required a daily dose of more than 10 mg based on glycemic control. A recent non-inferiority trial comparing saxagliptin to glipizide (but not conducted in the elderly) used more optimal doses of glipizide. Specifically, patients randomized to glipizide initiated 5 mg/day and underwent blinded uptitration during the first 18 weeks of the treatment period to a maximum daily dose of 20 mg/day (total daily doses > 10 mg/day were divided twice daily). In that study, the glipizide dose was increased in 5 mg increments in 3-week intervals to a goal fasting plasma glucose (FPG) ≤ 110 mg/dL or to the maximum tolerable dose.

In Study 303, randomization was stratified by Week -1 HbA1c ($< 8\%$ vs. $\geq 8\%$), presence of oral antidiabetic monotherapy at screening, and geographic region.

The primary efficacy endpoint was the change from baseline in HbA1c at Week 52 analyzed using a non-inferiority margin of 0.4%. If non-inferiority was established, the sponsor would then test for superiority of alogliptin over glipizide. The primary analysis was performed with an ANCOVA model that included study treatment, whether the patient was treatment naïve at screening, geographic region, and baseline HbA1c as a continuous covariate. This analysis used the per-protocol population (modified intent-to-treat population with no major protocol violations). As is our usual practice, results from both the per-protocol and intent-to-treat populations are important when determining non-inferiority.

Dr. Derr states that the chosen non-inferiority margin of 0.4% is too large based on the same concerns I mention above (i.e., low baseline HbA1c and low dose of glipizide). The sponsor did not provide a justification for this margin. Of note, the actual results show an upper bound of 0.13% for the 95% confidence interval for the treatment difference in HbA1c between alogliptin and glipizide. The interpretability of this finding is discussed in more detail in the efficacy results section.

Selected secondary endpoints included HbA1c responder rates, fasting plasma glucose, 2-hour postprandial glucose after a standardized meal, hypoglycemia, and body weight.

The sponsor estimated that at least 430 patients would be needed to provide $\geq 90\%$ power to declare non-inferiority assuming a standard deviation for HbA1c of 1.1%, a non-inferiority margin of 0.4%, no difference between treatment arms, a per-protocol population of 75% of the randomized population, and a one-sided alpha of 0.025.

Study 303 – Patient demographics (randomized dataset): The mean age of participants was 70 years. Most (86%) patients were <75 years old. There was a slight preponderance of women (55%) and a slight preponderance of treatment-naïve patients (54%). Most patients were Caucasian (73%), Asian (10%) or black (8%). One-third of patients were of Hispanic or Latino ethnicity. About 30% of patients were recruited from North America, 25% were recruited from Latin America and the remainder was recruited from Europe and the rest of the world. The mean duration of diabetes was 6 years and the mean baseline HbA1c was only 7.5%.

Study 303 – Patient disposition: A comparable but low percentage of the 441 randomized patients completed the trial (60% in the alogliptin group and 57% in the glipizide group). The low completion rates are partly attributable to discontinuations due to the need for hyperglycemic rescue (25% with alogliptin and 22% with glipizide). The incidence of glycemic rescue was low (1.9% for alogliptin and 0.5% for glipizide) until Week 12 (when fasting plasma glucose was used to determine the need for rescue and glipizide doses could still be uptitrated). Most of the rescue occurred between Weeks 12 and 52, triggered by confirmed HbA1c $\geq 8.0\%$. Although the mean baseline HbA1c was only 7.5%, about one-fourth of patients had baseline HbA1c $\geq 8\%$. In addition, for the primary efficacy analyses, the adjusted mean change from baseline at Week 52 in HbA1c was only -0.1% in both treatment groups. These findings may, at least partly explain the incidence of hyperglycemic rescue. It is difficult to compare the rates of glycemic rescue in this 52-week trial with rates in other trials because of differences in patient populations, trial durations and glycemic rescue criteria. For example, most phase 3 trials in type 2 diabetes have a six-month primary efficacy endpoint and use glycemic rescue criteria based only on fasting plasma glucose up until the primary efficacy endpoint.

Study 303 – Efficacy results: Of the 219 patients randomized to glipizide, only 21 (10%) uptitrated the dose from 5 mg to 10 mg during Weeks 1-12. Approximately 20% of the 198 patients in the glipizide arm who remained on the 5 mg dose of glipizide required glycemic rescue therapy.

As shown in Table 1, both treatment groups had a very small (-0.1%) mean change from baseline at Week 52 in HbA1c. The upper bound of the 95% confidence interval for the treatment difference is 0.1%, which is less than the prespecified non-inferiority margin of 0.4%. However, for reasons discussed above, the 0.4% non-inferiority margin is too large. From a statistical perspective, Dr. Derr states that this may not be a confirmatory finding of non-inferiority given the inappropriate choice of the margin and the *post-hoc* nature of deciding whether the actual upper bound is sufficiently far away from 0.4%. However, she states that the upper confidence bound may be sufficiently small from a clinical perspective to support a conclusion of non-inferiority. If we approve alogliptin and decide to label this trial, Dr. Derr recommends that these results be described descriptively in the label, omitting any discussion of non-inferiority. Labeling is further discussed under Section 13 of this memorandum.

As discussed under Section 11, concerns were raised about the reliability of data from one of the sites that recruited patients for this study. A sensitivity analysis excluding the 24 patients

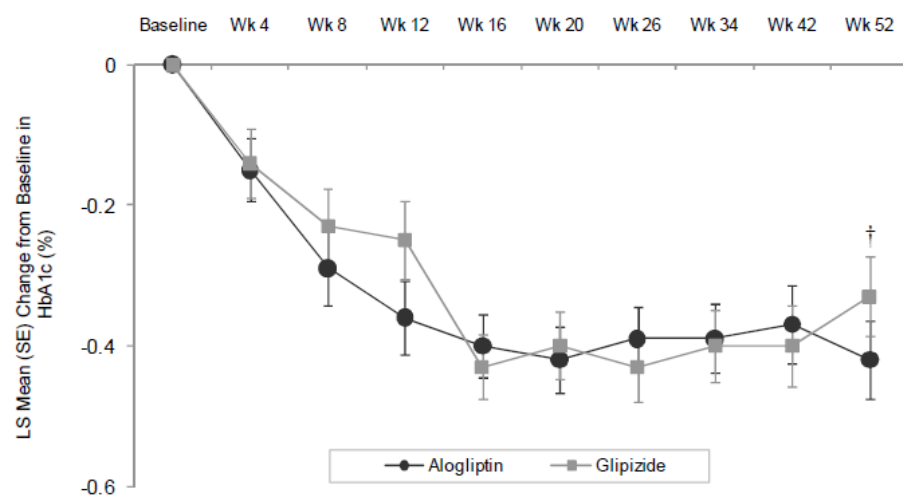
from this questionable site does not change any conclusions (the upper bound for the 95% confidence interval for the treatment difference is still 0.1% for both the intent-to-treat and per-protocol populations with last-observation-carried-forward).

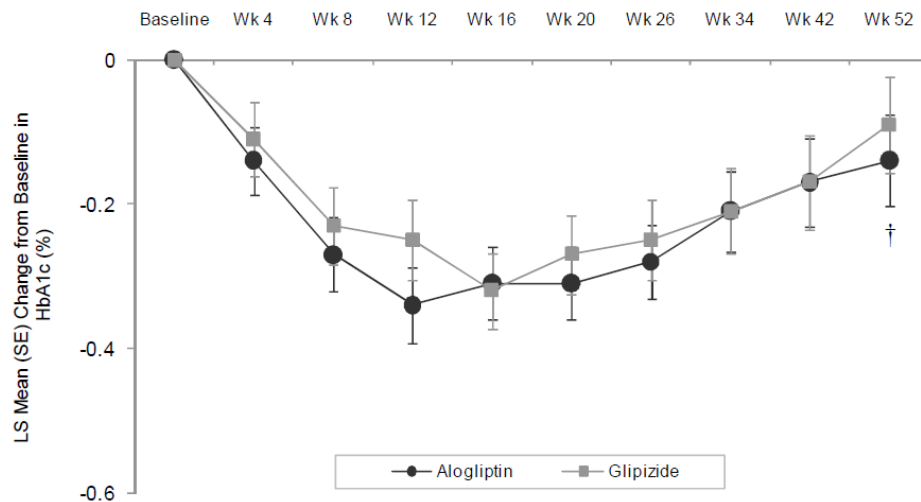
The percentage of patients achieving HbA1c $\leq 7.0\%$ at Week 52 was comparable in the two treatment groups (49% for alogliptin and 45% for glipizide; $p=0.59$).

Table 1. HbA1c change from baseline at Week 52 for Study 303 (Adapted from Table 17 in Dr. Janice Derr’s biostatistics review)				
Treatment Group	n	Baseline mean	LS mean change	Treatment difference LS mean change (95% CI); p-value
Intent-to-treat with last-observation-carried-forward				
Alogliptin	215	7.5	-0.1	0.0 (-0.2, 0.1); p=0.59
Glipizide	214	7.5	-0.1	
Per-protocol population with last-observation-carried-forward				
Alogliptin	180	7.5	-0.1	-0.0 (-0.2, 0.1); p=0.79
Glipizide	162	7.5	-0.1	
CI = confidence interval				

As shown in Figure 2, the greatest mean reduction in HbA1c in both treatment arms occurred around Weeks 12-20. These reductions were relatively maintained through Week 52 among completers in the per-protocol population (Figure 2a) but were not sustained using last-observation-carried-forward for missing data (Figure 2b). Therefore, results from these two approaches are not entirely concordant. In general, we use the completers population (as shown in Figure 2b) for graphical displays so that the same set of patients is shown over time without confounding by dropouts and imputed values.

**Figure 2. Study 303- changes from baseline in HbA1c over time
(a) per-protocol population with observed values**



(b) per-protocol population with last-observation-carried-forward

Study OPI-004: This was a double-blind, non-inferiority trial that randomized patients with inadequate glycemic control on metformin (≥ 1500 mg/day) and pioglitazone 30 mg/day to 52 weeks of either add-on alogliptin 25 mg once daily or uptitration of the pioglitazone from 30 mg to 45 mg.

Patients with a HbA1c of 7-10% on a stable dose of metformin ≥ 1500 mg/day and pioglitazone 30 mg/day for at least 2 months entered a 4-week run-in period and then entered the randomized treatment period. Those with a HbA1c $\geq 7.5\%$ on metformin plus another oral anti-diabetic medication (DPP-4 inhibitors not allowed) discontinued the other anti-diabetic medication, then entered a 12-week period receiving metformin ≥ 1500 mg/day and pioglitazone 30 mg/day. At the end of this 12-week period, patients with a HbA1c of 7-10% entered a 4-week run-in period and then entered the randomized treatment period.

Exclusion criteria included serum ALT $> 2.5 \times$ ULN, serum creatinine ≥ 1.5 mg/dL for men or ≥ 1.4 mg/dL for women, history of bladder cancer or unexplained, confirmed microscopic hematuria, or congestive heart failure.

Patients were to be withdrawn if they had a confirmed fasting plasma glucose ≥ 275 mg/dL (Weeks 2 to < 4), ≥ 250 mg/dL (Weeks 4 to < 8), or ≥ 225 mg/dL (Weeks 8 to < 12) or had HbA1c $\geq 8.5\%$ with $\leq 0.5\%$ reduction from baseline (Weeks 12-52).

The primary efficacy endpoint was change from baseline in HbA1c at both Weeks 26 and 52 using last-observation-carried-forward. Selected secondary endpoints included HbA1c responder rates, fasting plasma glucose, and body weight.

The primary analysis was conducted on the per-protocol population (same definition as used for Study 303). As mentioned previously, we consider results from both the per-protocol and intent-to-treat populations when determining non-inferiority. The sponsor used an ANCOVA

model that included study treatment, geographic region, baseline metformin dose, baseline HbA1c and whether patients underwent the 12-week period prior to run-in. The sponsor controlled type I error by testing for non-inferiority at Week 52 only after establishing non-inferiority at Week 26. The sponsor tested for superiority at Weeks 26 and 52 if non-inferiority was established at those timepoints. Note that the superiority test at Week 26 was considered exploratory because statistical superiority was not required at this timepoint to proceed with testing at Week 52.

The sponsor used a non-inferiority margin of 0.3% for the comparison of adding 25 mg of alogliptin vs. adding 15 mg of pioglitazone. I agree with Dr. Derr that this margin is likely too large based on the available placebo-controlled data with pioglitazone (see Dr. Derr's statistical review). Dr. Derr, therefore, determined that the non-inferiority evaluation is not useful and instead focused on the superiority evaluation at Weeks 26 and 52. Although Dr. Derr's *post-hoc* decision to focus on superiority at both timepoints (and bypass the non-inferiority evaluations) differs from the sponsor's prespecified gate-keeping strategy described above, Dr. Derr was satisfied that the available results (with low p-values) support the superiority of alogliptin to uptitrated pioglitazone at Weeks 26 and 52 (see the efficacy results below).

The sponsor estimated that 760 patients would be needed to provide $\geq 90\%$ power to declare non-inferiority at either Week 26 or 52 and at least 80% power to declare non-inferiority at both timepoints. This power calculation assumes a standard deviation for HbA1c of 1.1%, a non-inferiority margin of 0.3%, no difference between treatment arms, a per-protocol population of 75% of the randomized population, and a one-sided alpha of 0.025.

Study OPI-004 – Patient demographics (randomized dataset): The mean age of participants was 55 years and the mean duration of diabetes was 7 years. Most (82%) patients were <65 years old. There was a slight preponderance of men (52%) and a slight preponderance of patients who required the 12-week period prior to run-in (57%). Most patients were Caucasian (62%), Asian (20%), or black (10%). Only 8% of patients were of Hispanic or Latino ethnicity. About 30% of patients were recruited from the United States, about 20% were recruited from Western Europe, Australia and New Zealand combined, and the remaining 50% were recruited from the rest of the world.

Study OPI-004 – Patient disposition: A total of 404 patients were randomized to the alogliptin arm and 399 patients were randomized to the pioglitazone uptitration arm. Completion rates were 70% for alogliptin and 61% for uptitrated pioglitazone. This difference in completion rates was due to differences in the rates of glycemic rescue (11% for alogliptin vs. 22% for uptitrated pioglitazone). The incidence of glycemic rescue was lower in this 52-week study than in the 52-week elderly study despite the higher mean baseline HbA1c of 8.1-8.2% compared to 7.5% for Study 303. This may, in part, be related to the apparently greater reductions in HbA1c from baseline in both treatment groups in this trial (see below) as well as the different glycemic rescue criteria between trials. For example, after Week 12 in this trial, patients were to be withdrawn if they had HbA1c $\geq 8.5\%$ with $\leq 0.5\%$ reduction from baseline. In contrast, patients in Study 303 were withdrawn after Week 12 if the HbA1c was $\geq 8.0\%$ regardless of change from baseline.

Other reasons for discontinuation were relatively well-balanced between treatment groups (19% for alogliptin vs. 17% for uptitrated pioglitazone).

Study OPI-004 – Efficacy results: Data from five sites involving a total of 18 randomized patients were excluded from the analyses due to problems at those sites (e.g., investigator death prior to signing of electronic case report forms, non-compliance with Good Clinical Practices).

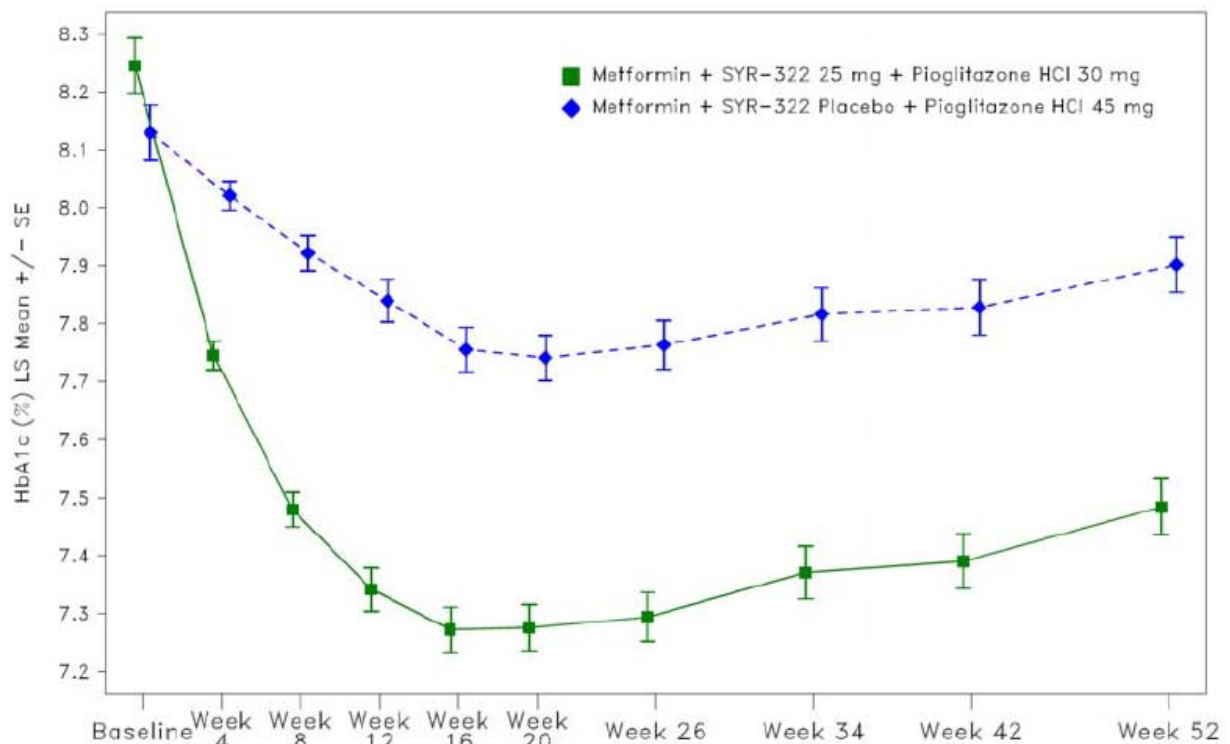
As shown in Table 2, in patients already on metformin and pioglitazone 30 mg, the addition of alogliptin 25 mg is statistically superior to the uptitration of pioglitazone from 30 mg to 45 mg at both Weeks 26 and 52 ($p < 0.0001$ at both timepoints). Dr. Derr notes that these results do not appear to be appreciably affected by gender, age group (< 65 vs. ≥ 65 years old), race, ethnicity, or geographical region.

Table 2. HbA1c change from baseline for Study OPI-004 (Adapted from Table 9 in Dr. Janice Derr’s biostatistics review)				
Treatment Group	n	Baseline mean	LS mean change	Treatment difference LS mean change (95% CI); p-value
Week 26 (intent-to-treat with last-observation-carried-forward)				
Alogliptin	397	8.2	-0.9	-0.5 (-0.62, -0.4); p<0.0001
Uptitrated pioglitazone	394	8.1	-0.4	
Week 52 (intent-to-treat with last-observation-carried-forward)				
Alogliptin	397	8.2	-0.7	-0.4 (-0.5, -0.3); p<00001
Uptitrated pioglitazone	394	8.1	-0.3	
CI = confidence interval				

As shown in Figure 3, the greatest mean reduction in HbA1c in both treatment arms occurred around Weeks 16-20 with slight loss of efficacy in both groups thereafter (although the curves for the two treatment groups remain roughly parallel after Week 20).

The secondary endpoints support the primary efficacy results. For example, the percentage of patients achieving HbA1c $< 7\%$ (intent-to-treat with last-observation-carried-forward for imputation) was 40% for alogliptin vs. 26% for uptitrated pioglitazone at Week 26 ($p < 0.001$) and 34% for alogliptin vs. 22% for uptitrated pioglitazone at Week 52 ($p < 0.001$). In addition, from a mean baseline fasting plasma glucose of 162 mg/dL, the LS mean treatment difference at Week 26 was -12 mg/dL (95% confidence interval -17, -7) and the LS mean treatment difference at Week 52 was -11 mg/dL (95% confidence interval -16, -6), with both treatment differences statistically significant ($p < 0.001$) and in favor of alogliptin.

Figure 3. Study OPI-004- changes from baseline in HbA1c over time (per-protocol population with last-observation-carried-forward)



Study 301: This was a double-blind study that randomized patients with type 2 diabetes and inadequate glycemic control to 16 weeks of treatment with alogliptin 25 mg, alogliptin 25 mg plus pioglitazone 30 mg, or placebo. Inclusion criteria included patients with a HbA1c of 6.5-9.0% who were treatment-naïve or who had been receiving at least 3 months of a stable dose of metformin, a sulfonylurea, or glinides. Patients immediately entered the randomized treatment period after screening without a run-in period.

Patients underwent a standardized meal after an 8-hour fast on Day 1 and Weeks 4 and 16. The primary endpoint was the change from baseline in postprandial incremental AUC for triglycerides at Week 16. Secondary endpoints included HbA1c, fasting plasma glucose, and postprandial changes over time in GLP-1, glucose, insulin, and glucagon. These endpoints were analyzed using the intent-to-treat dataset including patients who had a baseline assessment and at least one post-baseline assessment for the variable of interest with last-observation-carried-forward for missing data. All analyses were conducted at a nominal alpha of 0.05 with no adjustments for multiplicity.

Study 301 – Efficacy results: A total of 71 patients were randomized into the 3 treatment groups (25 to alogliptin, 22 to alogliptin+pioglitazone and 24 to placebo). All randomized patients except for one (who was in the alogliptin+pioglitazone arm) completed the study.

The sponsor is proposing to add the postprandial glucagon-like peptide (GLP)-1, postprandial glucagon and 2-hour postprandial glucose data from this study to the Pharmacodynamics section of the alogliptin and alogliptin/pioglitazone FDC labels. Therefore, I focus mostly on these results here.

Table 3 shows the findings for HbA1c, fasting plasma glucose and 2-hour postprandial glucose. Note that the change from baseline at Week 16 for 2-hour postprandial glucose is not due entirely to a reduction in the excursion of postprandial glucose following the meal. Instead, these results mostly reflect the fact that patients in the alogliptin and alogliptin+pioglitazone groups had lower fasting plasma glucose than placebo at the start of the standardized meal at Week 16. Labeling the descriptive results for the 2-hour postprandial glucose data in the Pharmacodynamics section is acceptable (there are no such data labeled for the phase 3 trials) but the contribution of the changes in fasting plasma glucose to the 2-hour postprandial data should be labeled, as well.

Table 3. HbA1c, fasting plasma glucose, and 2-hour postprandial glucose for Study 301 (intent-to-treat with last-observation-carried-forward)				
Treatment Group	n	Baseline mean	LS mean change	Treatment difference vs. placebo LS mean change (95% CI); p-value
HbA1c (%)				
Alogliptin	25	6.8	-0.4	-0.8 (-1.1, -0.4); p<0.001
Alogliptin+pioglitazone	22	6.6	-0.9	-1.3 (-1.7, -0.9); p<0.001
Placebo	24	6.6	0.4	
Fasting plasma glucose (mg/dL)				
Alogliptin	25	168	-17	-29 (-47, -11); p=0.002
Alogliptin+pioglitazone	22	154	-38	-50 (-69, -31); p<0.001
Placebo	24	161	12	
2-hour postprandial glucose (mg/dL)				
Alogliptin	25	220	-30	-47 (-71, -23); p<0.001
Alogliptin+pioglitazone	21	219	-62	-79 (-104, -54); p<0.001
Placebo	23	209	17	
CI = confidence interval LS mean treatment differences derived from an ANCOVA model with treatment and statin use as fixed effects along with baseline value as a covariate. p-values not adjusted for multiplicity.				

Figures 4, 5 and 6 graphically show postprandial GLP-1 and glucagon at baseline and Week 16 for each of the treatment groups (SYR-322 = alogliptin). Alogliptin increases postprandial “active” GLP-1 concentrations from baseline at Week 16 (Figure 5) but does not have an apparent effect on postprandial “total” GLP-1 concentrations (Figure 4). The study report does not provide details on the assays used for measuring GLP-1 and glucagon and does not explain the difference between total and active GLP-1 concentrations. It also appears that co-administration of alogliptin and pioglitazone leads to less beneficial effects on postprandial active GLP-1 than administration of alogliptin alone. These issues will need to be addressed before deciding on the acceptability of labeling these descriptive results.

Figure 4. Total postprandial GLP-1 concentrations at baseline (left) and Week 16 (right) [SYR322=alogliptin]

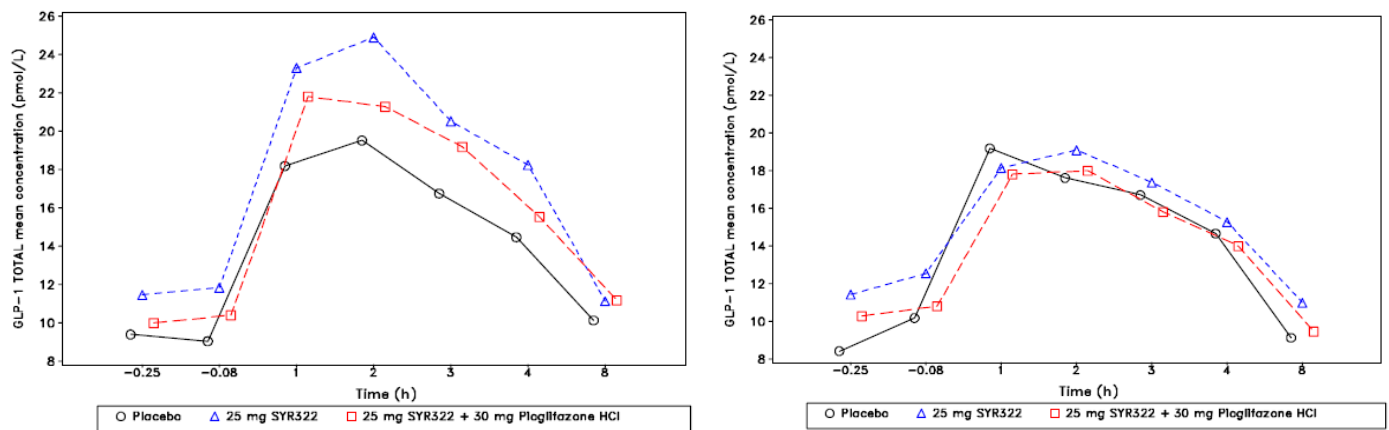


Figure 5. Postprandial active GLP-1 concentrations at baseline (left) and Week 16 (right)

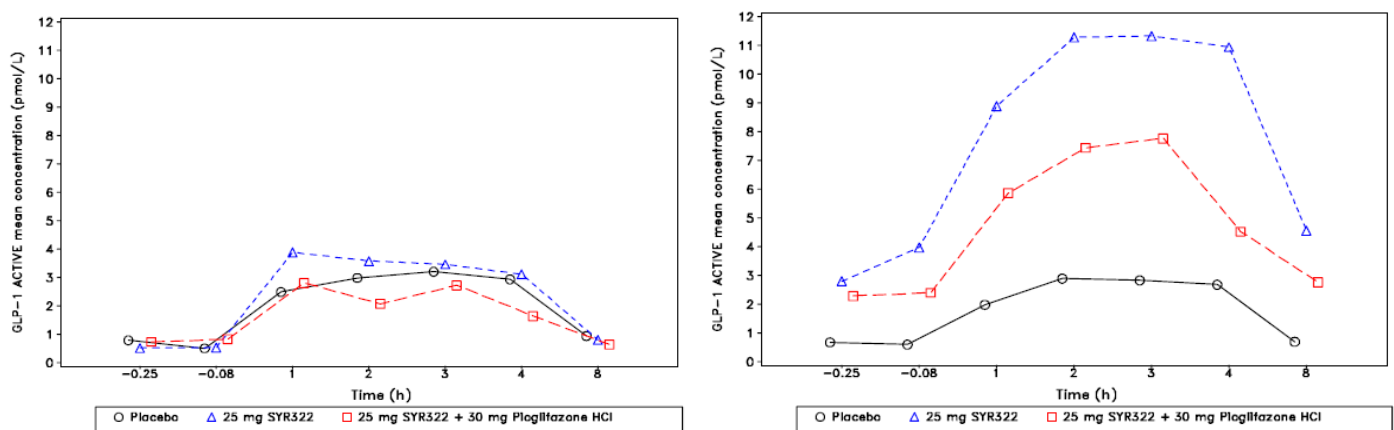
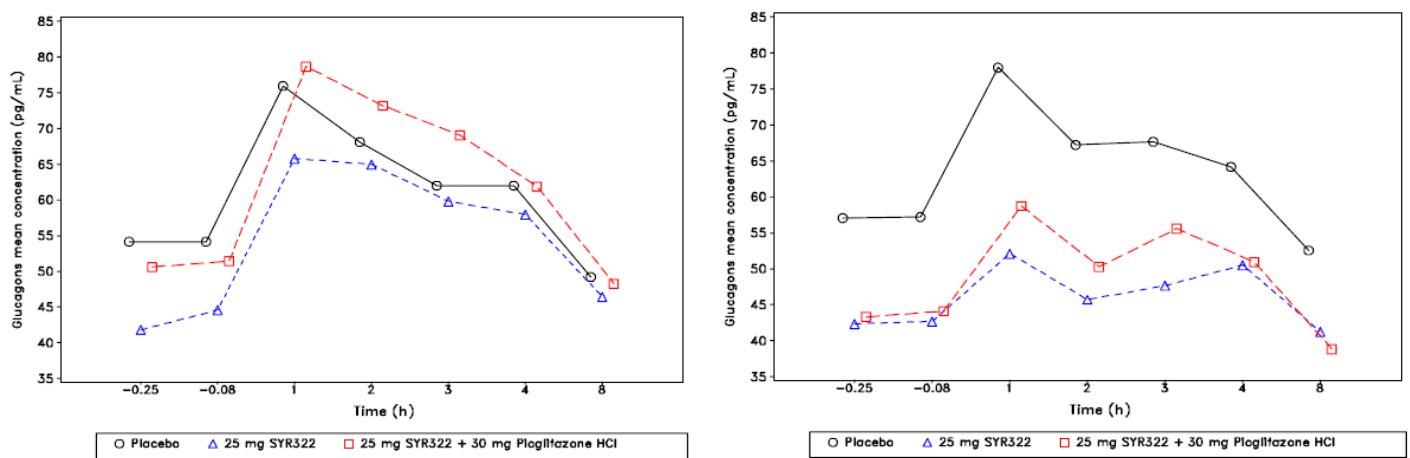


Figure 6. Postprandial glucagon at baseline (left) and Week 16 (right)



8. Safety

For most of the safety analyses, I focus on the controlled global phase 2/3 database, which consists of pooled data from 12 phase 2/3 trials. This pooled database includes the four phase 2/3 studies included in the resubmissions (Study OPI-004, 301, 303, and the ongoing cardiovascular outcomes trial, Study 402) as well as the following studies from the original NDAs. Note that the phase 2/3 supportive Japanese studies are not included in this pool.

- The 12-week placebo-controlled phase 2 dose-ranging study testing alogliptin doses from 6.25 mg to 100 mg daily (Study 003)
- The 26-week trials comparing alogliptin 12.5 mg and 25 mg to placebo as monotherapy (010), add-on to glyburide (007), add-on to metformin (008), add-on to pioglitazone (009), and add-on to insulin (011)
- The 26-week factorial 12-arm trial comparing alogliptin+pioglitazone, alogliptin alone, pioglitazone alone, and placebo as add-on therapy in patients with inadequate glycemic control on metformin (OPI-001). This study tested two doses of alogliptin (12.5 mg and 25 mg) and three doses of pioglitazone (15 mg, 30 mg, and 45 mg) alone and in combination.
- The 26-week trial comparing alogliptin 12.5 mg+pioglitazone 30 mg, alogliptin 25 mg+pioglitazone 30 mg, alogliptin 25 mg alone, and pioglitazone 30 mg alone in treatment-naïve patients (OPI-002)

I also discuss major findings from the ongoing four-year, open-label Study 012 (a non-controlled extension to the 26-week trials listed above, which has 9,024 patient-years of exposure), the controlled phase 2/3 trials conducted exclusively in Japan to support marketing there and the Japanese postmarketing data.

The controlled global phase 2/3 database consists of 5,232 patients exposed to any dose of alogliptin (6.25 mg to 100 mg), 3,500 patients exposed to alogliptin 25 mg (the dose the sponsor is proposing for patients with normal renal function or mild renal impairment), and 2,934 patients exposed to comparator (placebo, glipizide, or pioglitazone).

A total of 3,578 patients were exposed to alogliptin 12.5 mg or 25 mg for ≥ 6 months (2,331 of whom were exposed to alogliptin 25 mg for ≥ 6 months). At the End-of-Review meeting, we agreed that the sponsor can define 1-year of exposure as ≥ 335 days given that the cardiovascular outcomes study has a permitted ± 30 -day window for the one-year clinic visit. A total of 526 patients were exposed to alogliptin (all of whom received 25 mg) for ≥ 335 days, 496 of whom were exposed for ≥ 360 days and 265 of whom were exposed for ≥ 365 days.

As mentioned previously, there is an estimated 219,000 patient-years of exposure to alogliptin in the Japanese postmarketing setting as of February 2012.

Deaths: At the time of database lock, there were a total of 45 deaths in the controlled global phase 2/3 database. Thirty-six of these deaths were treatment-emergent (occurred ≤ 14 days after the last dose of study medication). Of these 36 deaths, 17 occurred in alogliptin-treated patients (0.3%; 0.7 per 100 patient-years) and 19 occurred among comparators (0.6%; 1.3 per 100 patient-years).

After excluding the deaths from Study 402, there are only seven deaths in the remaining controlled global phase 2/3 database (6/4168 or 0.14% for alogliptin vs. 1/1860 or 0.05% for comparator). Of these seven deaths, five occurred in patients randomized to alogliptin (myocardial infarction [n=2], sudden death, hypertensive heart disease, and myelofibrosis with secondary leukemia), one occurred in a patient randomized to alogliptin+pioglitazone (myocardial infarction) and one occurred in a patient randomized to pioglitazone (sudden cardiac death). However, two of the 5 deaths in the alogliptin group were not treatment-emergent – one of these patients died of a myocardial infarction after cholecystectomy 19 days after the last dose of alogliptin and the other died of myelofibrosis and secondary leukemia about 3 months after the last dose of alogliptin (she received alogliptin for <5 months, a short duration that makes a relationship to alogliptin unlikely). If these two patients are excluded, the incidence of treatment-emergent death in the global phase 2/3 database (excluding Study 402) is 0.096% for alogliptin (4/4168) vs. 0.054% for comparator (1/1860).

There were 38 deaths in Study 402 at the time of database lock (15 or 1.4% for alogliptin and 23 or 2.1% for placebo). Of these deaths, 22 (11 on alogliptin and 11 on placebo) were adjudicated as cardiovascular death. The remaining 4 deaths in the alogliptin group that were not adjudicated as cardiovascular were sepsis (n=2; one event due to bilateral pneumonia and another event due to mediastinitis after cardiac bypass surgery) and sudden death (n=2). One event of sudden death occurred about one week after being diagnosed with statin-induced rhabdomyolysis and renal failure. The other event was unwitnessed and no autopsy was performed.

As of the cutoff date for the resubmission, there have also been seven deaths in the completed phase 2/3 Japanese trials, 6/1098 (0.55%) occurring with alogliptin and 1/551 (0.18%) occurring in a comparator-treated patient. The six alogliptin deaths were myocardial infarction, sudden death, starvation, gas gangrene, lung cancer, and intraoperative hemorrhage during attempted left hepatic lobectomy for hepatocellular carcinoma (tumor identified 65 days after the last dose of study medication in a patient who was hepatitis C positive).

As of the cutoff date for the resubmission, there have also been 41 deaths in uncontrolled Study 012. One death was due to pancreatitis and is described in the pancreatitis section of this memorandum. About 45% (n=18) of these deaths were due to cardiovascular causes (e.g., myocardial infarction, sudden death, stroke). These deaths do not raise a safety concern, particularly given the lack of a control group, the high background rate of cardiovascular disease in this population and the Major Adverse Cardiovascular Event (MACE) results described in the Adverse Events of Interest section of this memorandum. Other causes of death reported in more than one patient included lung cancer (n=3), pneumonia (n=3) and leukemia (one case of acute and another of chronic lymphocytic leukemia).

In the Periodic Safety Update Reports completed to date (through the cut-off date of October 15, 2011), there have been five reported deaths temporally associated with alogliptin (a postmarketing fatal case of necrotizing pancreatitis that is discussed in the Pancreatitis Section of this memorandum and four deaths in ongoing studies – hepatocellular carcinoma, brain

tumor, pulmonary edema, and possible myocardial infarction/exacerbation of chronic obstructive pulmonary disease).

In summary, the data on deaths do not raise a unique safety concern for alogliptin.

Serious Adverse Events: In the controlled global phase 2/3 database, 5.8% of alogliptin-treated patients and 8.9% of comparator-treated patients reported at least one serious adverse event.

Pancreatitis was reported as a serious adverse event in 4/5232 (0.08%) alogliptin-treated patients and 1/2934 (0.03%) comparator-treated patient. A fifth patient randomized to alogliptin reported a serious adverse event of pancreatitis but this event occurred on Day 1, prior to the first dose of alogliptin and is, therefore, not treatment-emergent.

Hypoglycemia was reported as a serious adverse event in 6/5232 (0.1%) alogliptin-treated patients and 2/2934 (0.1%) comparator-treated patients.

There was one serious adverse event that coded to hypersensitivity and another that coded to serum sickness, both of which occurred in alogliptin-treated patients. The case of serum sickness was noted in the original NDA and is summarized by Dr. Pratt. The hypersensitivity case is discussed below in the Adverse Events of Interest Section.

Of note, there were no serious adverse events suggestive of hepatotoxicity.

The remaining preferred terms are well-balanced between treatment groups or occur in few patients and do not raise a particular safety concern.

In the Japanese controlled phase 2/3 trials, there is one report of a serious adverse event of pancreatitis and another of drug hypersensitivity. The other serious adverse events in the Japanese database occur in few patients and do not raise particular safety concerns. The patient with drug hypersensitivity was reported to develop generalized edema and nausea after taking alogliptin for about five months. One day prior to the onset of the symptoms she had started several medications to treat an upper respiratory tract infection. These medications and alogliptin were discontinued, the patient was hospitalized for a possible drug hypersensitivity reaction, and treatment with furosemide and an H₂-receptor blocker was initiated. The patient was not taking an ACE inhibitor or angiotensin receptor blocker. The narrative mentions that the edema and nausea persisted for more than two weeks after study medication was discontinued. The available information does not conclusively support a hypersensitivity reaction to alogliptin.

Serious adverse events of note in uncontrolled Study 012 include pancreatitis relapsing (n=1), pancreatitis (n=9), rhabdomyolysis (n=1), angioedema (n=3), allergic edema (n=1) and loss of consciousness/urticaria (n=1). These events are discussed under the Adverse Events of Interest section, except for the case of rhabdomyolysis, which is summarized below.

012/369-7020: This 49 year-old woman received alogliptin 25 mg for six months then entered Study 012 where she received alogliptin 12.5 mg. About 16 months after starting Study 012 (22 months after starting alogliptin), she presented with myalgia, muscle weakness, nausea and vomiting and was reported to have rhabdomyolysis with a creatine phosphokinase of 6530 U/L, acute renal failure, hyperkalemia, and metabolic acidosis. She underwent hemodialysis over a three week period. There was no statin use but the patient had been taking bezafibrate for 221 days, which has been reported to cause rhabdomyolysis and was discontinued at the time of the event. There were no other reported risk factors for rhabdomyolysis. A search using the text “rhabdo” in the controlled global phase 2/3 database identified another case in an alogliptin-treated patient. This case was diagnosed five days after starting alogliptin in Study 402 but the patient had been started on simvastatin less than two months prior to the event and the creatine phosphokinase was reported to already be elevated before alogliptin was started. A search of the three available Periodic Safety Update Reports using the text “rhabdo” identified only one other case of rhabdomyolysis but the patient is reported to be recovering despite continuing the alogliptin.

In the first three Periodic Safety Update Reports submitted thus far, there have been a total of 27 serious unlisted adverse events reported in the Japanese postmarketing setting, including one case of red blood cell aplasia (red blood cell aplasia has been reported with erythropoietin, which the patient was concurrently receiving), six cases of pancreatitis (one of which was necrotizing pancreatitis), one case of acute hepatitis, two cases of liver disorder, three cases of erythema multiforme, and two cases of Stevens-Johnson Syndrome. The pancreatitis, liver, and skin reports are discussed in the Adverse Events of Interest section.

Withdrawals due to Adverse Events: In the controlled global phase 2/3 database, 2.5% of alogliptin-treated patients and 3.0% of comparator-treated patients discontinued due to an adverse event.

A total of 6/5232 (0.11%) alogliptin-treated patients and 2/2934 (0.07%) comparator-treated patients discontinued due to liver function test abnormal, alanine aminotransferase increased, or hepatic enzyme increased. See the Hepatotoxicity section of this memorandum.

One alogliptin-treated patient and no comparator-treated patients discontinued due to pancreatitis. See the Pancreatitis section of this memorandum.

Other adverse events of interest leading to discontinuation included hypoglycemia (1 alogliptin-treated patient vs. 8 comparator-treated patients) and various skin adverse events, including dermatitis (2 with alogliptin vs. 0 with comparator), drug eruption (2 with alogliptin vs. 0 with comparator), rash (2 with alogliptin vs. 2 with comparator), rash papular (2 with alogliptin vs. 0 with comparator), rash pruritic (2 with alogliptin vs. 0 with comparator), rash generalized (1 with alogliptin vs. 0 with comparator), rash maculopapular (1 with alogliptin vs. 0 with comparator), and urticaria (1 with alogliptin vs. 1 with comparator). Also see the Hypoglycemia and Severe Cutaneous Adverse Reactions section of this memorandum.

The remaining preferred terms were well-balanced between treatment groups or occurred in few patients and do not raise a particular safety concern.

In the Japanese phase 2/3 trials, there were isolated alogliptin-treated patients who discontinued due to drug hypersensitivity (see narrative under Serious Adverse Events) as well as non-serious events of rash, toxic skin eruption (Day 102) and face edema (Day 236). There is inadequate information for these non-serious events to exclude relatedness to alogliptin.

Common Adverse Events: Common adverse events for most of the alogliptin trials are discussed in reviews from the original NDAs. Here I show the overall profile of common adverse events in the controlled global phase 2/3 dataset and also show the common adverse events separately for the two newly completed phase 3 trials (the study comparing alogliptin to glipizide in the elderly and the study comparing addition of alogliptin to pioglitazone 30 mg vs. uptitration of pioglitazone to 45 mg) (Table 4).

In the pooled phase 2/3 placebo-controlled trials in the original NDA, the percentage of patients who reported at least one adverse event was 64% for alogliptin-treated patients and 65% for placebo-treated patients. The following common adverse events (incidence $\geq 3\%$ with alogliptin) occurred at a numerically greater incidence with alogliptin than with placebo: edema peripheral (3.0% vs. 2.6%), headache (4.4% vs. 3.9%), and hypertension (3.1% vs. 3.0%).

In the pooled controlled global phase 2/3 database in the resubmission, the percentage of patients who reported at least one adverse event was 60% for alogliptin-treated patients and 56% for comparator-treated patients. The following adverse events (incidence $\geq 3\%$ with alogliptin) occurred at a numerically greater incidence with alogliptin than with comparator: nasopharyngitis (4.1% vs. 3.3%), upper respiratory tract infection (3.4% vs. 2.4%), urinary tract infection (4.1% vs. 3.7%), headache (4.1% vs. 3.5%), and hypertension (3.0% vs. 2.9%).

As shown in Tables 5 and 6, the overall profile of common adverse events reported with alogliptin in the two newly completed trials is consistent with the overall findings in the pooled phase 2/3 database.

Table 4. Common adverse events (incidence $\geq 5\%$ in the alogliptin group) in the elderly study comparing alogliptin to glipizide		
	Alogliptin N=222 n (%)	Glipizide N=219 n (%)
At least one adverse event	163 (73)	151 (69)
Urinary tract infection	26 (12)	23 (11)
Headache	16 (7.2)	15 (6.8)
Dizziness	13 (5.9)	19 (8.7)
Nasopharyngitis	13 (5.9)	10 (4.6)
Hypertension	12 (5.4)	10 (4.6)
Upper respiratory tract infection	12 (5.4)	5 (2.3)

Table 5. Common adverse events (incidence $\geq 5\%$ in the alogliptin group) in the study comparing alogliptin add-on to uptitration of pioglitazone		
	Alogliptin + pioglitazone +metformin N=404 n (%)	Uptitrated pioglitazone to 45 mg + metformin N=399 n (%)
At least one adverse event	289 (72)	275 (69)
Upper respiratory tract infection	29 (7.2)	16 (4.0)
Hypertension	24 (5.9)	22 (5.5)
Urinary tract infection	22 (5.4)	13 (3.3)

Other Adverse Events:

Based on a report of drug-induced interstitial pneumonia occurring after four months of treatment with alogliptin in ongoing Study 402, the sponsor queried their entire clinical trial and postmarketing database on March 15, 2012, for other cases of interstitial lung disease. The sponsor identified 12 potential cases using the Interstitial Lung Disease Standardised MedDRA Query (SMQ). The two cases reported in completed randomized clinical trials occurred in placebo-treated patients. Four cases have occurred in ongoing randomized blinded clinical studies. Five cases occurred in the Japanese postmarketing setting among the ~219,000 patient-years of exposure. The remaining case occurred in an ongoing open-label study. Few details are provided for these cases. Because I am recommending a Complete Response (see Section 13), I recommend that our Complete Response letter include a request for the sponsor to provide an updated, comprehensive analysis of interstitial lung disease events in the resubmission.

Adverse Events of Interest:

Major Adverse Cardiovascular Events (MACE): As discussed in the introductory section of this memorandum, a major deficiency of the original NDA was that the sponsor did not rule out an unacceptable increase in cardiovascular events with alogliptin. To address this deficiency, the sponsor has submitted interim data from an ongoing cardiovascular outcomes trial (Study 402, also known as EXAMINE) to meet the 1.8 non-inferiority margin recommended in the 2008 diabetes cardiovascular guidance. The trial design was thoroughly reviewed by FDA with input from internal cardiologists. See Dr. Pratt's clinical review and the statistical review by Dr. Eugenio Andraca-Carrera for further details. I agree with Drs. Pratt and Andraca-Carrera that the sponsor has adequately met the 1.8 criterion recommended in the diabetes cardiovascular guidance.

Briefly, Study 402 is a randomized, double-blind trial comparing alogliptin to placebo as add-on to standard of care therapy. The alogliptin dose is 25 mg for patients with normal renal function or mild renal impairment ($\text{eGFR} \geq 60 \text{ mL/min}$), 12.5 mg for patients with moderate renal impairment ($\text{eGFR} \geq 30$ to $<60 \text{ mL/min}$), and 6.25 mg for patients with severe renal impairment ($\text{eGFR} <30 \text{ mL/min}$), as assessed by the Modification of Diet in Renal Disease (MDRD) formula at screening. Alogliptin dosage adjustment occurs during the study if renal

function deteriorates. Investigators are encouraged to manage blood glucose and cardiovascular risk factors to regional standards of care.


Study 402 has no exclusion criteria related to liver tests. With regard to liver monitoring, study medication is to be interrupted if the serum ALT or AST is ≥ 3 x ULN with total bilirubin > 2 x ULN or if the serum ALT or AST is > 8 x ULN. Study medication is to be discontinued if the patient is experiencing symptoms or if these abnormal liver tests are confirmed on repeat testing within seven days. Patients are also to be discontinued if the serum ALT or AST is > 5 x ULN for more than two weeks or the serum ALT or AST is ≥ 3 x ULN with symptoms consistent with liver injury.

A total of 5,400 patients are to be randomized (2,134 patients have been randomized to double-blind treatment as of the April 29, 2011, cutoff date for the interim analysis). Inclusion criteria include patients with type 2 diabetes on at least one anti-diabetic medication (except for a DPP-4 inhibitor or GLP-1 agonist) who have had an acute coronary syndrome (myocardial infarction or unstable angina requiring hospitalization) within 15-90 days prior to randomization. Baseline HbA1c must be 6.5%-11% (7%-11% for patients on insulin).

During the protocol review, we expressed concern that randomization as early as 15 days after the acute coronary syndrome event could potentially make it easier for the trial to show non-inferiority when in fact there are differences between treatment groups. This is a potential concern because enrollment of very high risk patients may lead to a large number of recurrent events soon after randomization in both treatment groups that are independent of assigned treatment. Takeda acknowledged our concern and accepted the risk of their approach.

The primary endpoint is the time from randomization to the first occurrence of any event in the primary MACE composite (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) analyzed using a Cox proportional hazards ratio. The secondary endpoint is the time to occurrence of expanded MACE (MACE as defined above plus urgent revascularization due to unstable angina).

Interim analyses to meet 1.8 were to be conducted when 80, 100, 125 and 150 adjudicated primary MACE events had been accrued. The sponsor determined that the first interim analysis satisfied the 1.8 criterion and has submitted the results for our review. Therefore, as per the protocol, no additional interim analyses for 1.8 will be performed. The study will be continued until 550 adjudicated MACE events have occurred then the sponsor will attempt to meet the 1.3 criterion. If the 1.3 criterion is not met with these 550 events, the sponsor has two remaining opportunities to try to meet 1.3, one at 600 events and another at 650 events. The sponsor has appropriately controlled the overall type I error rate for all the analyses being conducted to meet 1.8 and 1.3. Assuming a placebo annual MACE rate of 3.5%, an annual loss to follow-up of 1%, and a true hazard ratio of 1.0%, the sponsor estimates that the design will have 90% power to meet 1.3 over an expected trial duration of 4.25 years. (b) (4)



Patients are to be followed until the study is complete even after experiencing a non-fatal MACE event or after discontinuing study medication.

The study has a Data Monitoring Committee that oversees the accruing safety data, an independent Cardiovascular Endpoints Committee (CEC) that blindly adjudicates suspected MACE events and an independent team that performs unblinded interim analyses.

Potential events for adjudication are identified in one of three ways: by the investigator, by a screen of reported adverse events against a pre-specified list of preferred terms (we provided input on this pre-specified list with assistance from Dr. Karen Hicks, a cardiologist in the Division of Cardio-Renal products), or by identification of additional events during the adjudication process.

Adjudication of events in the primary and secondary MACE composites is being conducted at the (b) (4). Phase I review is independently and blindly conducted by two cardiology fellows who have completed at least the first year of cardiology fellowship (for cardiac events) and by two board-certified neurologists (for neurological events). If there is agreement at Phase I then the adjudication process for that event is considered complete. If there is disagreement between the two Phase I reviewers then a Phase II review is conducted by the CEC Medical Director (a cardiologist) for cardiac events or by a senior neurologist for neurological events. The decision of the Phase II reviewer is final and supercedes any prior Phase I decisions.

Up to the April 2011 cutoff date, 1,058 patients have been randomized to alogliptin and 1,076 have been randomized to placebo in Study 402. Most patients (70%) are men. The mean age is 61 years (about one-third of patients are >65 years of age) and about 38% have had diabetes for >10 years. Most patients are Caucasian (67%) or Asian (24%). About 17% have been enrolled from North American sites. Most patients have mild (60% for alogliptin; 55% for placebo) or moderate (27% for alogliptin; 30% for placebo) renal impairment. Most patients (~72%) were randomized >30 days after the index acute coronary event.

Most patients have significant cardiovascular histories, including myocardial infarction (86% for alogliptin vs. 84% for placebo), percutaneous coronary intervention (55% for alogliptin vs. 58% for placebo), unstable angina requiring hospitalization (35% for alogliptin vs. 36% for placebo and congestive heart failure (24% in both treatment groups).

The median duration of exposure to study medication in Study 402 up to the cutoff date has been 4.7 months (25th-75th percentile: 2.4-8.0 months). Approximately 100 patients in both treatment groups have ≥335 days of exposure to study medication. A total of 62 (5.9%) alogliptin-treated patients and 65 (6.0%) placebo-treated patients have prematurely discontinued. Loss to follow-up has been low (0.3% for alogliptin and 0.4% for placebo).

The mean baseline HbA1c thus far is 8.0% in both treatment groups. The LS mean change from baseline in HbA1c to the last available visit is -0.6% (n=943) for alogliptin and -0.2% (n=940) for placebo (LS mean treatment difference -0.4% with 95% confidence interval -0.5, -0.3; p<0.001). The sponsor did not provide on-treatment data for blood pressure or lipid parameters. However, in the pooled global phase 2/3 database (which includes Study 402), there were no meaningful effects of alogliptin on systolic or diastolic blood pressure relative to comparator.

(b) (4)

Figure 7. Time to MACE in Study 402 (Figure 5 in Dr. Andraca-Carrera's review)

(b) (4)

(b) (4)

Hepatotoxicity: During our review of the NDA resubmissions, we identified a postmarketing report of Hy's Law from Japan. We also noted numerical imbalances in the incidence of serum ALT elevations not favoring alogliptin in the controlled phase 2/3 trials, and particularly for Study 402. Based on these data we requested that the sponsor conduct a comprehensive search of liver-related events in the alogliptin global clinical trial and postmarketing database. We classified the sponsor's response, which was received within three months of the action goal date, as a major amendment and extended the action goal date by three months to April 25, 2012.

We have received several follow-up submissions from the sponsor pertaining to liver-related events, including reports from the sponsor's two external consultants who reviewed the liver cases of interest (Dr. (b) (4) at (b) (4), conducted an unblinded review whereas Dr. (b) (4) conducted a blinded review). We consulted Dr. Leonard Seeff, a hepatologist in the Office of Surveillance and Epidemiology (OSE), to conduct an unblinded review of the most concerning liver cases reported with alogliptin. Dr. Seeff has experience adjudicating events of drug-induced liver injury in his capacity working at the National Institutes of Health (NIH). He is a co-author of the publication describing the grading system for likelihood of attribution and liver disease severity developed by the NIH's Drug-Induced Liver Injury Network (DILIN) Study Group (Fontana RJ, Seeff LB, Andrade RJ, et al. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. *Hepatology* 2010; 52: 73-742). This grading system is shown in Table 8 and was used by Dr. Seeff as well as by Drs. (b) (4).

Table 8. Likelihood of Drug-Induced Liver Injury
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Fontana RJ, Seeff LB, Andrade RJ, et al. *Hepatology* 2010; 52: 73-742

The sponsor used the Hepatic Disorders Standardised MedDRA Query as well as biochemical Hy's Law criteria (ALT ≥ 3 x ULN and total bilirubin > 2 x ULN) to search the alogliptin clinical trial and postmarketing database for liver-related adverse events. This strategy yielded 17 serious liver-related events in the clinical trial database (12 with alogliptin and 5 with comparator), 28 postmarketing liver-related cases, and 8 cases of biochemical Hy's Law among alogliptin-treated patients (4 cases in the clinical database and 4 cases in the postmarketing setting).

After we received the comprehensive liver analyses, Takeda submitted expedited reports for six subsequent postmarketing cases of liver injury in alogliptin-treated patients (TCI2011A06369, TCI2011A06481, TCI2011A06837, TCI2011A06892, and TCI2011A06333, TCI2012A01179). Cases 6481, 6837, 6892 and 1179 were also forwarded to Dr. Seeff for review. Case 6333 was not forwarded to Dr. Seeff as it did not have concerning features. Specifically, this 61 year-old man with a normal serum ALT at baseline was found to have a serum ALT of only 65 U/L (2.2x ULN) about two months after starting alogliptin, which was discontinued the next day. Follow-up serum ALT one month later was again normal.

Case 6369 involves a 77 year-old man with normal serum ALT at baseline who received alogliptin for about four months then presented with acute onset of inability to perform activities of daily living. He was found to have pancytopenia, serum LDL-cholesterol and HDL-cholesterol <10 mg/dL, serum ALT of 103 U/L (2.3x ULN) and normal total bilirubin. About two weeks earlier the serum ALT had been 174 U/L. Alogliptin was discontinued. He died within a few weeks from sepsis attributed to the pancytopenia. The available information is very limited but the unusual features (e.g., pancytopenia) suggest that this is not alogliptin hepatotoxicity. As of April 4, 2012, the sponsor has not been able to obtain additional information for this case. This case was not forwarded to Dr. Seeff given the scant information in the narrative and the conclusions by both Drs. (b) (4) that there is insufficient information to determine relatedness to alogliptin.

Serum ALT Elevations in the Controlled Alogliptin Clinical Trials

There were no liver test exclusion criteria for Study 402. For the other global phase 2/3 trials, patients were excluded if the serum ALT was >2x ULN (dose-finding Study 003), >2.5x ULN (the two add-on to pioglitazone trials) or >3x ULN (the remaining phase 3 trials). Table 9 shows an analysis of serum ALT elevations in the completed phase 2/3 double-blind trials (including the Japanese trials) as well as updated data from Study 402 (as of September 11, 2011). The alogliptin 25 mg dose group and the all alogliptin dose group had a numerically greater proportion of patients (0.4-0.5%) with serum ALT >3x ULN at baseline vs. all comparators (0.2%). However, the incidence of more extreme ALT elevations at baseline were better balanced between treatment groups ($\leq 0.1\%$). In contrast, there are numerical imbalances post-baseline not favoring the alogliptin 25 mg dose group and the all alogliptin dose group for serum ALT elevations >5x, >8x, >10x, and >20x ULN vs. comparator, regardless of whether the data are analyzed using percentages or adjusted for patient-year exposure. For example, six patients treated with alogliptin 25 mg developed serum ALT >10x ULN compared to no comparator-treated patients despite similar sample sizes (N=4680 for alogliptin 25 mg vs. N=4074 for all comparators).

**Table 9. Patients with at least one markedly elevated serum ALT elevation
(All completed controlled phase 2/3 trials and the ongoing cardiovascular outcomes trial)**

ALT	Baseline			During Treatment		
	Alogliptin 25 mg N=4829 n (%)	All* Alogliptin N=7187 n (%)	All Comparators N=4215 n (%)	Alogliptin 25 mg N=4680 n (%) [n/100 PY]	All* Alogliptin N=7011 n (%) [n/100 PY]	All Comparators N=4074 n (%) [n/100 PY]
>3x ULN	23 (0.5%)	30 (0.4%)	10 (0.2%)	52 (1.1%) [2.1]	71 (1.0%) [2.1]	39 (1.0%) [1.8]
>5x ULN	4 (0.1%)	6 (0.1%)	2 (<0.1%)	17 (0.4%) [0.7]	21 (0.3%) [0.6]	6 (0.1%) [0.3]
>8x ULN	3 (0.1%)	3 (<0.1%)	2 (<0.1%)	9 (0.2%) [0.4]	11 (0.2%) [0.3]	1 (<0.1%) [0.0]
>10x ULN	3 (0.1%)	3 (<0.1%)	2 (<0.1%)	6 (0.1%) [0.2]	8 (0.1%) [0.2]	0
>20x ULN	0	0	0	1 (<0.1%) [0.0]	2 (<0.1%) [0.1]	0

PY=patient-year; number in brackets = number of patients with the marked abnormality per 100 patient-years
*All alogliptin includes 6.25, 12.5, 50, and 100 mg dose groups.

A total of eight alogliptin-treated patients (and no comparator-treated patients) developed serum ALT >10x ULN in the entire controlled phase 2/3 database (including the Japanese studies and ongoing Study 402). These cases are summarized below (at the end of all the liver narratives, I show the adjudication conclusions for Drs. (b) (4) and Seeff). Note that even though this numerical imbalance exists, Dr. Seeff determined that six of these eight cases do not represent alogliptin hepatotoxicity. Of the remaining two cases, Dr. Seeff concluded that one may be possible alogliptin hepatotoxicity (although the serum ALT elevation appears to have resolved despite resuming alogliptin) and the last case appears to be hepatitis B (although the report is not entirely clear).

ALT >20x ULN:

OPI-002/831-2508: This 49 year-old man had minimally elevated serum aminotransferases at baseline (ALT 1.04x ULN, AST 1.1x ULN). His liver tests were essentially unchanged at Week 8 (Day 58). The narrative states that he was diagnosed with hepatitis B infection by serology on Day 64. He subsequently had markedly abnormal serum aminotransferases (ALT 689 U/L on Day 86 and 1771 U/L on Day 91, both with total bilirubin well within the reference range). Alogliptin was discontinued on Day 107 due to hepatitis B. His liver tests about one month after discontinuation had normalized. **Dr. (b) (4): unlikely; Dr. (b) (4): unrelated; Dr. Seeff: cause unclear (revised narrative requested).**

009/311-9003: This 49 year-old man had a baseline ALT of 66 U/L (2.6x ULN). On Day 32, his ALT was 646 U/L. The ALT was 46 U/L 10 days later. Serum bilirubin was normal throughout. Alogliptin was interrupted but the narrative does not state for how long. The patient voluntarily withdrew from the Study on Day 221. The investigator attributed the liver test abnormalities to alcohol although this seems unlikely as the serum ALT exceeded the AST elevation. The resolution of the serum ALT elevation and the fact that bilirubin remained normal despite resuming alogliptin is reassuring. **Dr. (b) (4): possible; Dr. (b) (4): unlikely; Dr. Seeff: possible.**

ALT >10x and ≤20x ULN:

009/307-9019: This 47 year-old man had normal serum aminotransferases but a borderline-high total bilirubin of 1.14 mg/dL (ULN = 1.10 mg/dL) at the beginning of the run-in period. On Day 1 his serum ALT was 430 U/L and his total bilirubin was 1.30 mg/dL. Alogliptin was discontinued on Day 8. Presumably the Day 1 measurements were obtained prior to the first dose of study medication although this is not explicitly stated in the narrative. Even if the liver tests were obtained after one dose of alogliptin was administered, the findings are unlikely to be related to alogliptin given the very short time course. **Dr. (b) (4): unlikely; Dr. (b) (4): unlikely; Dr. Seeff: definitely not alogliptin hepatotoxicity given that the abnormalities were noted on Day 1.**

402/8521-002: This 81 year-old woman was diagnosed with hepatitis C on Day 1 when her serum ALT was 349 U/L. Her serum ALT was 132 U/L at the screening visit. She was withdrawn from the study after 3 days of treatment due to the hepatitis C. **Dr. Seeff: chronic hepatitis C, not alogliptin hepatotoxicity.**

303/3128-003 – This 73 year-old man with a history of cholecystectomy had a baseline ALT of 144 U/L (5.8x ULN) with a normal total bilirubin. His ALT was 48 U/L on Day 6 (with normal total bilirubin and alkaline phosphatase) and 300 U/L on Day 15 (total bilirubin normal but alkaline phosphatase 3x ULN). On Day 20, his ALT was 181 U/L, his total bilirubin was 4.1 mg/dL (3.1x ULN), and his alkaline phosphatase was 318 U/L (2.8x ULN). Alogliptin was discontinued on Day 21. His serum ALT and total bilirubin were normal on Day 35. Of note, on Day 8 he reported several days of abdominal/epigastric pain with food ingestion. He was diagnosed with choledocholithiasis on clinical grounds although this diagnosis was not confirmed on magnetic resonance imaging (he was seen by a gastroenterologist who concluded that there may have been stone migration to the intestine). On Day 21, he had an abdominal ultrasound and the narrative only mentions the presence of chronic fatty liver disease. It appears that this presentation is most consistent with a biliary stone that has passed (these stones can form post-cholecystectomy). **Dr. (b) (4): unlikely; Dr. (b) (4): unlikely; Dr. Seeff: most likely a bile duct stone and not alogliptin hepatotoxicity.**

402/8260-010: This 58 year-old woman had normal liver tests at baseline and at Week 4. However, on Day 92 her ALT was 293 U/L (11.7x ULN) and the total bilirubin was 1.5x ULN. This event was associated with a serious adverse event of unstable angina reported on Day 91. Alogliptin was interrupted for 11 days. All remaining ALT, AST and total bilirubin concentrations while continuing alogliptin were normal. **Dr. (b) (4): unlikely; Dr. (b) (4): unlikely; Dr. Seeff: unlikely alogliptin hepatotoxicity, given the transient elevation.**

402/8070-002: This 60-year old man had hepatitis C and had elevated liver tests at baseline (ALT as high as 122 U/L or 4.9x ULN). The ALT peaked at 267 U/L (10.7x ULN) on Day 42. Alogliptin was discontinued on Day 47. ALT was 206 U/L on Day 97. By Day 292 the ALT was 133 U/L or 5.3x ULN, which is comparable to baseline values. Total bilirubin was normal at all times. Hepatitis C appears to be the most likely explanation for the abnormal liver tests

in this patient. Dr. (b) (4): unlikely; Dr. (b) (4): unrelated; Dr. Seeff: chronic hepatitis C, alogliptin hepatotoxicity unlikely.

OPI-001/395-3054: This 67-year old woman on alogliptin had an ALT of 26 U/L at baseline that increased to 257 U/L (10.3x ULN) on Day 112. Despite continuing alogliptin, the ALT was 27 U/L on Day 141 and 19 U/L on Day 183. Total bilirubin was normal at all times. Dr. (b) (4): unlikely; Dr. (b) (4): possible; Dr. Seeff: found the narrative to be confusing but stated that the resolution of liver test abnormalities while continuing alogliptin rules out alogliptin hepatotoxicity.

Biochemical Hy's Law Cases in the Alogliptin Clinical Trials

In the alogliptin clinical trial database, the sponsor identified four cases of biochemical Hy's Law (serum ALT >3x ULN and total bilirubin >2x ULN) among patients treated with alogliptin and four cases among comparator. Based on the available data, none of the four cases among alogliptin-treated patients appears particularly concerning.

303/3128-003: This case is described above. Dr. (b) (4): unlikely; Dr. (b) (4): unlikely; Dr. Seeff: most likely a bile duct stone and not alogliptin hepatotoxicity.

012/961-2501: This 66 year-old woman received alogliptin 25 mg for six months during Study OPI-002 then entered Study 012 and was randomized to continued treatment with alogliptin. Serum ALT was normal throughout Study OPI-002 and until Week 8 of Study 012. At Week 12 the ALT was 28 U/L. At Month 6 of Study 012 (1-year after starting alogliptin), the ALT was 360 U/L and total bilirubin was 1.7 mg/dL (the investigator reported "lab error" as the cause of these elevations). Nine days later the liver tests were normal and remained essentially normal until Month 39 when the ALT was 180 U/L and total bilirubin was 2.9 mg/dL. Follow-up liver tests obtained at Month 42, Month 45, and end-of-study were all normal. The patient reportedly had no symptoms of liver dysfunction and continued on alogliptin throughout. Dr. (b) (4): unlikely; Dr. (b) (4): unlikely; Dr. Seeff: poor narrative but does not appear to be a case of alogliptin hepatotoxicity.

012/961-3006: This 69 year-old woman with normal baseline serum ALT was found to have an ALT of 333 U/L and AST of 396 U/L on January 10, 2010, about two months after starting alogliptin. The narrative notes alcohol consumption during the holiday season. At Week 12 the liver tests had normalized but again became elevated around Week 26 (ALT 290 U/L and total bilirubin 2.35 mg/dL). The narrative states that the patient had pesticide exposure during the preceding week. Two weeks later the liver tests had normalized. ALT remained normal for the remainder of the trial except for intermittent mild elevations (32 U/L at Month 18, 33 U/L at Month 24, and 55 U/L at the end of the study). Total bilirubin was normal at all timepoints except Week 26, as mentioned above. Alogliptin was continued throughout, administered for approximately 4 years in total duration. Dr. (b) (4): unlikely; Dr. (b) (4): unlikely; Dr. Seeff: inadequate information.

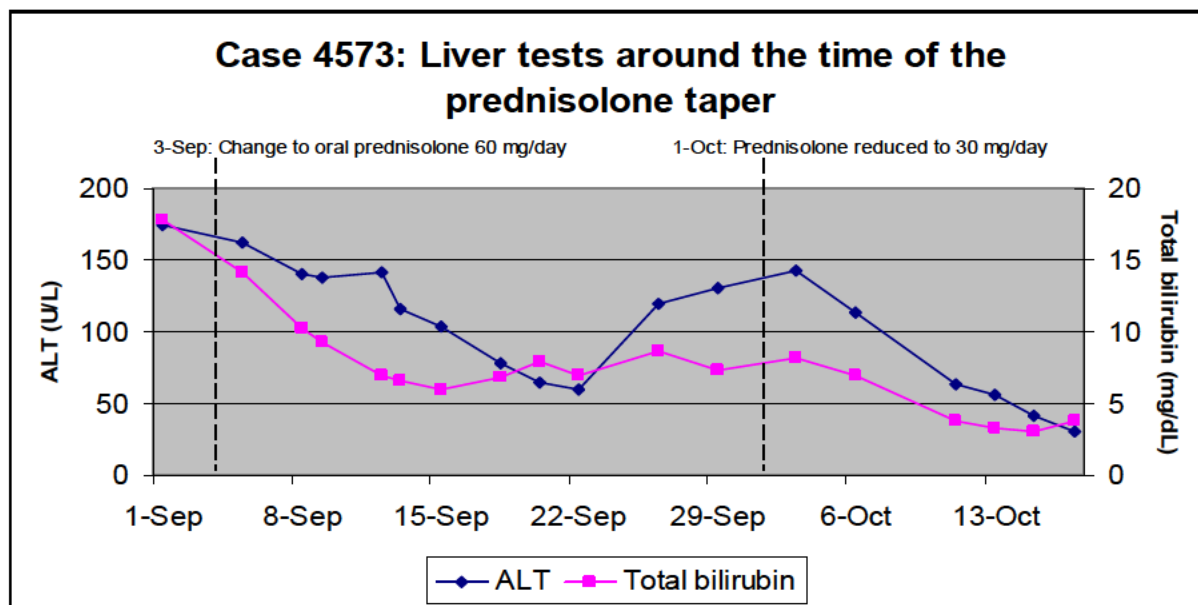
305/5304-055: This 45 year-old man from India had mild pre-treatment serum ALT elevations (up to 46 U/L). The ALT was 85 U/L at Week 4 and continued to increase thereafter, reaching 714 U/L about 2.5 weeks later at which point the patient tested positive for hepatitis E and alogliptin was discontinued. Three days later the ALT peaked at 1036 U/L with total bilirubin 2.4 mg/dL (total bilirubin had been normal at all other timepoints). Liver tests had normalized one month later. Dr. (b) (4): **unlikely**; Dr. (b) (4): **unrelated**; Dr. Seeff: **acute hepatitis E, not alogliptin hepatotoxicity**.

Biochemical Hy's Law Cases Reported in the Japanese Postmarketing Setting

There have been six cases of biochemical Hy's Law in the Japanese postmarketing setting, which are summarized below.

TCI2011A04573: This 77 year-old woman with Hashimoto's thyroiditis was started on levothyroxine about one month prior to starting alogliptin. Her baseline serum ALT and total bilirubin were normal. About two weeks later, the serum ALT was 75 U/L. About five weeks after starting alogliptin the serum ALT was 1176 U/L and total bilirubin was 6.3 mg/dL. Alogliptin was discontinued one day later. The patient was found to have an increased International Normalized Ratio (INR) of 1.7 and fever and the narrative mentions the liver disorder was on the "verge of becoming fulminant". Ten days later the INR peaked at 2.2 and total bilirubin had increased to 23 mg/dL. After another four days the total bilirubin was 33.5 mg/dL, the INR was 2.00, the serum ALT was 323 U/L and the patient was started on glucocorticoid therapy. About 5 weeks after that, when her serum ALT was 113 U/L, her INR was 1.30, and her total bilirubin was 7.0 mg/dL and while she was still on prednisolone 25 mg/day she was diagnosed with pneumonia that rapidly progressed, leading to death despite multiple antibiotics. Autopsy was not performed. The patient tested negative for autoimmune hepatitis serologies and tested negative for hepatitis A, B, and C, and Epstein-Barr virus and cytomegalovirus virus. Dr. Seeff notes that her death is clearly a result of fulminant liver disease or its complications. He notes that the patient was not tested for hepatitis E. He also acknowledges that autoimmune hepatitis (which presumably is the reason for the glucocorticoid therapy) should be considered in the differential diagnosis given that the patient had other evidence of autoimmune disease (Hashimoto's thyroiditis), but lowers the likelihood of this condition given the negative serologies. Dr. Seeff notes that the improvement in liver dysfunction with glucocorticoid therapy supports the possibility of autoimmune hepatitis but states that the response seems much quicker than is normally seen and that glucocorticoids can have some effect even in cases of non-autoimmune acute liver injury. He strongly disagrees with the "unlikely" attribution by Dr. (b) (4). Although Dr. (b) (4) assessed the case as only possibly due to alogliptin, Dr. Seeff concluded that drug-induced liver injury is more likely than autoimmune hepatitis given that the patient is a little older than is usual for first time onset of autoimmune hepatitis, that her serologies for auto-immune hepatitis were all negative and that the timing of the event is coincident with use of alogliptin. On April 16, 2012, we held a teleconference call with Takeda and Drs. (b) (4) to discuss the hepatic cases of concern. The call focused on this case. Drs. (b) (4) stated that they still considered autoimmune hepatitis to be more likely than alogliptin hepatotoxicity, stating that they were impressed with the rebound in liver test elevations when the glucocorticoid dose was tapered.

This rebound in liver tests does not convincingly coincide with the glucocorticoid taper as shown below. Specifically, the serum ALT and total bilirubin slightly increased while the patient was still on prednisolone 60 mg daily and these lab tests improved after the prednisolone was reduced to 30 mg daily. After the teleconference call, Dr. John Senior (another hepatologist in OSE) plotted the liver test abnormalities for this case and also noted that serum ALT began to fall following discontinuation of alogliptin before glucocorticoid therapy was started. Both Drs. Senior and Seeff conclude that there is no evidence that this patient had autoimmune hepatitis. Dr. (b) (4): possible; Dr. (b) (4): unlikely; Dr. Seeff: probable to highly likely.



TCI201A06837: This 66 year-old man with normal serum ALT at baseline was found to have a serum ALT of 1512 U/L, a total bilirubin of 3.9 mg/dL, and an INR of 1.20 on a routine visit on (b) (6), about one month after starting alogliptin. He was reportedly asymptomatic although in retrospect stated that he may have had mild malaise. Alogliptin was discontinued and he was hospitalized. At the time of the markedly elevated serum ALT, he tested negative for hepatitis B and C. No abdominal imaging was performed. On (b) (6) the serum ALT had declined to 425 U/L, total bilirubin was 1.3 mg/dL and the INR was 0.91. The ALT further declined to 273 U/L on (b) (6) then to 55 U/L on (b) (6) and had normalized by January 26, 2012. The improvement in liver tests occurred despite the patient continuing all the other medications he had been taking. On (b) (6) he tested negative for hepatitis A (by IgM and IgG), negative for hepatitis E (by RNA and by IgG), negative for markers of autoimmune hepatitis and positive for prior infection with cytomegalovirus (negative IgM but positive IgG). Prior to the (b) (6) test results, Dr. Seeff had adjudicated this case as probable alogliptin hepatotoxicity, whereas Dr. (b) (4) had stated that the data were insufficient to reach a reasonable conclusion and Dr. (b) (4) had concluded that this case is "barely possible" alogliptin hepatotoxicity. Based on the updated test results from (b) (6), Drs. (b) (4) now also consider this to be a probable case of alogliptin hepatotoxicity. An updated adjudication is pending from Dr. Seeff based on the (b) (6), test results.

TCI2011A02221: This 70 year-old man was noted to have jaundice and liver test abnormalities (ALT 6x ULN, total bilirubin 7.6 mg/dL) about one week after starting alogliptin but about a week later was diagnosed with cancer of the head of the pancreas. This case was not among those sent to Dr. Seeff for review because there clearly appears to be an alternative etiology for the liver test abnormalities. Dr. (b) (4): **unlikely; Dr. (b) (4): unrelated.**

TCI2011A03338: This 85 year-old woman with normal ALT at baseline was diagnosed with acute pancreatitis and acute hepatitis 18 days after starting alogliptin. The ALT was 640 U/L (16x ULN), alkaline phosphatase was 922 U/L (2.6x ULN), total bilirubin was 2.9 mg/dL and serum amylase was 1175 U/L (9.4x ULN). Abdominal CT scan was reported as unremarkable. Intake by mouth was restricted and the patient was given intravenous fluids and antibiotics). Additional information is not available but the simultaneous markedly abnormal serum amylase with the obstructive liver test findings (e.g., increased alkaline phosphatase) support biliary obstruction as the cause of the patient's symptoms. Dr. (b) (4): **unlikely; Dr. (b) (4): unlikely; Dr. Seeff: cannot rule out the possibility of alogliptin hepatotoxicity but if present it is trivial.**

TCI2011A02923: This case initially had limited data and was classified as unlikely by Dr. (b) (4) and as possible by Dr. (b) (4). We received updated information on April 4, 2012, which is incorporated into the narrative below. This 64 year-old man with normal serum ALT about 7 months earlier was found to have an ALT of 358 U/L (8x ULN) on March 30, 2011, about four weeks after starting alogliptin. Total bilirubin is not provided for this timepoint. Alogliptin was discontinued one week later (April 6). However, eight days later (April 14) the ALT was 1030 U/L (23x ULN) with a total bilirubin of 1.3 mg/dL. On April 18 the ALT was 1025 U/L with a total bilirubin of 2.1 mg/dL (peaking at 2.2 mg/dL on April 19) and a normal alkaline phosphatase. On April 21 he was found to be hepatitis C positive based on quantitative hepatitis C RNA of 6.1 log IU/mL and positive anti-hepatitis C antibody. He tested negative for acute hepatitis B (but had evidence of prior infection) and did not undergo testing for hepatitis A or E. The narrative does not mention testing for autoimmune hepatitis. On May 18 the ALT was 264 U/L (5.9x ULN) and total bilirubin was 1.2 mg/dL. The serum ALT had normalized on July 20. The narrative states that based on subsequent increases in liver tests (the narrative shows a serum ALT of 138 U/L on August 17 and 101 U/L on September 7), the patient underwent a liver biopsy on (b) (6) which showed mild piecemeal necrosis with lymphocyte infiltration and fibrous portal expansion. Five days later he started interferon therapy. On September 20 the hepatitis C RNA was 1.2 log IU/mL and by October 12 the hepatitis C RNA was undetectable. Follow-up serum ALT on September 28, November 9, 2011, January 5, 2012, and February 1, were all normal. (b) (4) stated that he cannot definitively attribute the abnormal liver tests in March and April 2011 to acute hepatitis C even though the patient was found to have positive hepatitis C RNA and anti-hepatitis C antibody around the time of the markedly abnormal liver tests. He explains that a definitive diagnosis of acute hepatitis C would require evidence of positive hepatitis C RNA and negative anti-hepatitis C antibody. Because the patient had hepatitis C antibodies, he either had recently formed the antibodies (perhaps the antibodies would have been negative if he was tested around March 30, when he first presented with the liver test abnormalities) or he had

chronic hepatitis C. Because chronic hepatitis C is a possibility, Dr. (b) (4) concludes that he cannot exclude acute (alogliptin hepatotoxicity) on chronic (hepatitis C) liver injury. Other factors that he mentions includes the positive alogliptin dechallenge (supporting alogliptin hepatotoxicity) and the lack of testing for all alternative causes such as hepatitis A and E (weakening the assertion that this is a true case of Hy's Law). In sum, Dr. (b) (4) concludes that this is a possible case of alogliptin hepatotoxicity. Dr. (b) (4) classifies this as an unlikely case of alogliptin hepatotoxicity, stating that a more likely diagnosis is either acute hepatitis C or a flare of chronic hepatitis. He also notes that all competing diagnoses such as hepatitis A and E have not been excluded. (b) (4): **possible (based on prior limited data) then updated to unlikely; Dr. (b) (4): unlikely (based on prior limited data) then updated to possible; Dr. Seeff: insufficient information (based on prior limited data) – updated adjudication is pending.**

TCI2012A01179: We received this expedited report from Takeda on March 22, 2012. This 65 year-old man reportedly had two episodes of jaundice at 20 and 39 years of age and underwent a cholecystectomy at 55 years of age. He had normal liver tests about one month after starting alogliptin but four months after that developed malaise and dark urine. He was not febrile and did not report abdominal pain at the time of the event. Alogliptin was discontinued the next day and one day after that his serum ALT was 481 U/L, alkaline phosphatase was 1288 U/L and total bilirubin was 14.4 mg/dL. Abdominal ultrasound and CT scan were reportedly unrevealing. Testing for hepatitis B and C was negative. Liver biopsy showed features “not inconsistent” with drug-induced liver injury. Liver tests improved considerably over the subsequent three weeks but had not normalized (serum ALT 65 U/L, alkaline phosphatase 336 U/L and total bilirubin 4.4 mg/dL). Follow-up information shows that the patient tested positive for hepatitis E RNA two days after alogliptin was discontinued. Dr. (b) (4) states that the hepatitis E RNA results exclude alogliptin hepatotoxicity whereas Dr. (b) (4) states that testing for anti-IgM antibodies to hepatitis E would be helpful. Dr. (b) (4): **initially probable (prior to the availability of the hepatitis E results) updated to possible; Dr. (b) (4): initially possible (prior to the availability of the hepatitis E results) updated to excluded; Dr. Seeff: initially possible to probable (prior to the availability of the hepatitis E results) – updated adjudication is pending.** The sponsor has subsequently submitted an updated report stating that the patient tested positive for IgA antibodies to hepatitis E two days after alogliptin was discontinued. The sponsor included a publication by Tian D-Y, et al. *World J Gastroenterol.* 2006; 12: 3919-23, showing that IgA antibodies to hepatitis E can support an acute infection. In 60 patients with hepatitis E, IgA antibodies were positive in ≥93% of patients up to three months after disease onset and positive in fewer patients at months four (63%) and five (30%).

Other Liver Cases Sent to Dr. Seeff for Adjudication

The most concerning cases among the 48 liver-related events reported in alogliptin-treated patients were identified and these 11 cases were forwarded to Dr. Seeff for review. The two additional postmarketing cases of potential interest that we received in January 2012 (6837 and 6892 – see above) were forwarded to Dr. Seeff, as well. He has completed his assessment of these 13 cases, as shown in the Table at the end of his review. The five most concerning cases (the two that Dr. Seeff initially graded as probable to highly likely – TCI2011A04573 and

TCI2011A06837 – the two that he graded as probable – TCI2011A03640 and TCI2010A05612 – and the one that he graded as possible/probable – TCI2011A04039) are summarized in this memorandum. Please refer to Dr. Seeff's review for his summaries of the seven less concerning cases (classified as possible) and the remaining case that had insufficient data (this patient discontinued alogliptin due to a serum ALT of 237 U/L; total bilirubin was normal).

The following five liver cases were determined by Dr. Seeff to be the most concerning:

TCI2011A04573 (discussed above)

TCI2011A06837 (discussed above)

TCI2011A03640: This postmarketing case involves a 64 year-old man with normal baseline ALT who received only four doses of alogliptin then discontinued the alogliptin due to nausea and vomiting. Liver tests obtained about two weeks after stopping alogliptin showed an ALT of 869 U/L, an alkaline phosphatase of 1169 U/L and a total bilirubin of 0.5 mg/dL. The ALT returned to normal over the next two months. Dr. Seeff notes that the liver test abnormalities are consistent with a hepatocellular/cholestatic liver injury, with the cholestatic pattern predominating. No other workup (e.g., imaging studies, serologies) was obtained, but Dr. Seeff notes that these alternative etiologies are unlikely (e.g., viral hepatitis and autoimmune hepatitis are not supported by the pattern of liver test abnormalities and there is no support for extrahepatic obstruction). Dr. Seeff also notes that the other medications the patient was receiving had been used for over a year, excluding them as possible causes for the liver injury. Given the absence of another plausible explanation, Dr. Seeff states that alogliptin is the probable cause here but notes that this case was not life-threatening. **Dr. (b) (4): possible; Dr. (b) (4): possible; Dr. Seeff: probable.**

TCI2010A05612: This postmarketing case involves a 64 year-old man with unknown serum ALT at baseline who had an ALT of 230 U/L, alkaline phosphatase of 1260 U/L, and total bilirubin of 0.87 mg/dL about two months after starting alogliptin. He was asymptomatic. Alogliptin was discontinued a day later. Testing for hepatitis A, B and C were negative and an abdominal ultrasound showed only hepatic steatosis. The ALT returned to normal over the next six weeks. Total bilirubin remained normal throughout. Liver tests improved despite the patient continuing his other medications, which rule out those drugs as a cause of the liver test abnormalities. Dr. Seeff notes that this case shows a predominantly cholestatic pattern of injury without an alternative explanation and states that alogliptin is the probable cause here. **Dr. (b) (4): possible; Dr. (b) (4): possible; Dr. Seeff: probable.**

TCI2011A04039: This postmarketing case involves a 77 year-old man who started alogliptin two days after undergoing angioplasty. His baseline ALT one day prior to starting alogliptin was normal. Three days later he developed anorexia and then started vomiting one day after that. Three days after starting alogliptin his ALT was 106 U/L, alkaline phosphatase was 336 U/L and total bilirubin was 0.3 mg/dL. By the next day the ALT peaked at 627 U/L and alogliptin was discontinued. Total bilirubin remained normal throughout. Four days after the ALT peak it was 60 U/L. Dr. Seeff notes that it is unfortunate that no efforts were undertaken

to exclude alternative etiologies but states that those etiologies are unlikely given the rapid recovery. He states that liver dysfunction associated with cardiac failure could explain the liver tests but notes that there is no mention of cardiac instability following the angioplasty. Dr. Seeff concludes that he would have judged alogliptin to be a probable cause but given the short latency and potential for a cardiac etiology, renders a final determination of a possible-probable mild case of alogliptin hepatotoxicity. **Dr. (b) (4): possible; Dr. (b) (4): possible; Dr. Seeff: possible-probable.**

Teleconference call with Japan's Pharmaceuticals and Medical Devices Agency

On March 21, 2012, we held a teleconference call with Japan's counterpart to the FDA, the Pharmaceuticals and Medical Devices Agency (PMDA), to obtain their perspective on the Japanese postmarketing liver cases associated with alogliptin. As of February 29, 2012, PMDA reports a total of eight serious postmarketing liver cases with alogliptin (among (b) (4) dispensed tablets), 70 cases with sitagliptin (among (b) (4) dispensed tablets) and none with linagliptin (among (b) (4) dispensed tablets). Saxagliptin is not yet approved in Japan. PMDA identified these liver cases by searching their database using selected preferred terms in the Hepatobiliary Disorders System-Organ-Class (e.g., gamma-glutamyltransferase increased, alanine aminotransferase increased, hepatic enzyme increased, blood bilirubin increased).

All eight PMDA cases are covered in this memorandum (3338, 3640, 4573, 6481, 6837, 6333, 6369 and 6892). To date, Dr. Seeff has completed a review for six of these cases (3338, 3640, 4573, 6481, 6837 and 6892). He classified cases 4573, 6481, 6837 and 3640 as probable alogliptin hepatotoxicity and found cases 4573 and 6837 to be particularly concerning. Case 3338 involves a patient with coincident pancreatitis. Dr. Seeff stated that he cannot rule out alogliptin hepatotoxicity for this case but, if present, it would be considered trivial. Dr. Seeff concluded that Case 6892 has a low possibility for alogliptin hepatotoxicity. Note that these eight cases reported by PMDA do not include Case 5612, which Dr. Seeff has classified as another probable case of alogliptin hepatotoxicity.

Case 6333 was not forwarded to Dr. Seeff because it did not have concerning features – the serum ALT was only 65 U/L or 2.2x ULN about two months after starting alogliptin, which was discontinued the next day. Follow-up serum ALT one month later was again normal.

Takeda submitted Case 6481 as an expedited report to the NDA after we received their comprehensive liver analyses. A narrative, together with Dr. Seeff's assessment, is provided below.

TCI2011A06481: This 53 year-old man presented with chest pain about three months after starting alogliptin. He was thought to have gastroesophageal reflux disease but laboratory testing during workup showed a serum ALT of 1583 U/L, alkaline phosphatase of 447 U/L and total bilirubin of 0.8 mg/dL. Alogliptin was discontinued two days later when the ALT was 982 U/L. Two weeks later the ALT had declined dramatically to 52 U/L. Total bilirubin was normal at all timepoints. Testing for hepatitis A, B and C and autoimmune hepatitis was negative. Anti-cytomegalovirus (CMV) IgM and IgG were positive but a test for CMV

antigenemia was negative. CT and ultrasound imaging were reportedly normal. It appears that most alternative etiologies have been excluded but the role of alogliptin may be less likely given that the ALT had already considerably improved on the same day that the patient took the last alogliptin dose. Dr. Seeff raises the possibility that the improved liver tests while taking alogliptin could represent adaptation to the drug. He concluded that this is a probable case of alogliptin hepatotoxicity because the most important alternative diagnoses have been excluded except hepatitis E. Takeda confirmed that hepatitis E testing was not performed for this patient but is inquiring whether there are retention samples of serum available for testing. **Dr. (b) (4): possible (based on the conflicting CMV test results and the improving liver tests before alogliptin was discontinued); Dr. (b) (4): probable (but notes that this case did not meet Hy's Law criteria and that there was no testing for hepatitis E); Dr. Seeff: probable.**

The eighth report identified by PMDA is TCI2011A06369, which is the patient previously described who had a serum ALT of only 103 U/L with a normal total bilirubin and coexisting pancytopenia.

Postmarketing reports of liver injury reported with the approved DPP-4 inhibitors

PMDA: As mentioned above, PMDA has identified 70 serious postmarketing liver reports for sitagliptin and no reports for linagliptin. Of these 70 sitagliptin cases, eight are of particular interest because they coded to drug-induced liver injury (n=3), jaundice (n=2), blood bilirubin increased (n=1), hepatitis (n=1) and hepatitis acute (n=1). The remaining 62 liver cases are coded to more non-specific terms such as alanine aminotransferase increased, liver function test abnormal and liver disorder or are coded to terms that do not suggest drug-induced liver injury (e.g., bile duct stone, cholecystitis acute). However, conclusions are substantially limited based only on this list of preferred terms and it is not possible to conclusively determine from the PMDA materials whether any of these 70 cases reflect concerning cases of sitagliptin hepatotoxicity.

OSE: We consulted OSE to search the Adverse Event Reporting System (AERS) and published literature for worrisome postmarketing cases of liver injury associated with the three already approved DPP-4 inhibitors. See the review by Dr. Sarita Boyd for further details.

OSE used the same search strategy that it has used when looking for serious liver injury with other medications. Specifically, OSE searched AERS for events with a serious outcome (e.g., death, hospitalization) that coded to any of the following MedDRA terms:

- Hepatic failure and associated disorders (High Level Term), which consists of the following preferred terms (PTs):
 - Acute hepatic failure
 - Asterixis
 - Chronic hepatic failure
 - Coma hepatic
 - Hepatic encephalopathy
 - Hepatic failure

- Hepatorenal syndrome
 - Subacute hepatic failure
- Bilirubin conjugated increased (PT)
- Blood bilirubin increased (PT)
- Hepatic necrosis (PT)
- Hepatitis fulminant (PT)
- Hyperbilirubinemia (PT)
- Jaundice (PT)
- Liver transplant (PT)

OSE then limited its evaluation to identified cases that resulted in death, liver transplant or hospitalization with or without discrete objective evidence of liver failure (DILIN severity grade 3 or higher).

Note that sponsors are required to submit foreign postmarketing reports to AERS if the events meet the regulatory definition of serious and are not included in the FDA-approved label (of if they reflect an increased risk beyond what is included in the FDA-approved label). Therefore, the AERS search by OSE should identify concerning global postmarketing reports of liver injury with the marketed DPP-4 inhibitors, if such cases exist.

OSE has confirmed that their AERS search strategy would identify the two most concerning alogliptin liver cases (4573 and 6837) but would not identify cases 3640 and 5612 (two other probable, but less severe cases). Therefore, it is reasonable to expect that OSE's search strategy will detect liver cases with the other DPP-4 inhibitors that are at least as severe as the two most concerning alogliptin cases, if such cases exist.

OSE's search strategy identified 45 reports for sitagliptin. After applying the case definition described above and accounting for duplicate reports, OSE identified eight AERS cases and one published literature case of liver injury associated with sitagliptin use that met the DILIN severity grade of 3 or higher with possible causality. No cases had a definite, highly likely or probable causality. There were no cases that resulted in death or liver transplantation. In addition, OSE did not identify concerning liver cases for saxagliptin or linagliptin. Based on these findings, OSE is not recommending regulatory action for sitagliptin, saxagliptin or linagliptin related to hepatotoxicity.

As discussed below, there is an estimated 16 million patient-years of global exposure to sitagliptin. Assuming the worst-case scenario that all nine cases identified by OSE reflect definite sitagliptin hepatotoxicity, the rate of concerning liver toxicity with sitagliptin would be 1 case per 1.8 million patient-years exposure, well below the estimated rate of 2 concerning cases with alogliptin per 219,000 patient-years exposure.

Merck: We asked Merck, the sponsor of sitagliptin, which is by the far the most heavily used DPP-4 inhibitor, to also perform a search for concerning postmarketing liver events reported with sitagliptin products using the same strategy that OSE is using but to also search for non-serious events. This approach identified 54 events (38 serious and 16 non-serious) for sitagliptin and 16 (4 serious and 12 non-serious) events for Janumet (the sitagliptin/metformin

fixed-dose combination tablet). The 42 total serious reports with the sitagliptin products is similar to the 45 serious AERS reports identified by OSE that OSE then further narrowed down to eight reports.

Merck's search strategy identified only six serious liver reports in Japan in contrast to the 70 serious liver reports mentioned by PMDA. This discrepancy is explained by the different list of preferred terms used by Merck and PMDA when searching the database. For example, Merck searched the database using the same terms that OSE used. These are the search terms that we asked Merck to use. In contrast, PMDA generally used more non-specific terms in the Hepatobiliary disorders System-Organ-Class, as discussed above.

The six serious liver reports from Japan involved patients with events that coded to hepatitis fulminant (n=1), blood bilirubin increased (n=1) and jaundice (n=5) [one patient had an event that coded to both blood bilirubin increased and jaundice]. The report of hepatitis fulminant (WAES 1106USA03005) involves a patient with a history of stroke who presented with hematemesis and died of fulminant hepatitis about five months after starting sitagliptin. The MedWatch form states that the most likely explanation is hepatic failure with hypoxemia due to circulatory collapse or multi-organ failure but the information is too limited to reach any conclusions. Narratives for the five other Japanese cases could not be readily identified because none of the narratives state Japan as the country of origin.

Worldwide, there is only one other report with a fatal outcome. This patient (WAES 0707USA03188) had end-stage liver disease when she started sitagliptin. The MedWatch form states that sitagliptin was discontinued (duration of treatment not reported) and that the patient died a few weeks later. There is no other information in the narrative but given the report of end-stage liver disease at baseline it is unlikely that sitagliptin played a major role in the death. Merck states that there have been no worldwide reports of a hepatic event leading to liver transplant.

Table 10 shows the number of liver events that Merck identified worldwide and in Japan (based on our requested search criteria) as well as overall reporting rates for all cases. The narratives for these cases were only recently submitted and will need to undergo more detailed hands-on review to determine whether regulatory action is needed for the sitagliptin products. In addition, patient identifiers for these cases should be compared with the cases identified by OSE.

In the worst-case scenario, if we assumed that every case identified by Merck's search reflects concerning sitagliptin hepatotoxicity, the reporting rates would be 1 per (b) (4) PY worldwide and 1 per (b) (4) PY in Japan. However, several cases have likely alternative etiologies as the cause of the liver test abnormalities and for several cases the information is too limited to reach any conclusions. Selected examples among serious cases where the role of sitagliptin is likely limited are shown below:

- An event of chronic hepatic failure (described above) occurred in a patient with baseline end-stage liver disease.
- An event of hepatic encephalopathy while on sitagliptin occurred in a patient with a history of cirrhosis and prior hepatic encephalopathy.

- An event of jaundice occurred in a patient who was subsequently diagnosed with pancreatic cancer.

Therefore, the rates of concerning liver cases with sitagliptin will undoubtedly be more rare than 1 per (b) (4) PY worldwide and 1 per (b) (4) PY in Japan when all these cases have been fully reviewed. In addition, most of the serious cases did not meet OSE's case definition for concern (the same criteria that would have detected the two concerning cases for alogliptin). Therefore, rates with sitagliptin are considerably lower than the rates for alogliptin (2 most concerning cases per (b) (4) PY or 1 case per 110,000 PY).

**Table 10. Postmarketing liver reports with sitagliptin products
(from Merck, using our requested search strategy)**

Preferred Term	Worldwide		Japan	
	All	Serious Only	All	Serious Only
Acute hepatic failure	3	3	0	0
Chronic hepatic failure	1	1	0	0
Hepatic encephalopathy	4	4	0	0
Hepatic failure	12	12	0	0
Bilirubin conjugated increased	3	1	0	0
Blood bilirubin increased	18	9	1	1
Hepatitis fulminant	1	1	1	1
Hyperbilirubinemia	2	0		
Jaundice	35	17	6	5
TOTAL ¹	70	42	7	6
Total patient-years (PY) ²	(b) (4)		(b) (4)	
Reporting rates	1 per (b) (4) PY	1 per (b) (4) PY	1 per (b) (4) PY	1 per (b) (4) PY

¹Totals are less than the sum of the individual preferred terms because some reports included more than one preferred term

²Estimated by dividing distributed tablets by 365 for sitagliptin (which is dosed once-daily) and by 730 for Janumet (which is dosed twice-daily). Excludes sitagliptin/simvastatin, which has (b) (4) patient-years of global exposure.

Takeda: On April 4, 2012, Takeda provided an analysis of reporting rates for serious hepatic events for DPP-4 inhibitors approved in Japan up to a cutoff date of November 2011. Takeda estimated the patient-year exposures based on IMS data and searched for serious hepatic events using the SMQ for hepatic disorders. Note that this search strategy is less specific for acute liver injury than the search strategy used by OSE. For example, Takeda identified cases that coded to bile duct stone, cholecystitis, cholecystitis acute as well as more non-specific terms such as liver function test abnormal, gamma-GT increased and liver disorder. Based on this search strategy, Takeda concluded that the reporting rates of serious hepatic events for alogliptin is similar to that of sitagliptin and lower than that of vildagliptin. However, this analysis based only on preferred terms, many of which are non-specific, does not provide convincing evidence that alogliptin and sitagliptin have a similar propensity to cause drug-induced liver injury. One would need to perform a hands-on review of all these cases to determine the likelihood of serious drug-induced liver injury based on the liver test findings

and the exclusion of alternative causes. For this reason, I place more emphasis on OSE's analyses.

I provide an overall conclusion regarding hepatotoxicity in the Risk-Benefit section.

Hypoglycemia: Here I focus on the hypoglycemia data from the two newly completed phase 3 trials. Refer to my CDTL memorandum for the original NDA for a discussion of hypoglycemia in previously reviewed trials.

In Study 303 (the elderly study comparing alogliptin to glipizide), severe hypoglycemia (requiring third-party assistance with a blood glucose, if available, <70 mg/dL) was reported in no alogliptin-treated patients and in 3 (1.4%) glipizide-treated patients. Two of the patients with severe hypoglycemia experienced the event around Month 4. The remaining patient had severe hypoglycemia during the first few days following initiation of glipizide. Confirmed symptomatic hypoglycemia (blood glucose <70 mg/dL) was reported in 2 (0.9%) alogliptin-treated patients and 35 (16%) glipizide-treated patients. Confirmed hypoglycemia (blood glucose <70 mg/dL) with or without symptoms was reported in 9 (4.1%) alogliptin-treated patients and 52 (24%) glipizide-treated patients. These findings are consistent with the known hypoglycemic profile of DPP-4 inhibitors (which stimulate insulin release in a glucose-dependent manner) and sulfonylureas (which stimulate insulin release in a glucose-independent manner). Hypoglycemia rates with glipizide may have been even higher if a higher dose of glipizide had been allowed in the study.

Study OPI-004 (comparing add-on alogliptin vs. uptitration of pioglitazone) had slightly different pre-specified definitions of hypoglycemia compared to the definitions used in Study 303. In OPI-004, severe hypoglycemia (requiring third-party assistance with a blood glucose, if available, <60 mg/dL) was reported in 2 (0.5%) alogliptin-treated patients and no patients in the uptitrated pioglitazone arm. Confirmed symptomatic hypoglycemia (blood glucose <60 mg/dL) was reported in 8 (2.0%) alogliptin-treated patients and 2 (0.5%) patients in the uptitrated pioglitazone arm. Confirmed hypoglycemia (blood glucose <50 mg/dL) with or without symptoms was reported in 7 (1.7%) alogliptin-treated patients and 2 (0.5%) patients in the uptitrated pioglitazone arm.

Pancreatitis: The sponsor searched for reports of pancreatitis in the controlled phase 2/3 database, the supportive Japanese phase 2/3 clinical trials and the postmarketing setting. The search strategy used the narrow scope terms from the SMQ for acute pancreatitis. Findings are shown below.

- 5/5232 (0.10%) alogliptin-treated patients (4 serious, 1 non-serious) and 1/2934 (0.03%) comparator-treated patient reported an adverse event of pancreatitis in the pooled, controlled phase 2/3 database. For the five alogliptin-treated patients with treatment-emergent pancreatitis, two had associated cholecystitis, one had a normal serum lipase at the time of the event but had a history of recurrent pancreatitis, and the remaining two patients had insufficient information regarding workup for alternative causes.
- No cases of pancreatitis were identified in the Japanese phase 2/3 controlled trials.

- 6 cases of pancreatitis were reported in the postmarketing setting (up to October 27, 2011, with over 100,000 patient-year exposure).

In addition, there were 10 serious adverse events of pancreatitis (one of which was fatal) reported in ongoing uncontrolled Study 402 as well as one event of pancreatitis reported in an open-label Japanese extension trial.

Since the resubmissions, a few more reports of treatment-emergent pancreatitis have been received - 2 among alogliptin-treated patients and one in a blinded patient (these 3 events are from studies that were ongoing at the time of the resubmissions) and 2 among placebo-treated patients (which occurred after the cutoff date for the resubmissions).

Brief narratives for the 24 treatment-emergent cases of pancreatitis among the alogliptin-treated patients and the one patient who is still blinded are provided below. Among alogliptin-treated patients there are two reported fatalities related to pancreatitis (one of these patients underwent autopsy, which showed pancreatic necrosis) and one severe case of pancreatitis complicated by acute renal failure and disseminated intravascular coagulation. Seven of the 24 cases with alogliptin appear to have an alternative explanation, many of the remaining cases have inadequate information, several occurred after long-term treatment with alogliptin, and none of the patients who were rechallenged with alogliptin had recurrent pancreatitis. Most of the cases with alogliptin occurred in uncontrolled settings (e.g., Study 012 and postmarketing), further limiting conclusions. Despite these limitations, it is not possible to exclude alogliptin as the cause of the pancreatitis in some cases.

Controlled phase 2/3 trials:

OPI-001/436-3004: This 48 year-old woman with a history of pancreatitis and cholecystectomy developed recurrent pancreatitis on Day 113 while taking alogliptin 12.5 mg. Serum lipase was ~4900 U/L. She was hospitalized for 2 days and alogliptin was interrupted for 8 days but she subsequently resumed the alogliptin and completed the study. There is no information as to whether a work-up was undertaken to determine the cause of the pancreatitis.

OPI-002/750-2501: This 60 year-old woman developed pancreatitis about 4 weeks after starting alogliptin. She was subsequently hospitalized, diagnosed with cholecystitis and underwent laparoscopic cholecystectomy with resolution of the event.

011/269-5004: This 56 year-old woman was diagnosed with pancreatitis in the setting of cholecystitis about 3 months after starting alogliptin and underwent cholecystectomy 3 days after hospitalization. Alogliptin was interrupted for 5 days then restarted.

402/001-8093: This 48 year-old woman with a history of chronic pancreatitis (>5 hospitalizations within the preceding 10 years) developed recurrent pancreatitis 46 days after starting alogliptin. The narrative mentions that the serum lipase was normal and that abdominal ultrasound was unrevealing. Alogliptin was continued. The patient responded to an antiemetic and narcotic and was discharged after one day.

011/256-5004: This 45 year-old woman was diagnosed with a non-serious event of pancreatitis after taking alogliptin for 73 days. She was withdrawn from the study on Day 78. There is no additional information regarding work-up for alternative causes.

Postmarketing reports:

TCI2010A04635: This 81 year-old woman with a history of gallstones developed nausea, vomiting and abdominal pain about two months after starting alogliptin. She was hospitalized and alogliptin was discontinued. CT scan showed acute pancreatitis with stones in the gallbladder. The common bile duct was dilated but the size could be consistent with age. She developed shock and died one day later. Autopsy showed pancreatic necrosis and stones in the gallbladder, but no stones in the common bile duct.

TCI2011A02785: This 70 year-old man developed nausea, vomiting, abdominal pain and anorexia about two months after starting alogliptin. Serum lipase was markedly elevated. CT scan confirmed pancreatitis. Magnetic resonance cholangiopancreatography did not identify gallstones. Alogliptin was discontinued and the patient recovered. He did not have hypertriglyceridemia and his alcohol consumption was limited. Therefore, a relationship to alogliptin was considered possible.

TCI2011A03338: This case is described under the Hepatotoxicity section and involves an 85 year-old woman who developed acute onset of nausea and vomiting about 2.5 months after starting alogliptin. CT imaging was reported as unremarkable. She was diagnosed with pancreatitis (serum amylase 9.4x ULN) and hepatitis (serum ALT 16x ULN, alkaline phosphatase 2.6x ULN and total bilirubin 2.4x ULN). Additional information is not available but the simultaneous markedly abnormal serum amylase with the obstructive liver test findings (e.g., increased alkaline phosphatase) support biliary obstruction as the cause of the patient's symptoms.

TCI2011A04401: This 61 year-old man with a history of cholecystectomy developed abdominal pain about two weeks after starting alogliptin. CT scanning showed findings consistent with pancreatitis and the serum amylase was 28x ULN. No gallstones were noted. Serum triglycerides were in the 300 mg/dL range, which is not high enough to cause pancreatitis. Alcohol use was reported to be low. Alogliptin was interrupted during the hospitalization but subsequently discontinued by the patient's physician about a week after it was restarted.

TCI2011A04813: This 48 year-old man developed acute abdominal pain and was diagnosed with pancreatitis about nine months after starting alogliptin. There are no results for serum lipase/amylase or imaging around the time of the event. Serum triglycerides were 408 mg/dL about 3 weeks prior to the pancreatitis event but only 171 mg/dL <2 weeks after the event (no lipid-lowering medication appears to have been started in the interim). Alogliptin was discontinued.

TCI2011A04936: This 58 year-old man was diagnosed with pancreatitis about 2 weeks after starting alogliptin. The pancreatitis was complicated by acute renal failure and disseminated

intravascular coagulation. Serum amylase was markedly elevated. CT findings were consistent with pancreatitis. No common bile duct stone was seen. There is no mention of necrotizing or hemorrhagic pancreatitis. He required mechanical ventilation, hemodialysis, broad-spectrum antibiotics, and anti-thrombin III treatment. At the end of the narrative the events were resolving but the patient had not fully recovered.

Uncontrolled Study 012:

012/412-3011: This 65-year old woman was diagnosed with pancreatitis after taking alogliptin for nearly 2.5 years. She presented with upper abdominal pain and vomiting and had a serum amylase of 3900 U/L. She received standard treatment for pancreatitis but died one day after admission. The narrative states that infections, toxins, drugs, trauma and obstructive causes had been ruled out but detailed information is not provided. The investigator stated that the death certificate, discharge summary and other hospital records were not available.

012/053-2520: This 54 year-old man with a history of pancreatitis was hospitalized with recurrent pancreatitis about two years after starting alogliptin. He reported drinking 12 beers per day for about one week prior to hospitalization. Lipase was 4x ULN. CT scanning showed changes consistent with chronic pancreatitis. There were no gallstones seen on abdominal ultrasound.

012/116-3001: This 64 year-old man presented with pancreatitis 16 months after starting alogliptin. An abdominal ultrasound showed gallstones with sludge. He underwent endoscopic retrograde cholangiopancreatography with drainage of gravel from the common bile duct. He was diagnosed with a possible pseudocyst on CT imaging but improved clinically and was discharged.

012/296-3010: This 43 year-old man was hospitalized with pancreatitis about two years after starting alogliptin. He stopped the alogliptin and recovered fully within a few days with standard treatment. Lipase was reported to be 3.2x ULN (but timing of this test relative to his symptoms is not provided). An ultrasound did not show gallstones. No other relevant information is provided.

012/326-4005: This 61 year-old woman was hospitalized with pancreatitis about 10 months after starting alogliptin. Lipase was about 6x ULN. No gallstones were noted on ultrasound. Serum triglycerides were not elevated. Alogliptin was interrupted for about one month then restarted.

012/371-3016: This 56 year-old man presented with pancreatitis about 14 months after starting alogliptin. Lipase was 2279 U/L and bilirubin was elevated (no other liver tests provided), supporting the admission diagnosis of biliary pancreatitis, although ultrasound did not report gallstones or common bile duct dilatation. Alogliptin was interrupted for about 10 days.

012/395-5019: This 71 year-old man presented with pancreatitis about 18 months after starting alogliptin. Amylase was 768 U/L and total bilirubin was 10.7 mg/dL (no other liver tests were provided), suggesting biliary obstruction. Serum triglycerides were normal. He was reported to

have multiple gallstones at the time of his presentation; however, no gallstones or common bile duct dilatation was seen on endoscopic retrograde cholangiopancreatography performed two weeks later. About 15 months later he underwent cholecystectomy.

012/648-3012: This 56 year-old man developed pancreatitis about 22 months after starting alogliptin. Serum amylase was 1766 U/L. An ultrasound reported no gallstones. In the hospital, alogliptin was permanently discontinued due to inadequate glycemic control.

012/666-2503: This 67 year-old woman with a reported history of chronic pancreatitis was hospitalized with pancreatitis about eight months after starting alogliptin. She presented with nausea, abdominal pain and anorexia. The discharge diagnoses were “dyspeptic syndrome and chronic pancreatitis”. There is inadequate information in the narrative to reach further conclusions.

012/900-3015: This 37 year-old man developed pancreatitis almost three years after starting alogliptin. His lipase was 2318 U/L. Alogliptin was interrupted for two days then restarted upon hospital discharge. His serum triglycerides around the time of hospitalization were ~750 mg/dL, which is the likely cause of the pancreatitis.

Japanese open-label extension trial:

OCT-001/0013-114: This 60-year old man developed pancreatitis (confirmed by elevated serum amylase and CT imaging) about 7 months after starting alogliptin. Hepatopancreatobiliary MRI did not identify an anatomic/obstructive cause for the pancreatitis. Alogliptin was interrupted for about one week. The patient recovered with standard treatment for pancreatitis.

Events occurring after resubmissions:

MET-302/5166-007: This 70 year-old woman had elevated serum amylase and lipase <3x ULN about 3 months after starting alogliptin. These laboratory tests were drawn in error. The patient was asymptomatic and follow-up testing three days later showed that the amylase and lipase had normalized.

MET-302/5082-004: This 77 year-old man reported a non-serious event of pancreatitis about two months after starting alogliptin. He reported nausea although the timing of these symptoms relative to the diagnosis is not clear. The serum lipase was 3.2x ULN. The pancreas appeared normal on CT imaging one week later. Alogliptin was discontinued. The narrative mentions that the patient used alcohol but the amount of alcohol is not stated and there is no other information regarding workup for alternative causes.

308/4011-003 (blinded): This 50 year-old man was hospitalized with pancreatitis about two weeks after starting blinded study medication and one day after drinking wine. The narrative does not clarify the amount of wine consumed. Serum lipase was about 8x ULN. The narrative mentions hypertriglyceridemia but does not provide the actual serum triglyceride values. Ultrasound revealed possible hepatic calcifications – no other abnormalities were reported.

Hypersensitivity reactions:

Angioedema: Table 11 summarizes potential cases of angioedema identified in the entire phase 2/3 controlled database (including the Japanese studies and ongoing Study 402). These cases were identified using the narrow scope (more specific) terms in the Angioedema SMQ. All these events were classified as non-serious, except for one report of hypersensitivity in an alogliptin-treated patient. This 34 year-old man with no history of allergic reactions started candesartan on Day -7 and was hospitalized with difficulty breathing and swallowing four days after starting alogliptin. Physical examination showed edema of the uvula, face, and part of the neck. He was treated with an antihistamine and was discharged the same day. Alogliptin was interrupted for 1-2 days then he resumed taking it until discontinuing from the study on Day 167 due to lack of efficacy. He also continued the concomitant candesartan. The negative rechallenge makes an association with alogliptin less likely.

As shown in Table 11, a few alogliptin-treated patients in the entire phase 2/3 database reported events that coded to preferred terms of angioedema (n=1), face edema (n=6), swelling face (n=3), swollen tongue (n=1) and tongue edema (n=1). None of these events clearly represent a concerning hypersensitivity reaction to alogliptin. In all but one of these patients, the symptoms resolved despite continued treatment with alogliptin or persisted without leading to discontinuation of alogliptin. The remaining patient developed face, hand and leg edema on Day 41 that resolved on Day 51 then recurred on Day 61. Alogliptin was discontinued and the events resolved on Day 91.

In uncontrolled Study 012, serious adverse events of note include angioedema (n=3) and allergic edema (n=1). These cases are summarized below. For several of these cases the patients continued alogliptin after the allergic event resolved, making a relationship to alogliptin less likely. However, it is not possible to exclude alogliptin as the cause in some instances.

012/370-5013: This 35 year-old man presented with swallowing difficulties and trouble talking about 11 months after starting alogliptin and was suspected of having angioedema. The symptoms resolved after two doses of an antihistamine. Valsartan, which the patient had been taking for about five months, was permanently discontinued. Alogliptin was interrupted for two days then restarted. The narrative mentions that the patient also reported an allergic reaction of the face and uvula about 3 days after first starting alogliptin. It seems unlikely that these reactions are due to alogliptin given that he tolerated continued treatment with alogliptin for prolonged periods. The patient also saw an allergist who thought that a relationship to alogliptin was unlikely.

012/435-4002: This 71 year-old woman who had been treated with alogliptin for two years was diagnosed with angioedema after presenting with swollen tongue, pruritis, and difficulty swallowing. These symptoms occurred 1.5 hours after drinking a new brand of coffee. She recovered despite continuing the alogliptin. She was not on an ACE inhibitor or angiotensin receptor blocker (ARB).

012/451-4005: This 51 year-old woman was hospitalized with facial swelling and diagnosed with angioedema more than two years after starting alogliptin. She recovered despite continued treatment with alogliptin. She was not on an ACE inhibitor or ARB.

012/487-7013: This 74 year-old man developed edema of the right side of the face about nine months after starting alogliptin. He had a recurrent event 15 months later. He recovered in both instances despite continuing the alogliptin. He was also on an ACE inhibitor that was continued, as well.

Up to the October 27, 2011, cutoff date, there have been three serious postmarketing cases of angioedema. Narratives for the three serious cases are summarized below.

TCI2010A06345: This 52 year-old woman developed generalized urticaria about two weeks after starting alogliptin. A day later she also developed swelling of the face and head. Alogliptin was discontinued and she was treated with glucocorticoids. She was not on an ACE inhibitor or ARB.

TCI2011A05420: This 74 year-old woman developed generalized urticaria 11 days after starting alogliptin. The patient discontinued alogliptin. No other details are provided.

TCI2011A04779: This 63 year-old man developed facial and lower extremity edema three days after starting alogliptin. The narrative states that he was diagnosed with heart failure and was started on furosemide and digoxin. Alogliptin was discontinued.

Table 11. MedDRA SMQ for Angioedema (All phase 2/3 controlled trials, including the Japanese studies and ongoing Study 402)						
Preferred Term	Alogliptin N=6330		Placebo N=2234		All Comparators* N=3485	
	n (%)	Events per 100 PY	n (%)	Events per 100 PY	n (%)	Events per 100 PY
Narrow Scope Terms	35 (0.6)	1.3	8 (0.4)	1.1	19 (0.5)	1.4
Angioedema	1 (<0.1)	<0.1	1 (<0.1)	0.1	3 (0.1)	0.2
Conjunctival oedema	1 (<0.1)	<0.1	0	0	0	0
Corneal oedema	1 (<0.1)	<0.1	0	0	0	0
Eyelid oedema	3 (<0.1)	0.1	1 (<0.1)	0.1	2 (0.1)	0.1
Face oedema	6 (0.1)	0.3	0	0	1 (<0.1)	0.1
Lip swelling	0	0	0	0	1 (<0.1)	0.1
Periorbital oedema	0	0	1 (<0.1)	0.1	2 (0.1)	0.1
Swelling face	3 (<0.1)	0.1	0	0	2 (0.1)	0.2
Swollen tongue	1 (<0.1)	<0.1	0	0	0	0
Tongue oedema	1 (<0.1)	<0.1	0	0	0	0
Urticaria	19 (0.3)	0.7	5 (0.2)	0.6	9 (0.3)	0.6
Urticaria chronic	0	0	1 (<0.1)	0.1	1 (<0.1)	0.1
*All comparators includes placebo and active-comparators PY = patient-years						

Severe Cutaneous Adverse Reactions: Table 12 summarizes potential cases of severe cutaneous skin reactions identified in the entire phase 2/3 controlled database (including the Japanese studies and ongoing Study 402). These cases were identified using the narrow scope (more specific) terms in the Severe Cutaneous Adverse Reactions SMQ. Few events were identified and all were classified as non-serious. Narratives for the alogliptin-treated patients with dermatitis exfoliative and exfoliative rash are not concerning for a severe drug-related skin reaction (the skin lesions were reported on localized areas of the body – e.g., neck, toe – and did not lead to discontinuation of alogliptin).

Table 12. MedDRA SMQ for Severe Cutaneous Adverse Reactions (All phase 2/3 controlled trials, including the Japanese studies and ongoing Study 402)						
Preferred Term	Alogliptin N=6330		Placebo N=2234		All Comparators* N=3485	
	n (%)	Events per 100 PY	n (%)	Events per 100 PY	n (%)	Events per 100 PY
Narrow Scope Terms	6 (0.1)	0.3	3 (0.1)	0.4	6 (0.2)	0.4
Dermatitis bullous	3 (<0.1)	0.1	0	0	1 (<0.1)	0.1
Dermatitis exfoliative	2 (<0.1)	0.1	1 (<0.1)	0.1	2 (0.1)	0.1
Erythema multiforme	0	0	1 (<0.1)	0.1	1 (<0.1)	0.1
Exfoliative rash	1 (<0.1)	<0.1	0	0	0	0
Skin necrosis	0	0	0	0	1 (<0.1)	0.1
Toxic skin eruption	0	0	1 (<0.1)	0.1	1 (<0.1)	0.1
*All comparators includes placebo and active-comparators PY = patient-years						

Postmarketing serious cases of severe skin reactions include four reports of Stevens-Johnson syndrome and five reports of erythema multiforme, as summarized below. Erythema multiforme is an inflammatory reaction with characteristic skin lesions and possible involvement of the oral mucosa. It is diagnosed clinically, can occur as a reaction to a drug or infection (e.g., herpes simplex virus), and is generally self-limited. There appear to be some reasonable cases of alogliptin-induced erythema multiforme based on the narratives, particularly for those cases diagnosed by dermatologists. Stevens-Johnson Syndrome is a severe hypersensitivity reaction that can occur with certain medications (e.g., sulfa drugs) and presents as a rash that spreads rapidly leading to blistering and sloughing of skin. There have been postmarketing reports of Stevens-Johnson with sitagliptin, another DPP-4 inhibitor. Based on the narratives below, most of the reported cases do not provide clear and convincing evidence of alogliptin-induced Stevens-Johnson syndrome (e.g., one patient was on another drug that has been reported to cause Stevens-Johnson syndrome, another case had very limited information, and a third case recovered in only two days).

Postmarketing reports of Stevens-Johnson Syndrome:

TCI2011A04457: This 78 year-old woman received alogliptin for 10 days then stopped the medication due to pruritis. Two days later there was concern for a severe drug eruption so she was seen by dermatology then hospitalized with a suspicion of Stevens-Johnson syndrome.

She recovered after receiving glucocorticoid therapy and was discharged after about 2.5 weeks. The skin reaction was attributed to glimepiride (which is labeled for Stevens-Johnson syndrome) and which was also discontinued. The duration of glimepiride use is unknown.

TCI2011A02510: This 80 year-old woman developed generalized erythema, conjunctival redness and fever 10 days after starting alogliptin. She was hospitalized due to a suspicion for Stevens-Johnson syndrome (based on a telephone conversation that the reporting physician had with a dermatologist who did not examine the patient). Alogliptin was discontinued and glucocorticoids were started.

TCI2011A04420: This case was reported to the Takeda call center by a pharmacist. The report only states the following “Date unknown: The patient developed Stevens-Johnson syndrome. The outcome was unknown.”

TCI2012A00131: This case involving an 83 year-old woman was reported to the alogliptin IND after we had received the NDA resubmissions. The patient developed severe oral mucosal erosions and oral mucosal desquamation 10 days after starting alogliptin. She sought medical care three days later and was noted to have symptoms that were “Stevens Johnson syndrome-like.” Alogliptin was discontinued and she recovered in two days after receiving an antihistamine and combination product of glycyrrhizin/glycine/cysteine. She was not given glucocorticoids because of concern for worsened diabetes.

Postmarketing reports of erythema multiforme:

TCI2011A04343: This 82 year-old woman developed erythema and pruritis on the neck and back about 10 days after starting alogliptin. She was seen by dermatology who noted diffuse erythematous lesions (erythema exudativum multiforme), particularly on the trunk. She was hospitalized after developing involvement of the face the next day. Alogliptin and recently started herbal medications were discontinued and glucocorticoid therapy was started with resolution over about three weeks.

TCI2011A04366: This 70 year-old woman developed fever, pruritis and generalized erythema 17 days after starting alogliptin. She was hospitalized, started glucocorticoid therapy, discontinued alogliptin and recovered after about 12 days.

TCI2011A05092: This case was reported by a physician via a medical representative and contains limited information. It involves a woman of unknown age who was reported to develop erythema exudativum multiforme about 10 days after starting alogliptin. The alogliptin was discontinued.

TCI2011A05698: This case was reported by a physician via a medical representative and involves a 60 year-old woman who developed a severe generalized rash with fever 12 days after starting alogliptin. She was seen by dermatology who diagnosed drug-induced erythema multiforme. Alogliptin was discontinued.

TCI2011A06360: This 76 year-old man developed generalized pruritis two weeks after starting alogliptin. He was seen by dermatology and diagnosed with erythema multiforme exudativum. Alogliptin was discontinued and symptoms improved within two weeks.

Anaphylaxis: Table 13 summarizes potential cases of anaphylactic reaction identified in the entire phase 2/3 controlled database (including the Japanese studies and ongoing Study 402). These cases were identified using the Anaphylactic Reactions SMQ. Few potential events were identified and all identified events in alogliptin-treated patients were classified as non-serious except one. The patient with the serious event was a 63 year-old man who died of cardiac arrest about 6 months after starting alogliptin in Study 402 (he had extensive cardiovascular disease and had unstable angina about 3 weeks prior to randomization). He had reported a non-serious event of dyspnea about 3 months prior to his death. Note that this patient did not have an anaphylactic reaction (the broad search strategy under the Angioedema SMQ captured this patient because of the dyspnea and cardiac arrest – which occurred 3 months apart). This case illustrates some of the limitations of these SMQ searches, which are sensitive but not necessarily specific strategies for identifying potential clinical events of interest.

Table 13. MedDRA SMQ for Anaphylactic Reaction (All phase 2/3 controlled trials, including the Japanese studies and ongoing Study 402)			
Preferred Term	Alogliptin N=6330 n (%)	Placebo N=2234 n (%)	All Comparators* N=3485 n (%)
A or (B and C) or (D and (B or C))	11 (0.2)	4 (0.2)	7 (0.2)
A	0	1 (<0.1)	1 (<0.1)
B and C	9 (0.1)	2 (0.1)	4 (0.1)
D and (B or C)	2 (<0.1)	1 (<0.1)	2 (0.1)
<p>*All comparators includes placebo and active-comparators A=narrow scope terms B=preferred terms related to respiratory distress C=preferred terms related to pruritis, generalized flushing, and urticaria D=preferred terms related to vascular collapse Patients are considered to have a potential anaphylaxis event if they have at least one event in Category A or an event in both Category B and C or an event in Category D and an event from either Category B or C</p>			

In non-randomized Study 012, there were two serious adverse events that met the criteria for the anaphylactic reaction SMQ, as summarized below:

012/435-4002: This patient is discussed in the angioedema section.

012/228-9002: This patient did not have anaphylaxis. He was hospitalized for pneumonia for 2 days then 3 days after discharge was found unresponsive and died of cardiac arrest.

There have been no serious postmarketing cases of anaphylactic reaction.

Infections: DPP-4 has many substrates other than the incretin hormones, including chemokines involved in immune development and function. In addition, DPP-4 is expressed on a subset of

CD4+ and CD8+ T-cells and natural killer cells. Therefore, infections are adverse events of interest for all DPP-4 inhibitors. In the controlled phase 2/3 database, 25% of alogliptin-treated patients and 22% of comparator-treated patients reported at least one event in the Infections and Infestations System-Organ Class. The following infections were reported in >1% of alogliptin-treated patients and at a numerically greater incidence with alogliptin than comparator: nasopharyngitis (4.1% vs. 3.3%), urinary tract infection (4.1% vs. 3.7%), upper respiratory tract infection (3.4% vs. 2.4%), bronchitis (2.0% vs. 1.8%) and pharyngitis (1.4% vs. 1.1%). The remaining types of reported infections were infrequent and reasonably balanced between treatment groups.

There are no unusual infections noted in the Periodic Safety Update Reports completed to date (through the cut-off date of October 15, 2011).

Safety in patients with mild renal impairment: As discussed under the Clinical Pharmacology section there is a 45-76% increase in alogliptin exposures in patients with mild renal impairment compared to those with normal renal function. The Clinical Pharmacology reviewers are recommending dosage adjustment to 12.5 mg for patients with mild renal impairment only if there is a safety concern with the 25 mg dose in this patient population. In the alogliptin phase 3 trials (including Study 402) there was no dosage adjustment of alogliptin for patients with mild renal impairment. Because many of the trials included alogliptin 12.5 mg and 25 mg treatment arms, some patients with mild renal impairment received alogliptin 12.5 mg and others received 25 mg. As shown in Table 14, using both the MDRD and Cockcroft-Gault formulas, the incidence of adverse events among patients with mild renal impairment who received alogliptin 25 mg was comparable to that of patients with mild renal impairment who received 12.5 mg. In addition, there are decent safety margins based on the non-clinical data. Based on these considerations, it is reasonable to not require a dosage adjustment of alogliptin for patients with mild renal impairment.

Table 14. Adverse events* reported in alogliptin-treated patients with mild renal impairment						
Preferred Term	MDRD			Cockcroft-Gault		
	Placebo N=1019 n (%)	Alogliptin 12.5 mg N=1074 n (%)	Alogliptin 25 mg N=2235 n (%)	Placebo N=626 n (%)	Alogliptin 12.5 mg N=486 n (%)	Alogliptin 25 mg N=1149 n (%)
At least one adverse event	199 (20)	305 (28)	581 (26)	113 (18)	141 (29)	295 (26)
Oedema peripheral	14 (1.4)	28 (2.6)	58 (2.6)	6 (1.0)	11 (2.3)	26 (2.3)
Influenza	11 (1.1)	22 (2.0)	50 (2.2)	9 (1.4)	7 (1.4)	35 (3.0)
Upper respiratory tract infection	25 (2.5)	41 (3.8)	83 (3.7)	17 (2.7)	15 (3.1)	30 (2.6)
Nasopharyngitis	32 (3.1)	45 (4.2)	92 (4.1)	16 (2.6)	17 (3.5)	47 (4.1)
Urinary tract infection	28 (2.7)	49 (4.6)	90 (4.0)	16 (2.6)	30 (6.2)	49 (4.3)
Arthralgia	16 (1.6)	35 (3.3)	59 (2.6)	9 (1.4)	18 (3.7)	29 (2.5)
Back pain	16 (1.6)	28 (2.6)	60 (2.7)	8 (1.3)	16 (3.3)	26 (2.3)
Dizziness	16 (1.6)	36 (3.4)	41 (1.8)	9 (1.4)	19 (3.9)	26 (2.3)
Headache	22 (2.2)	44 (4.1)	92 (4.1)	15 (2.4)	22 (4.5)	42 (3.7)
Hypertension	26 (2.6)	39 (3.6)	70 (3.1)	13 (2.1)	15 (3.1)	39 (3.4)
*in >2% of alogliptin-treated patients and at a higher incidence with alogliptin 12.5 mg than with placebo						

Laboratory data: Renal tests are covered separately below and liver tests are covered under the Adverse Events of Interest section. In the pooled phase 2/3 trials (excluding 16-week Study 301, which used a local laboratory with different laboratory ranges), there are no clinically meaningful differences between alogliptin and comparator with respect to mean changes from baseline for the other chemistry as well as the hematology laboratory parameters.

With regard to markedly abnormal test results, there were minor imbalances for the percentage of patients with at least one treatment-emergent serum potassium value >5.8 mEq/L (3.0% for alogliptin vs. 2.4% for all comparators) although this imbalance is less apparent for alogliptin (3.0%) vs. active comparator (2.7%). The mean and median changes from baseline in serum potassium with alogliptin in the pool of phase 2/3 controlled trials were both 0.0 mEq/L. In addition, there has not been a signal in the controlled trials for adverse events associated with hyperkalemia.

There were also minor imbalances for the percentage of patients with uric acid >10.5 mg/dL for men or >8.5 mg/dL for women (2.9% for alogliptin vs. 2.6% for comparator). Despite this minor numerical imbalance for uric acid, the incidence of gout in the pool of controlled phase 2/3 trials was low and comparable between treatment groups (0.2% for placebo, 0.3% for all comparators, 0.2% for all alogliptin).

Renal function: In the pool of controlled phase 2/3 trials, there were no clinically meaningful changes from baseline to endpoint for serum creatinine (0.0 mg/dL for alogliptin vs. 0.0 mg/dL for all comparators). The median change from baseline to endpoint in the urinary albumin/creatinine ratio was -1.0 mcg/mg for all comparators vs. -3.0 mcg/mg for alogliptin-treated patients.

No concerning pattern is seen based on shift analyses for renal function (Table 15). For example, numerically fewer alogliptin-treated patients than comparator-treated patients shifted from normal renal function at baseline to abnormal renal function at endpoint, regardless of whether the MDRD or Cockcroft-Gault formula is used. Findings for the other shift categories are inconsistent – for example, with MDRD more alogliptin-treated patients than comparator-treated shifted from mild to moderate or severe renal impairment whereas the converse was true with the Cockcroft-Gault formula. A similar inconsistency was seen for the shift from moderate to severe renal impairment.

Table 15. Shift analyses from baseline to endpoint for renal function

Shift	MDRD		Cockcroft-Gault	
	All Alogliptin	All Comparators	All Alogliptin	All Comparators
Normal to abnormal	34.9%	36.2%	8.2%	9.1%
Mild to moderate or severe	8.6%	6.6%	6.4%	7.5%
Moderate to severe	1.3%	2.6%	2.6%	1.3%

In addition, no concerning pattern is seen with regard to outlier analyses using the pool of controlled phase 2/3 data, as illustrated by the examples below:

- The incidence of serum creatinine $>1.5\times$ baseline and $>ULN$ was 0.7% for all comparators vs. 0.5% for alogliptin.
- The incidence of serum creatinine >2 mg/dL was 1.4% for all comparators and 1.0% for alogliptin
- $>50\%$ decrease from baseline in renal function occurred in 0.2% of all comparators vs. 0.2% of alogliptin-treated patients (based on Cockcroft-Gault) and in 0.4% of all comparators vs. 0.3% of alogliptin-treated patients (based on MDRD)

In our Complete Response letter for the alogliptin/pioglitazone FDC, we noted a greater incidence in elevations of serum creatinine and urinary albumin/creatinine ratios in the combination alogliptin+pioglitazone treatment group compared to the alogliptin and pioglitazone monotherapy groups. We also noted that more patients in the combination group experienced a shift from normal to mild or moderate renal impairment compared to the individual treatment groups. The sponsor conducted updated renal analyses that pools data for the trials supporting the FDC (the previously reviewed phase 3 studies OPI-001 and OPI-002 and the newly completed OPI-004). Findings are summarized below:

- The mean change from baseline to endpoint in serum creatinine is 0.0 mg/dL for alogliptin+pioglitazone, alogliptin alone and pioglitazone alone.
- The percentage of patients who had a shift in serum creatinine from normal at baseline to high at endpoint was 1.0% for alogliptin+pioglitazone vs. 0.3% for alogliptin alone vs. 0.3% for pioglitazone. There is a suggestion of perhaps a mild effect on serum creatinine as further reflected by the percentages of patients who had at least one serum creatinine $>ULN$ with a >0.3 mg/dL increase from baseline (1.1% for alogliptin+pioglitazone vs. 0.7% for alogliptin alone vs. 0.6% for pioglitazone alone). However, more extreme elevations are balanced between treatment groups. For example, at least one serum creatinine $>1.5\times$ baseline occurred in 1.3% of patients in the alogliptin+pioglitazone group, 1.2% of patients in the alogliptin alone group and 1.0% of patients in the pioglitazone alone group. The clinical significance of this finding is unclear but should be labeled.
- With regard to the urine albumin/creatinine ratio, the mean change from baseline to endpoint was +13.5 mcg/mg for alogliptin+pioglitazone, -2.6 mcg/mg for alogliptin alone and -0.2 mcg/mg for pioglitazone alone. However, these means are skewed because of outliers as reflected by the very large standard deviations (467 mcg/mg for alogliptin+pioglitazone, 132 mcg/mg for alogliptin alone and 156 mcg/mg for pioglitazone alone). The median change from baseline (which is a better reflection of central tendencies in this setting because of the reason stated above) was -6.0 mcg/mg for alogliptin+pioglitazone, -4.0 mcg/mg for alogliptin alone, and -5.0 mcg/mg for pioglitazone alone – differences that are not clinically meaningful. Outlier analyses of urinary albumin/creatinine ratios also yield reassuring results. For example, the percentage of patients with at least one post-baseline urinary albumin/creatinine ratio that was $\geq 2\times$ the baseline value was 14.4% for alogliptin+pioglitazone, 13.5% for alogliptin alone and 16.6% for pioglitazone alone. The corresponding percentages using a $\geq 3\times$ criterion instead of a $\geq 2\times$ criterion were 7.9% for alogliptin+pioglitazone, 6.4% for alogliptin alone and 8.2% for pioglitazone alone.

Vital signs: I agree with Dr. Pratt that there are no clinically meaningful effects of alogliptin on systolic blood pressure, diastolic blood pressure or heart rate in the pooled phase 2/3 database.

In the previously reviewed add-on to sulfonylurea trial, the mean baseline body weight was approximately 80 kg, and the mean change in body weight from baseline to Week 26 in the modified intent-to-treat population with last-observation-carried-forward was +0.6 kg with alogliptin 12.5 mg, +0.7 kg with alogliptin 25 mg, and -0.2 kg with placebo. Therefore, in this trial, alogliptin 12.5 mg resulted in a mean modest weight gain of +0.8 kg relative to placebo ($p=0.02$) and alogliptin 25 mg resulted in a mean modest weight gain of +0.9 kg relative to placebo ($p=0.01$). In the remaining placebo-controlled phase 3 trials alogliptin had no effect on body weight.

Below I focus on the body weight changes for the two newly completed phase 3 trials (Table 16). For the study comparing alogliptin to glipizide in the elderly, alogliptin resulted in a mean decrease from baseline in body weight at Week 52 of 0.6 kg compared to a mean increase of 0.6 kg for glipizide (treatment difference -1.2 kg; 95% confidence interval -1.9, -0.6). Although this treatment difference is statistically significant ($p<0.001$), it is modest. It is possible that a greater treatment difference may have been seen if glipizide was more appropriately uptitrated. For the trial comparing alogliptin as add-on therapy to metformin and pioglitazone 30 mg vs. metformin and pioglitazone uptitration to 45 mg, there were no clinically relevant or statistically significant differences between treatment groups.

Table 16. Body weight (kg) change from baseline for Study 303 and OPI-004 (Study OPI-004 results adapted from Table 11 in Dr. Janice Derr’s biostatistics review)				
Treatment Group	n	Baseline mean	LS mean change	Treatment difference LS mean change (95% CI); p-value
Study 303 – Week 52				
Alogliptin	215	78.7	-0.6	-1.2 (-1.9, -0.6); p<0.001
Glipizide	204	78.7	0.6	
Study OPI-004				
Week 26				
Alogliptin add-on	395	87.9	0.7	-0.2 (-0.7, 0.2); p=0.25
Pioglitazone uptitration	394	88.5	1.0	
Week 52				
Alogliptin add-on	395	87.9	1.1	-0.5 (-1.0, 0.0) ; p=0.07
Pioglitazone uptitration	394	88.5	1.6	
CI = confidence interval				

Electrocardiograms: As mentioned by Dr. Pratt, there is no clinically meaningful effect of alogliptin on the QT interval based on results of a Thorough QT Study reviewed as part of the original NDA. I agree with Dr. Pratt that there are no clinically meaningful changes in electrocardiogram parameters based on the locally-read electrocardiograms for the pool of controlled phase 2/3 trials.

9. Advisory Committee Meeting

These submissions were not taken to advisory committee.

10. Pediatrics

Alogliptin: The sponsor is requesting a waiver from the requirements of the Pediatric Research Equity Act (PREA) for children <10 years of age and a deferral for those 10-17 years of age. This request for a waiver (too few children <10 years of age with type 2 diabetes to feasibly study) and deferral is consistent with our approach to other oral antidiabetic medications and is acceptable. The sponsor's pediatric plan for alogliptin was discussed with the Pediatric Review Committee (PeRC) during the first review cycle. A few modifications have been made (see below) but this did not trigger another meeting with PeRC (we communicated these modifications to PeRC via email and informed PeRC that the modifications are in-line with our approach to other recent oral antidiabetic medications).

The sponsor initially proposed two pediatric studies to satisfy PREA:

- Study 104: A pediatric clinical pharmacology study comparing the pharmacokinetics and pharmacodynamics of alogliptin in children to that of adults. This study is ongoing and we have received several protocol amendments which have been reviewed and determined to be acceptable. The proposed study completion date is October 2012 and the report submission date is April 2013.
- Study 309: A phase 3, (b) (4) randomized, double-blind trial (b) (4)

During this review cycle, we informed the sponsor that other recently-approved treatments for type 2 diabetes have been expected under PREA to conduct efficacy and safety trial(s) in pediatric patients who are treatment naïve as well as pediatric patients who have failed metformin. We stated that this can be accomplished in a single trial or two separate trials. We also informed the sponsor that we have been expecting at least one year of controlled pediatric data (an extension trial after the primary efficacy endpoint is acceptable).

Based on these comments, the sponsor has proposed to revise Study 309 so that the double-blind treatment period is 52 weeks. (b) (4)

The sponsor proposes a protocol submission date of December 2013, a study completion date of January 2019, and a report submission date of July 2019.

Based on our comments above, the sponsor is now also proposing a second phase 3, randomized, double-blind trial (Study 307). (b) (4)

(b) (4)

The sponsor proposes a protocol submission date of December 2013, a study completion date of January 2019, and a report submission date of July 2019.

Overall, the scope of the revised pediatric plan is acceptable and consistent with other trials conducted under PREA for type 2 diabetes. We may have additional comments after we receive the draft full protocols (e.g., we may request a primary efficacy timepoint of at least 16 weeks for the monotherapy efficacy and safety trial).

Alogliptin/pioglitazone FDC: The sponsor is requesting a full pediatric waiver for the alogliptin/pioglitazone FDC product based on the known safety concerns with pioglitazone. PeRC agreed with the waiver but recommended that we more explicitly state the safety concerns in Section 8.4 (Pediatric Use) of the labels for all pioglitazone-containing products, including the alogliptin/pioglitazone FDC. The sponsor has already agreed to the following strengthened language for Actoplus Met (pioglitazone/metformin FDC), which we will use for the alogliptin/pioglitazone FDC as well:

“Safety and effectiveness of DRUG in pediatric patients have not been established. DRUG is not recommended for the treatment of diabetes in pediatric patients based on adverse effects observed with pioglitazone in adults, including fluid retention and congestive heart failure, fractures, and urinary bladder tumors [see *Warnings and Precautions* (5.X, 5.X, 5.X, 5.X)].”

11. Other Relevant Regulatory Issues

Tradename Review: The Division of Medication Error Prevention and Analysis (DMEPA) determined that the tradename Nesina (for alogliptin) is acceptable. See the reviews by Dr. Anne Tobenkin and Sarah Vee for details. On December 23, 2011, DMEPA determined that the tradename Oseni (for the alogliptin/pioglitazone FDC) is acceptable. See the review by Dr. Reasol Agustin for details. Note that these DMEPA review for Oseni was finalized more than 90 days prior to the action goal date of April 25, 2012. Therefore, we will request that it undergo re-review later this month if there is a possibility that the NDAs will be approved.

Office of Scientific Inspections (OSI): OSI inspected the sponsor as well as six clinical sites that enrolled patients in at least one of the following studies: the ongoing cardiovascular outcomes trial (Study 402), the trial comparing add-on therapy with saxagliptin vs. uptitration of pioglitazone (Study PI-004), and the elderly study comparing alogliptin to glipizide (Study 303). We chose sites based on large numbers of study patients, participation in more than one study, history of protocol violations and complaints, and ranking in the risk based model site selection tool. Four of the inspected sites were classified as NAI (no deviation from regulations). One site (Dr. Jeffrey Rosen, Coral Gables, Florida) was classified as VAI (deviations from regulations) because of failures to maintain adequate case histories. However, OSI determined that these violations were isolated in nature and unlikely to significantly impact data reliability. The remaining site (Dr. Pedro Lagrosa, Huntington Park, California)

(b) (7)(A)

had isolated violations pertaining to the alogliptin NDA

(b) (7)(A)

This site randomized 24 patients into Study 303 (alogliptin vs. glipizide in the elderly). As per OSI's recommendations, we conducted a sensitivity analysis of the primary efficacy endpoint, excluding the data from this site (see Section 6 for details).

OSI also inspected Takeda with regard to organizational duties and responsibilities, Standard Operating Procedures, the monitoring and auditing program, sponsor-clinical site correspondence, sponsor site audits, data management, drug accountability and Contract Research Organization contracts. No significant concerns were identified.

12. Labeling

We have completed two rounds of labeling revisions with the sponsor and will continue with labeling edits unless Dr. Curtis Rosebraugh, the signatory authority, confirms that alogliptin will not be approved.

Our main approach has been to align the alogliptin label (and the alogliptin portion of the FDC label) with the labels of the already approved DPP-4 inhibitors and to conform to the Physician's Labeling Rule (PLR) format.

If a decision is made to approve alogliptin, the label will need to include adequate information on hepatotoxicity.

Given that there are cases of pancreatitis and hypersensitivity reactions for which we cannot exclude alogliptin as the cause, it is reasonable to label these reactions, particularly because these types of reactions are included in the labels for other approved DPP-4 inhibitors and GLP-1 agonists. Discussions will need to involve Dr. Amy Egan, Deputy Director for Safety, as to whether there should be a Medication Guide for these reactions, similar to the Medication Guides for sitagliptin and saxagliptin.

The sponsor is proposing a dose of 25 mg for patients with normal renal function or mild renal impairment. I agree that no dosage adjustment is needed for patients with mild renal impairment. However, as shown in my original alogliptin NDA, the 12.5 mg and 25 mg doses have comparable efficacy. Therefore the recommended dose for patients with normal renal function or mild renal impairment should be 12.5-25 mg, similar to how we labeled the dosing for saxagliptin.

I am in favor of including some results from the elderly study in the label even though there are some important limitations that will need to be included. For one, this study shows the modest efficacy of alogliptin in this patient population. It also shows the significant risk of hypoglycemia with glipizide even when used at suboptimal doses.

It is acceptable to include the results from the study comparing add-on alogliptin vs. uptitration of pioglitazone to the label. A similar trial with uptitrated comparator is included in the saxagliptin label (in that case the comparator was glipizide).

Other labeling recommendations are covered throughout my memorandum.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

COMPLETE RESPONSE

- Risk Benefit Assessment

The sponsor has adequately addressed the deficiencies communicated in our 2009 Complete Response letter. Specifically, the sponsor met the 1.8 criterion recommended in the diabetes cardiovascular guidance, provided agreed-upon long-term (1-year) exposures to alogliptin in controlled clinical trials, analyzed the safety of the 25 mg dose of alogliptin in patients with mild renal impairment, conducted an adequate embryofetal development study in rats testing alogliptin in combination with metformin, and provided updated analyses of renal function. In addition, all manufacturing facilities are adequate and a 6.25 mg dose of alogliptin is not needed to support approval of the alogliptin/pioglitazone FDC, as agreed-upon at the End-of-Review meeting.

Safety concerns identified with alogliptin, such as pancreatitis and hypersensitivity reactions, have been seen with other drugs that work through the incretin pathway (including other DPP-4 inhibitors and GLP-1 receptor agonists). These safety concerns would need to be adequately labeled but do not rise to the level of impacting approvability of alogliptin.

However, there is a new signal in the Complete Response resubmission for drug-induced liver injury with alogliptin. This signal was not present in the original NDA and has emerged based on postmarketing data from Japan, where there is ~219,000 patient-years of exposure to alogliptin. There are no convincing Hy's Law cases in the clinical trial database (i.e., all cases of biochemical Hy's Law with alogliptin appear to have reasonable alternative etiologies). In the pool of the controlled phase 2/3 trials (including the Japanese studies and the ongoing cardiovascular outcomes trial) there are numerical imbalances not favoring alogliptin for serum ALT elevations >5x, >8x, >10x, and >20x ULN vs. comparator. For example, 8/7011 alogliptin-treated patients and 0/4074 comparator-treated patients developed serum ALT >10x ULN. Review by Dr. Seeff has determined that at least six of the eight cases with alogliptin appear to have alternative etiologies and are not likely to be due to alogliptin. However, the ALT imbalances are still noteworthy given the concerning postmarketing liver cases and the expectation that a similar extent of serum ALT elevations would generally be expected in a relatively large dataset consisting of randomized, controlled trials.


Furthermore, we have identified concerning cases of liver injury among patients exposed to alogliptin in the postmarketing setting. The postmarketing data available from ~219,000 patient-years of exposure to alogliptin provide a glimpse of what may occur with alogliptin when it is used more widely, if approved in the United States. Dr. Seeff has identified five cases of probable alogliptin-induced drug injury, one case that he states is possible-to-probable, and several cases that he states are possibly attributable to alogliptin. The two most concerning cases (TCI2011A04573 and TCI201A06837) presented with jaundice and significant hepatocellular injury. In one instance (4573), the patient developed fulminant hepatitis even though alogliptin was discontinued and ultimately died after developing pneumonia, possibly a consequence of treatment with glucocorticoids. The second case (6837) involved a man who recovered after discontinuation of alogliptin. As discussed previously, Dr. Seeff's and Dr. Senior's conclusion for Case 4573 differs from that reached by the consultants hired by Takeda. However, I find Dr. Seeff's and Dr. Senior's rationale (see the Hepatotoxicity section) more convincing than I do the rationale provided by Takeda's consultants. Note that we cannot definitively state that alogliptin caused hepatotoxicity in these cases (e.g., a "highly likely" attribution has a 75-94% likelihood and a "probable" attribution has a "50-74" likelihood of causality). However, these cases raise concerns that alogliptin has the potential to cause severe liver injury and one has to ask if there are any reasons to approve alogliptin now.

There are currently three other FDA-approved DPP-4 inhibitors – sitagliptin (approved in October 2006), saxagliptin (approved in July 2009) and linagliptin (approved in May 2011). Putting aside the hepatotoxicity issue, there are no unique efficacy or safety findings with alogliptin when compared to these other DPP-4 inhibitors – all lead to modest reductions in HbA1c, carry a generally low risk of hypoglycemia, are weight neutral and have an association with pancreatitis and hypersensitivity reactions. The remaining question is whether these other DPP-4 inhibitors are also associated with concerning postmarketing reports of hepatotoxicity and, if so, whether these reports occur at a similar rate to those seen with alogliptin.

As explained below I conclude based on the available data that there appears to be a stronger hepatotoxicity signal for alogliptin than for the other DPP-4 inhibitors.

As mentioned previously, Takeda estimates that there are ~219,000 patient-years of postmarketing exposure to alogliptin. This estimate was obtained by dividing the total number of tablets shipped by 365 (365 tablets represent one-patient year of exposure because alogliptin is dosed once-daily). Therefore, the two most concerning cases of hepatotoxicity associated with alogliptin use equates to 1 case per 110,000 patient-years. Including the three other probable cases of alogliptin hepatotoxicity increases the risk to 1 case per 44,000 patient-years.

Like alogliptin, sitagliptin is also dosed once per day and 365 tablets represent one patient-year of exposure. (b) (4)



(b) (4)

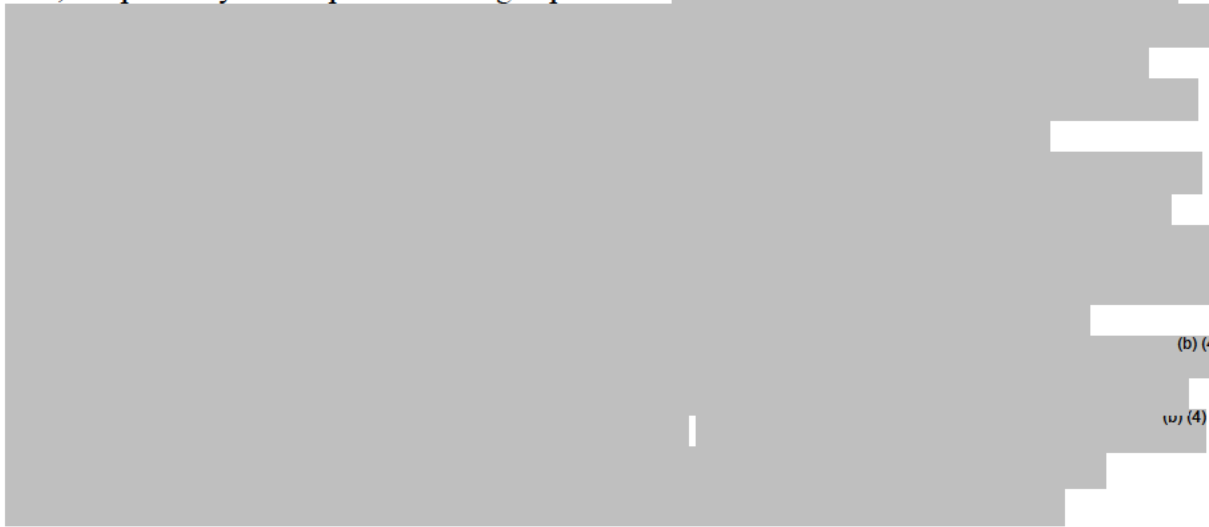
(b) (4)

(b) (4)

Note that the above calculations for all DPP-4 inhibitors likely overestimate patient-year exposures because not all of the shipped tablets are necessarily consumed by patients as of the cutoff date used for the calculations.

In summary, alogliptin has not been shown to have a unique benefit over approved DPP-4 inhibitors and has the potential liability of serious drug-induced liver injury that appears stronger than that seen for the other DPP-4 inhibitors. Therefore, it is hard to justify approving alogliptin now. One could ask why not approve alogliptin with a Warning about postmarketing reports of liver injury and recommendations to promptly measure liver tests in patients who report symptoms that may indicate liver injury as well as recommendations on when to interrupt or discontinue alogliptin. A labeling approach will likely not be effective in mitigating risk in all patients (e.g., it requires patients to recognize symptoms and seek medical care promptly) and is unlikely to prevent all cases of drug-induced liver injury, as reflected by the troglitazone experience. Given the potential frequency of serious liver injury with alogliptin, even if some cases are averted, the cases that are not averted seem too high a price to pay when there are other members of the drug class that do not appear to have this concerning a liability with regard to the liver.

So what should the sponsor do to obtain approval? Clearly more postmarketing experience from countries that choose to market alogliptin (currently only Japan) is needed. Clinical trial data (e.g., the completed cardiovascular outcomes trial) is not expected to be of sufficient scope to put the liver issues to rest given that the two most worrisome cases come from the 219,000 patient-years of postmarketing experience. (b) (4)



It took about 18 months to generate 117,000 patient-years of exposure to alogliptin in Japan and another four months after that to generate an additional ~100,000 patient-years of exposure to alogliptin. The sponsor estimates that its next interim analysis for Study 402 is planned for August 2014 (the final analysis, if needed, is planned for July 2015). Therefore, the earliest date for submission of the completed Study 402 is estimated to be in December 2015. In these next 3.75 years, the sponsor should be able to generate substantially more postmarketing data, particularly if alogliptin is approved elsewhere or if uptake in Japan quickens. Then, these additional postmarketing data could be viewed together with the final cardiovascular assessment to determine whether there is a favorable risk-benefit analysis to support approval. It is possible that the sponsor may be able to submit before 2015 without the completed Study 402 if there are reassuring results from substantial postmarketing use before then. In any case, the sponsor should be strongly encouraged to perform enhanced pharmacovigilance going forward for all reports of liver abnormalities to ensure that as much information as possible is obtained for these cases.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Not applicable as I am recommending a Complete Response.

- Recommendation for other Postmarketing Requirements and Commitments

Not applicable as I am recommending a Complete Response.

- Recommended Comments to Applicant

None.

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/s/

HYLTON V JOFFE
04/20/2012

MARY H PARKS
04/20/2012

CLINICAL REVIEW

Application Type	NDA Complete Response
Application Number(s)	22-271 and 22-426
Priority or Standard	Standard

Submit Date(s)	7-25-11
Received Date(s)	7-25-11
PDUFA Goal Date	4-25-12
Division / Office	DMEP/ODEII/OND

Reviewer Name(s)	Valerie S.W. Pratt, M.D.
Review Completion Date	02-29-12

Established Name	Alogliptin and alogliptin/pioglitazone FDC
(Proposed) Trade Name	Nesina and Oseni
Therapeutic Class	DPP4 inhibitor and DPP4 inhibitor/TZD FDC
Applicant	Takeda

Formulation(s)	Tablet
Dosing Regimen	Alogliptin: 6.25, 12.5, or 25 mg daily FDC: 12.5/15, 12.5/30, 12.5/45, 25/15, 25/30, 25/45 mg daily
Indication(s)	Type 2 diabetes mellitus
Intended Population(s)	Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Unless the February 22, 2012 Office of Surveillance and Epidemiology (OSE) consult demonstrates a similar propensity for serious liver injury with alogliptin when compared to other dipeptidyl peptidase-4 (DPP4) inhibitors, I recommend a complete response (CR) for the following two new drug applications (NDAs):

- NDA 22-271: Alogliptin (SYR-322) for the use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)
- NDA 22-426: Alogliptin/pioglitazone fixed dose combination (FDC) for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both alogliptin and pioglitazone is appropriate

1.2 Risk Benefit Assessment

The efficacy of alogliptin and alogliptin/pioglitazone FDC was previously demonstrated in the original NDA submissions. Alogliptin results in a 0.4% - 0.6% reduction in HbA1c from baseline at week 26 relative to placebo. Alogliptin/pioglitazone FDC results in an additional reduction of 0.4% - 0.6% over pioglitazone monotherapy and 0.4% - 0.9% over alogliptin monotherapy. Since 12.5 and 25 mg daily result in similar efficacy (see Section 6.1.8), I would recommend both doses for use in subjects with normal renal function if approved.

To increase the controlled safety population and address the deficiencies specified in the complete response letters (see section 2.5), the applicant submitted the following four new clinical studies, which are described more in section 5:

- SYR-322_303 (303): *A multicenter, randomized, double-blind study to evaluate the efficacy and safety of alogliptin compared to glipizide in elderly subjects with T2DM*
- 01-06-TL-322OPI-004 (OPI-004): *A multicenter, randomized, double-blind study to determine the efficacy and safety of the addition of SYR-322 25 mg versus dose titration from 30 mg to 45 mg of Actos pioglitazone HCl in subjects with T2DM who have inadequate control on a combination of metformin and 30 mg of pioglitazone HCl therapy*
- SYR-322_301 (301): *A multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing SYR-322 alone and combination SYR-322 with pioglitazone versus placebo on postprandial lipids in subjects with T2DM*

- SYR-322_402 (402, EXAMINE): *A multicenter, randomized, double-blind, placebo-controlled study to evaluate CV outcomes following treatment with alogliptin in addition to standard of care in subjects with T2DM and acute coronary syndrome*

The risks of alogliptin and alogliptin/pioglitazone FDC are as follows:

- Hepatotoxicity: As shown in Table 58, there is an imbalance in the number and percentage of subjects with markedly abnormal ALT values, including ALT >10x and 20x ULN, in the clinical trials. As described in the July 2009 guidance, *Drug-Induced Liver Injury: Premarketing Clinical Evaluation*, ALT is generally considered more liver-specific than AST. The finding of a higher rate of ALT elevation in drug-treated subjects than in a control group is a sensitive (but not necessarily specific) signal of the potential for drug induced liver injury (DILI). Greater aminotransferase increases (e.g., 10x-, 15xULN) in clinical trials, such as those shown in Table 58 are a more specific signal for DILI but not as specific as Hy's Law. Furthermore, I am concerned by postmarketing Hy's law cases TC12011A04573 and TC12011A06837 which describe moderate to severe liver injury and a probable or highly likely association to alogliptin. I am concerned that these two cases have potentially been identified after only 117,359 patient-years exposure in Japan. More cases of alogliptin-associated liver toxicity may occur if the drug is used more widely. There are also four clinical trial cases of biochemical Hy's law (303/3128-003, 012/961-3006, 012/961-2501, and 305/5304-005) that appear to have alternative explanations. These four cases as well as cases of ALT elevation >10x ULN in the clinical trial database are undergoing review by Dr. Leonard Seeff, a hepatologist within OSE, and will be further addressed in the CDTL memorandum. However, based on even the 2 postmarketing cases of moderate/severe liver injury, unless the pending OSE consult demonstrates a similar propensity for liver injury with other DPP-4 inhibitors, I recommend a complete response to this application and require the applicant to more clearly demonstrate the liver safety of alogliptin. Specifically, I recommend the applicant analyze serious liver events in postmarketing data and the ongoing, controlled, double-blind clinical studies 305, 402, and 308, which were described in the December 2011 annual report (IND 69,707 SDN 691).
- Hypersensitivity: Narrow Anaphylactic Reaction, Angioedema, and Severe Cutaneous Adverse Reactions (SCAR) Standardized MedDRA Queries (SMQ) searches do not suggest alogliptin subjects are at increased risk for hypersensitivity events. However, there have potentially been two angioedema, four Stevens-Johnson syndrome (SJS), and five erythema multiforma serious Japanese postmarketing reports, in addition to the Skin Lesion findings described below. This is consistent with other DPP-4 inhibitors and is not an approvability issue but would need to be adequately labeled when alogliptin can be approved. I therefore recommend that use of alogliptin be contraindicated in subjects with a history of serious hypersensitivity reaction to alogliptin. I also recommend a warning and description of the postmarketing events. Hypersensitivity should be

monitored as an adverse event (AE) of special interest in the controlled CV study 402 and the PSURs.

- Skin lesions: The percentage of subjects reporting at least one potential cutaneous drug reaction (PCDR) AE in the completed clinical trials was numerically greater in the alogliptin groups (8.1% and 8.4%) than all comparators (6.6%). (The list of preferred terms comprising PCDRs was agreed upon with the sponsor prior to resubmission.) The incidence of rash, pruritis, dermatitis, rash papular, and rash macular was numerically greater in the alogliptin groups than all comparator group. Although these skin reactions are not likely related to the necrotic lesions seen with other DPP4 inhibitors, they suggest that sensitive individuals may be hypersensitive to alogliptin. The incidence of PCDR serious adverse events (SAEs) and AEs leading to discontinuation, however, were low (0.1-0.3%). This is not an approvability issue but would need to be adequately labeled when alogliptin can be approved.
- Pancreatitis: Pancreatitis events have been observed in alogliptin subjects in clinical trials and postmarketing in Japan, including one fatal case (TCI2010A04635) of necrotizing pancreatitis (although a dilated extrahepatic common bile duct consistent with multiple gallbladder stones was seen on autopsy). This is consistent with other DPP4 inhibitors and is not an approvability issue but would need to be adequately labeled when alogliptin can be approved.
- Infection: The pooled clinical trial safety data was searched for events in the infections and infestations systems organ class (SOC). Events that occurred at >1% incidence in the alogliptin 25 mg group and more commonly than the all comparator group were the following: nasopharyngitis (3.9% vs. 3.3%), upper respiratory tract infection (3.5% vs. 2.4%), bronchitis (1.9% vs. 1.8%), and pharyngitis (1.2% vs. 1.1%). This is consistent with other DPP4 inhibitors and is not an approvability issue but would need to be adequately labeled when alogliptin can be approved.
- Malignancy (including bladder, thyroid, and pancreatic cancer): The incidence of AEs of malignancy was similar in the alogliptin 25 mg, all alogliptin, and all comparator groups (0.4-0.5%), although pioglitazone is associated with a potential risk for bladder cancer and relatively short-term trials with limited exposures are not the best way to assess this safety risk.
- Fractures: In the limited clinical trial database, the use of alogliptin with pioglitazone does not increase the risk of fracture significantly more than the use of pioglitazone alone (FDC 0.8% vs. pioglitazone 0.5%).
- Hypoglycemia: Alogliptin does not appear to increase one's risk of hypoglycemia when compared to placebo. However, a lower dose of insulin or sulfonylurea may be required to reduce the risk of hypoglycemia when used with alogliptin. This is consistent with other DPP4 inhibitors and is not an approvability issue but would need to be adequately labeled when alogliptin can be approved.

The applicant proposes alogliptin 25 mg daily for use in subjects with normal renal function and 12.5 mg and 6.25 mg for subjects with moderate and severe renal

impairment (RI), respectively. The sponsor's proposed alogliptin dosage adjustment for RI is acceptable. No consistent, clinically relevant changes were noted in the following CR data:

- Number and percentage of subjects with abnormal renal function parameters in the alogliptin and alogliptin/pioglitazone FDC NDAs
- Incidence of abnormal urine albumin:creatinine ratio in the FDC NDA
- Shifts in renal function (CG and MDRD formulas) in the alogliptin NDA
- Renal function-related discontinuations and SAEs in the alogliptin and alogliptin/pioglitazone FDC NDAs

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Given my recommendation for a complete response, no postmarketing risk evaluation and mitigation strategies should be put in place at this time.

However, if alogliptin and/or alogliptin/pioglitazone FDC were approved in the future, based on my current understanding of the drug products, I would recommend the following. (Please note these recommendations do not pertain to the potential liver safety signal, as in my opinion this signal should be better defined before approval.)

- Alogliptin
 - A medication guide (MG) which includes information about alogliptin's risk of pancreatitis and hypersensitivity reactions (as was done for sitagliptin and saxagliptin).
- Alogliptin/pioglitazone FDC
 - A MG, similar to alogliptin
 - A Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drug outweigh the risk of congestive heart failure (CHF) and bladder cancer in patients being treated with pioglitazone. The REMS should include a medication guide (MG) and timetable for submission of assessments of the REMS, as discussed with the Office of Surveillance and Epidemiology (OSE). This recommendation is based on the fact that pioglitazone has a REMS. There have been discussions about discontinuing the pioglitazone REMS. The same decision-making pertaining to the pioglitazone REMS should apply to the alogliptin/pioglitazone FDC.

1.4 Recommendations for Postmarket Requirements and Commitments

Given my recommendation for a complete response, no postmarketing requirements (PMRs) should be put in place at this time.

However, if alogliptin and/or alogliptin/pioglitazone FDC were approved in the future, based on my current understanding of the drug products, I would recommend the following alogliptin PMRs. (Please note again that these recommendations do not pertain to the potential liver safety signal, as in my opinion this signal should be better defined before approval.)

- Completion of SYR-322_402 (402, EXAMINE): *A multicenter, randomized, double-blind, placebo-controlled study to evaluate CV outcomes following treatment with alogliptin in addition to standard of care in subjects with T2DM and acute coronary syndrome*
- Pediatric studies under the Pediatric Research Equity Act (PREA) and as further described in section 7.6.3:
 - SYR-322_104 (104): *A comparative, randomized, open-label, multicenter, single dose, pharmacokinetic, pharmacodynamic and safety study of alogliptin (12.5 mg and 25 mg) between children, adolescents, and adults with type 2 (non-insulin dependent) diabetes mellitus*
 - SYR-322_307 (307): *A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of alogliptin compared with placebo as monotherapy (with a metformin control arm) in pediatric subjects with T2DM*
 - SYR-322_309 (309): *A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of alogliptin compared with placebo when added on to metformin in pediatric subjects with type 2 diabetes*

I would also recommend the Periodic Safety Update Reports (PSURs) summarize the adverse events (AEs) of interest (e.g., hypersensitivity [including skin and subcutaneous tissue disorders] and pancreatitis).

2 Introduction and Regulatory Background

2.1 Product Information

Takeda Global Research and Development Center, Inc. (TGRD) has submitted CRs to NDAs 22-271 and 22-426 for new molecular entity (NME) alogliptin (a dipeptidyl peptidase-4 [DPP4] inhibitor) and alogliptin/pioglitazone FDC, respectively.

In NDA 22-271, the applicant proposes use of 6.25, 12.5, or 25 mg alogliptin daily as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The recommended dose of alogliptin is 25 mg daily, taken with or without food as mono- or combination therapy. The sponsor recommends dosage adjustment in patients with moderate or severe RI and in patients with end stage renal disease (ESRD) requiring dialysis as shown in Table 1.

Table 1. NDA 22-271: Sponsor-proposed alogliptin dosage adjustment for moderate, severe, and ESRD

Degree of renal insufficiency	Serum creatinine levels (mg/dl)	Creatinine clearance (ml/min)	Recommended dosing
Moderate	Men > 1.7 to ≤ 3.0 Women > 1.5 to ≤ 2.5	≥ 30 to < (b) (4)	12.5 mg once daily
Severe/ESRD	Men > 3.0 Women > 2.5	< 30	6.25 mg once daily*
*Without regard to timing of dialysis in patients with ESRD			

In NDA 22-426, the applicant proposes the use of alogliptin/pioglitazone FDC 12.5/15, 12.5/30, 12.5/45, 25/15, 25/30, or 25/45 mg daily as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both alogliptin and pioglitazone is appropriate. Pioglitazone is a thiazolidinedione (TZD), specifically a peroxisome proliferator-activated receptor γ [PPAR γ] agonist. The applicant recommends a dose reduction for the alogliptin component from 25 mg to 12.5 mg daily in patients with moderate RI. Use of the FDC is not recommended in patients with severe RI or ESRD, because a FDC formulation has not been developed that provides the dose of alogliptin (6.25 mg) required for these patients. On February 23, 2010, the agency agreed that, due to low expected use (<2%), the applicant need not manufacture FDC doses containing 6.25 mg alogliptin. Product labeling can appropriately address dosing of patients with severe RI through co-administration of alogliptin and pioglitazone.

During the first review cycle clinical pharmacology recommended dose adjustment to 12.5 mg for subjects with mild renal impairment due to a mean AUC increase of 69% in these subjects. Please refer to Sang Chung's January 18, 2012 review of the CRs which revised this position and accepted the applicant's proposed dosing regimen.

2.2 Tables of Currently Available Treatments for Proposed Indications

Medications currently approved for the treatment of T2DM include the following:

- Insulin
- Sulfonylureas (SUs)
 - Tolazamide (Tolinase)
 - Chlopropramide (Diabinese)
 - Glyburide (Micronase)
 - Glipizide (Glucotrol and Glucotrol XL)
 - Glimepiride (Amaryl)
- Meglitinide analogs: Repaglinide (Prandin)
- D-Phenylalanine: Nateglinide (Starlix)
- Biguanides: Metformin (e.g., Glucophage and Glucophage XR)

- Thiazolidinediones
 - Rosiglitazone (Avandia)
 - Pioglitazone (Actos)
- α -Glucosidase inhibitors
 - Acarbose (Precose)
 - Miglitol (Glyset)
- GLP-1 receptor agonists
 - Exenatide (Byetta and Bydureon)
 - Liraglutide (Victoza)
- Amylinomimetics
 - Pramlintide (Symlin)
- Dipeptidyl peptidase 4 inhibitors
 - Sitagliptin (Januvia)
 - Saxagliptin (Onglyza)
 - Linagliptin (Tradjenta)
- Bile acid sequestrants
 - Colesevelam (WelChol)
- Dopamine receptor agonists
 - Bromocriptine mesylate (Cycloset)
- FDCs of the various oral medications listed above

2.3 Availability of Proposed Active Ingredient in the United States

Alogliptin is not currently approved for use in the United States (US). Pioglitazone has been approved for the treatment of T2DM since July 15, 1999.

Alogliptin was approved for use in Japan on April 16, 2010. The alogliptin/pioglitazone FDC was approved for use in Japan on July 1, 2011.

2.4 Important Safety Issues With Consideration to Related Drugs

Labeled safety issues for other DPP4 inhibitors include the following:

- A contraindication for patients with a history of a serious hypersensitivity reaction, such as anaphylaxis or angioedema
- Pancreatitis
- Acute renal failure, sometimes requiring dialysis
- Hypoglycemia when used with insulin or an insulin secretagogue
- Serious allergic and hypersensitivity reactions
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with pioglitazone or any other anti-diabetic drug

Additional safety concerns with DDP4 inhibitors include the following:

- Infections: DPP4 has many substrates other than glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), including chemokines involved in immune development and function. DPP-4 is expressed on a subset of CD4+ and CD8+ T-cells and natural killer cells. Thus, there is a theoretical concern that DPP-4 inhibition may increase the risk for infections.
- Skin lesions: Necrotizing skin lesions, which have been observed in monkeys given other DPP4 inhibitors, were not seen in alogliptin studies in mice, rats, dogs, or monkeys. The NOAEL for skin-related toxicity in the 13 week monkey study was 30 mg/kg/d (the highest tested dose), which provided approximately 31x expected human exposure. The lack of cutaneous toxicity may be due to alogliptin's high selectivity for DPP4, as opposed to DPP8 and/or DPP9.
- Hepatotoxicity: Vildagliptin, another DPP4 inhibitor which is currently in development, may cause hepatotoxicity. Vildagliptin's sponsor was asked to conduct a dedicated hepatic safety study.
- Malignancy: Studies suggest that DPP4 (CD26) may have a role in human tumor progression.¹ Diabetic individuals may be at increased risk of malignancy. Furthermore, long-acting GLP-1 analogues, such as liraglutide and exenatide once-weekly, increase thyroid C-cell adenomas and/or carcinomas in rats and/or mice. The alogliptin NOAEL for rat thyroid C-cell tumors was 32x. Exposure multiples were higher (≥188x) for doses that caused increased combined thyroid C-cell adenomas and carcinomas in male rats. There is no evidence of increased C-cell tumors with 3 other DPP4 inhibitors, sitagliptin, (b) (4) and saxagliptin. There was an absence of other drug-related tumors in rats (>400x female MRHD) or mice (60x MRHD).

Labeled safety issues for pioglitazone include the following:

- A boxed warning for congestive heart failure (CHF) and contraindication for patients with established New York Heart Association (NYHA) Class III or IV heart failure
- A contraindication for patients with a history of serious hypersensitivity reaction to pioglitazone or its ingredients
- Warnings and precautions for the following:
 - Dose-related edema
 - Hepatic effects
 - Increased incidence of fractures in female patients
 - Bladder cancer
 - Hypoglycemia when used with insulin or an insulin secretagogue
 - Macular edema

¹ Kajiya H, Shibata K, Ino K, Mizutani S, Nawa A, Kikkawa F. The expression of dipeptidyl peptidase IV (DPPIV/CD26) is associated with enhanced chemosensitivity to paclitaxel in epithelial ovarian carcinoma cells. Cancer Sci 2010;101(2):347-54.

- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with pioglitazone or any other anti-diabetic drug

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- April 27, 2009: Meeting was held to discuss proposed cardiovascular (CV) trial SYR-322_402 (402). Key agreements were as follows:
 - The agency recommended a traditional major adverse CV events (MACE) analysis (i.e. CV death, non-fatal myocardial infarction [MI], and non-fatal stroke). The results of CV study 402 should stand alone for assessing CV safety, although a pooled analysis of controlled data from phase 2/3 trials will be considered supportive.
 - The applicant proposed randomizing subjects 15-60 days after the diagnosis of acute coronary syndrome (ACS). The agency agreed but conveyed in a post-meeting comment that the applicant should not enroll subjects with ACS within 2 months from the index event, because early events could add noise to the trial and bias towards non-inferiority. On June 3, the sponsor stated its intent to keep the 15-60 day inclusion criterion. The agency cautioned that if there are many early events, the adequacy of the findings would be a review issue. This was reiterated to the sponsor in a communication dated October 26, 2009.
 - As ~300 subjects in study 402 will be on background pioglitazone, and assuming no evidence of interaction between the alogliptin and pioglitazone, a separate CV study of the FDC will not be required.
 - The applicant and agency agreed that ≥ 100 subjects with severe RI should have ≥ 1 year exposure to alogliptin. (See correspondence below for February 23, 2010, and September 23, 2010, regarding timing of these data).
- June 26, 2009: CR letter was issued for NDA 22-271 due to the following:
 - A numerical imbalance in serious CV adverse events, not favoring alogliptin therapy such that the sponsor was unable to meet the 1.8 cutpoint described in the December 2008 diabetes cardiovascular guidance.
 - Lack of controlled data beyond week 26: At least 500 subjects from controlled trial(s) should be exposed to alogliptin for ≥ 1 year
 - Increase in mean exposure to alogliptin (AUC) by ~70% in subjects with mild RI compared to subjects with normal renal function: Thus, a dose adjustment may be needed in subjects with mild RI. The applicant should include analyses of the controlled phase 2/3 program comparing safety and tolerability in subjects with normal renal function and those with mild RI.
 - Nonclinical: A signal for potential teratogenicity in an embryofetal development study testing the combination of another DDP-4 inhibitor and

metformin. The applicant should conduct an embryofetal development study in rats that includes separate alogliptin and metformin arms in addition to the combination groups.

- September 2, 2009: CR letter was issued for NDA 22-426 due to the three clinical bullets listed for NDA 22-271 above and the following:
 - Greater incidences of elevations in blood urea nitrogen (BUN), serum creatinine (Cr), and urinary albumin/Cr ratios in the FDC treatment group compared to the individual alogliptin and pioglitazone treatment groups. More FDC subjects experienced a shift from normal to mild or moderate RI when compared to the individual treatment groups. The sponsor should manufacture FDC dose strengths with 6.25 mg alogliptin. (See follow-up agreement reached under February 23, 2010, correspondence.)
 - Facility inspections: There were deficiencies at the (b) (4) manufacturing facility. Satisfactory compliance with Current Good Manufacturing Practices for Drugs is required.
- January 4, 2010: Comments were conveyed on CV protocol 402, the case report form, data monitoring committee charter, and updated standard of care guidelines. (See also related DMEP and Division of Cardiovascular and Renal Products [DCRP] reviews.)
- January 14, 2010: A teleconference was held to discuss the January 4, 2010 recommendations.
- February 23, 2010: The End of Review (EOR) meeting was held to discuss the NDA resubmissions. Key agreements were as follows:
 - The agency agreed, due to low expected use (<2%), that applicant need not manufacture FDC doses containing 6.25 mg alogliptin. Product labeling can appropriately address dosing of patients with severe RI through co-administration of alogliptin and pioglitazone.
 - If ≥25% of subjects in study 402 experience a change in renal severity status, the applicant should conduct a secondary analysis by renal severity status at study endpoint.
 - A postmarketing study in the severe RI population is acceptable if sufficient exposure is not obtained in that population prior to submission. (See clarification under September 23, 2010 bullet below.)
 - The applicant clarified that one year is often defined as 365±30 days, because subjects do not always present themselves for study visits at precisely one year. This definition was used in the previous NDA submissions. The division agreed the definition is acceptable for meeting the one year exposures requested in the CR letter but asked that the applicant also calculate exposure at >365 days.
 - Concerns pertaining to the planned pediatric development program were conveyed. Specifically, the applicant was encouraged to postpone the primary efficacy assessment until weeks 18-24, consider use as add-on to metformin, and expand the inclusion criteria.

- Relevant safety data from the individual Japanese studies will be summarized and the final clinical study reports provided.
- September 23, 2010: A communication was issued containing the agency's responses to the applicant's requested revisions of the EOR meeting minutes.
 - For SAEs, the applicant agreed to submit infectious organism information, if it was available.
 - The applicant anticipates sufficient exposure in the moderate RI population (i.e. 200 alogliptin-treated subjects) in the CV trial, but not for the severe RI population. Because there are not concerning clinically relevant renal safety signals based on nonclinical pharmacology/toxicology data, the agency agreed that conduct of an additional postmarketing study in the severe RI population is acceptable if sufficient exposure (i.e. 100 alogliptin-treated subjects) is not obtained in the CV trial.
- June 20, 2011: A teleconference was held with the applicant to discuss the upcoming NDA resubmissions.
 - There was discussion of how to protect the integrity of blinded data from the CV trial. *Comment: In this review, I labeled, as best as possible, interim data from CV study 402 (EXAMINE) to aid redaction. It was labeled as "study 402", except when it was combined with other studies in the pooled safety data.*
 - Final decision about inclusion in the label of selected information from the interim results of CV study 402 will be made after the submissions have been reviewed.
 - The applicant agreed to submit a meeting request for further discussion of the statistical analysis of CV study 402. After further consideration, the sponsor decided that it will not make any modifications to the pre-specified statistical analysis plan for this study.

2.6 Other Relevant Background Information

On August 25, 2011, the applicant submitted to both NDAs a response to our August 15, 2011 information request. The response included a reanalysis of AEs by renal function, clarification of the number of subjects in CV study 402's combined dataset, a revised pediatric development plan, and a list of ongoing phase 3 alogliptin studies.

On September 9, 2011, the applicant submitted to NDA 22-426 a REMS and REMS supporting document.

On October 6, 2011, the applicant submitted a revised pediatric deferral request for 10 to less than 18 years.

On October 11, 2011, the applicant submitted a response to our September 27, 2011 information request regarding studies 301 and 303.

On November 7 and December 2, 2011, the applicant submitted responses to our request for liver safety information. The November 7, 2011, submission was determined to be a major amendment and extended the PDUFA goal date to April 25, 2012.

On November 17, 2011, the applicant submitted a response to our request for pancreatitis and hypersensitivity information.

On November 22, 2011, the applicant submitted an updated alogliptin pediatric deferral request.

On December 15, 2011, the applicant submitted pediatric PK protocol 104 amendment 7 to IND 69,707. (See also my review of this submission in DARRTS.)

On December 20, 2011, the applicant submitted a reanalysis of HbA1c results from study 303 without Lagrosa site 3018, as there were significant inspection findings at this site.

On January 20, 2012, as requested, the applicant submitted Investigational New Drug (IND) liver safety information to the NDAs and the third Japanese Periodic Safety Update Report (PSUR). Takeda also submitted a revised pediatric plan to evaluate alogliptin as monotherapy and as add on to metformin and to include a one year study period.

On February 1, 9, 14, and 22, 2012, as requested, the applicant submitted IND liver safety information to the NDAs.

On February 9, 2012, the applicant submitted a new case of erythema multiforme (TCI2011A06360) to alogliptin INDs 69707, 73193, and 101628.

On February 13, 2012, the applicant submitted a response to our information request regarding subject 402/8364-001.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The electronic submissions were of reasonable quality. As described in section 2.5, multiple discussions were held with and communications sent to the applicant regarding the design of CV study 402 and the NDA resubmissions. The information was well organized.

3.2 Compliance with Good Clinical Practices

The key clinical studies that are part of the alogliptin/alogliptin-pioglitazone FDC resubmissions [402, 01-06-TL-322OPI-004 (OPI-004), SYR-322_301 (301), and SYR-322-303 (303)] were conducted according to the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP).

The Office of Scientific Investigations (OSI) was consulted to inspect study sites for studies 402, OPI-004, and 303. The following sites were inspected based on number of enrolled patients and active participation in other INDs:

- Roberto Botelho's Site 8247 in Uberlandia, Brazil, which enrolled 25 subjects in study 402, was categorized as No Action Indicated (NAI) on January 20, 2012.
- Adriana Dumitrescu's Site 0886 in Bucharest, Romania which enrolled 31 subjects in study OPI-004 was categorized as NAI on January 25, 2012.
- Based on a preliminary review by the Enforcement Branch of the GCP division of OSI (GCPEB), the data for study 303 from Dr. Pedro Lagrosa's Site 3018 in Huntington Park, CA is unreliable. However, the applicant's December 20, 2011 reanalysis of study 303's change in HbA1c from baseline to week 52 without data from Lagrosa's site 3018 was consistent with the original analysis described in section 6.1.4.

Table 2. Study 303: Change in HbA1c from baseline to week 52 without data from Lagrosa's site 3018

Analysis population Study week Treatment groups	N	Baseline mean (SD)	Adjusted mean change from baseline at endpoint \pm SE ₁	Difference in adjusted mean change (95% CI) ¹	P-value
1. HbA1c change from baseline at week 52					
A. FAS/LOCF					
Alogliptin	204	7.48 (0.686)	-0.13 (0.055)	-0.02	—
Glipizide	201	7.43 (0.633)	-0.10 (0.056)	(-0.18, 0.13)	
B. PPS/LOCF					
Alogliptin	171	7.52 (0.679)	-0.13 (0.064)	-0.06	—
Glipizide	149	7.44 (0.648)	-0.07 (0.068)	(-0.24, 0.13)	
2. HbA1c \leq 7.0; Week 52; FAS/LOCF					
	N	n (%)	Odds Ratio ² (95% CI)		P-value
Alogliptin	204	103 (50.5%)	1.447		0.129
Glipizide	201	91 (45.3%)	(0.898, 2.331)		
Notes:					
1 Analysis for HbA1c change from baseline: The adjusted mean change from baseline at week 26 52 and the difference in the adjusted mean change were estimated from the primary analysis of covariance model, with treatment, study schedule and geographic region as class variables, and baseline HbA1c as a covariate.					
2 Analysis for HbA1c \leq 7.0: The logistic regression model included effects for treatment, geographic region, study schedule and baseline HbA1c.					

Source: December 20, 2011 submission (NDA 22-271 SDN 60)

- Oscar Minuchin's Site 8538 in Haifa, Israel, which enrolled 17 and 11 subjects in studies 402 and 303 respectively, was categorized as NAI on January 20, 2012
- Sergiy Polyvoda's Site 8520 in Zaporizhzhya, Ukraine, which enrolled 30 subjects in study 402, was categorized as NAI
- Jeffrey Rosen's Site 1037 in Coral Gables, FL 33134, which randomized 18 subjects in study OPI-004, was categorized as Voluntary Action Indicated (VAI) due to 1) failure to address complaints of pain, discomfort, anxiety, and depression in office notes and 2) failure to report an event of "left knee pain" and its associated prescription. These findings most likely did not affect data integrity.

3.3 Financial Disclosures

All active clinical investigators certified that no financial interests or arrangements existed during the conduct of the clinical study, (b) (6). Both noted "significant payments of other sorts on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria". However, both investigators enrolled (b) (4) subjects at their sites in (b) (4), respectively.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Alogliptin

Please refer to Suong Tran's March 3, 2009 review which recommended approval of alogliptin.

Alo/pio FDC

Please refer to Tapash Ghosh's biopharmaceutics reviews of the dissolution methods. Please also refer to Theodore Carver's July 16, 2009 CMC review which recommended nonapproval based on the Office of Compliance's (OC) withhold recommendation on July 15, 2009. (See September 2, 2009, correspondence under Section 2 above.)

CR

Please refer to John Hill's January 4, 2012 alogliptin and alogliptin/pioglitazone FDC reviews which recommend approval.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Alogliptin

Please refer to David Carlson's August 27, 2008 nonclinical review which recommended approval of alogliptin as well as Todd Bourcier's June 17, 2009 review which requested the results of the rat embryofetal development study with the alogliptin/metformin combination be submitted with the alogliptin CR to support appropriate labeling of alogliptin monotherapy.

Alo/pio FDC

Please refer to David Carlson's June 8, 2009 nonclinical review which recommended approval of the FDC.

CR

Please refer to David Carlson's and Todd Bourcier's January 18, 2012 reviews, which include discussion of the alogliptin/metformin rat embryofetal development study. No drug-related fetal abnormalities considered relevant to human subjects were identified in the combination embryofetal toxicology study conducted in rats. The non-clinical pharmacology/toxicology reviewers continue to recommend approval of the alogliptin NDA.

4.4 Clinical Pharmacology

Alogliptin

Please refer to Sang Chung's August 28, 2008 clinical pharmacology review which recommended approval of alogliptin albeit with dose adjustment to 12.5 mg for subjects with mild RI because of mean exposure increase by 69% in these subjects.

Alo/pio FDC

Please refer to Ritesh Jain's June 8, 2009 clinical pharmacology review which recommended approval of the FDC, after OSI's Samuel Chan determined on July 30, 2009 that bioequivalence (BE) study 322OPI-101 was acceptable for review.

CR

Please refer to Sang Chung's January 18, 2012 reviews. He accepts the applicant's proposed dosing regimen (including the use of alogliptin 25 mg daily in patients with mild RI) based on the pharmacokinetic data and recommends approval..

4.4.1 Mechanism of Action

Alogliptin is a DPP4 inhibitor, which slows the inactivation of incretin hormones (including GLP-1 and GIP) and thus increases insulin levels and decreases glucagon levels in a glucose-dependent manner. Pioglitazone is a PPAR γ agonist. Activation of PPAR γ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism. Please refer to my May 13 and July 1, 2009 reviews of the alogliptin and alogliptin/pioglitazone FDC NDAs for full details.

4.4.2 Pharmacodynamics

Single-dose administration of alogliptin to healthy subjects produced rapid and nearly complete inhibition of DPP-4. Peak inhibition occurred within 2 to 3 hours after dosing and exceeded 93% across doses of 12.5 mg to 800 mg. Inhibition of DPP-4 remained above 80% at 24 hours for doses of 25 mg and above.

Comment: There is no clear relationship between degree or duration of GLP-1 inhibition and glycemic control. Although applicants often use the percent inhibition data for early potential dose selection, it is unclear how these findings and GLP-1 concentrations relate to changes in glycemic control in T2DM patients. Therefore, the change in HbA1c compared to baseline remains to be the most significant information when determining efficacy. (See also Section 6.1.8.)

Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, and improves hepatic sensitivity to insulin. In patients with T2DM, the decreased insulin resistance produced by pioglitazone results in lower plasma glucose concentrations, lower plasma insulin concentrations, and lower A1C values.

Please refer to my May 13 and July 1, 2009 reviews of the alogliptin and alogliptin/pioglitazone FDC NDAs as well as the clinical pharmacology reviews for full details.

4.4.3 Pharmacokinetics

The absolute bioavailability of alogliptin is approximately 100%. As total and peak exposure were not altered by administration with a high-fat meal, alogliptin may be administered with or without food. It is well distributed into tissues and negligibly bound to plasma proteins (20%). Alogliptin does not undergo extensive metabolism and 60-71% of the dose is excreted as unchanged drug in the urine.

Following oral administration of pioglitazone hydrochloride, peak concentrations of pioglitazone were observed within 2 hours. Food slightly delays the time to peak serum concentration (T_{max}) to 3 to 4 hours, but does not alter the extent of absorption (AUC).

Pioglitazone is extensively protein bound (>99%) in human serum, mainly to serum albumin. Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Following once daily administration of pioglitazone, steady-state serum concentrations of both pioglitazone and its major active metabolites are achieved within 7 days.

Please refer to my May 13 and July 1, 2009 reviews of the alogliptin and alogliptin/pioglitazone FDC NDAs as well as the clinical pharmacology reviews for full details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3. Controlled phase 2 and 3 studies conducted under the US IND in the CR

Study	Study Design Primary Objective	Population No. and Type	Treatment Duration	Treatment
Previously Submitted and Reviewed				
SYR-322-003 Dose-ranging	Randomized, double blind, placebo controlled, comparison Efficacy (HbA1c)	265 T2DM on no treatment, SU, Met or a combination of SU + Met	12 weeks	Placebo Alogliptin 6.25, 12.5, 25, 50, or 100 mg QD
SYR-322-SULF-007 Add-on to SU	Randomized, double blind, placebo controlled, 3 treatment arm Efficacy (HbA1c)	500 T2DM receiving SU	26 weeks	Alogliptin 12.5 + SU Alogliptin 25 + SU Placebo + SU
SYR-322-MET-008 Add-on to Met	Randomized, double blind, placebo controlled, 3 treatment arm Efficacy (HbA1c)	527 T2DM receiving Met	26 weeks	Alogliptin 12.5 + Met Alogliptin 25 + Met Placebo + Met
SYR-322-TZD-009 Add-on to TZD	Randomized, double blind, placebo controlled, 3 treatment arm Efficacy (HbA1c)	493 T2DMs receiving pioglitazone alone or in combination with Met or SU	26 weeks	Alogliptin 12.5 + pioglit Alogliptin 25 + pioglit Placebo + pioglit
SYR-322-PLC-010 Monotherapy	Randomized, double blind, placebo controlled, 3 treatment arm Efficacy (HbA1c)	329 T2DM	26 weeks	Alogliptin 12.5 Alogliptin 25 Placebo
SYR-322-INS-011 Add-on to insulin	Randomized, double blind, placebo controlled, 3 treatment arm	390 subjects with T2DM receiving insulin alone or in combination with Met	26 weeks	Alogliptin 12.5 + insulin Alogliptin 25 + insulin Placebo + insulin

Clinical Review
Valerie S.W. Pratt, M.D.
NDAs 22-271 and 22-426
Nesina (alogliptin) and (b) (4) (alogliptin/pioglitazone FDC)

	Efficacy (HbA1c)			
01-05-TL-322OPI-001 Combination add-on to Met	Randomized, double blind, placebo controlled, parallel group factorial Efficacy (HbA1c)	1554 T2DM on Met	26 weeks	Placebo + placebo or pioglit 15, 30, or 45 Alogliptin 12.5 + placebo or pioglit 15, 30, or 45 Alogliptin 25 + placebo or pioglit 15, 30, or 45
01-06-TL-322OPI-002 Initial combination therapy	Randomized, double blind, active controlled Efficacy (HbA1c)	655 T2DM	26 weeks	Alogliptin 12.5 + placebo or pioglit 30 Alogliptin 25 + placebo or pioglit 30
Newly Submitted				
SYR-322_303 (303) Elderly	Randomized, double blind, active controlled Efficacy (HbA1c)	441 T2DM aged 65-90 years	52 week	Alogliptin 25 Glipizide 5 or 10
SYR-322_301 (301) Postprandial lipids	Randomized, double blind, active and placebo controlled Efficacy (triglycerides)	71 T2DM on no treatment, Met, SU, nateglinide, or repaglinide	16 weeks	Alogliptin 25 Alogliptin 25 + pioglit 30 Placebo
SYR-322_402 (402) CV outcomes	Randomized, double blind, placebo controlled Safety (CV outcomes)	2149 T2DM (interim) 5400 T2DM (planned)	Up to 4.75 years	Alogliptin 25 or placebo + standard of care
01-06-TL-322OPI-004 (OPI-004) Add-on to pioglitazone and Met	Randomized, double blind, active controlled Efficacy (HbA1c)	803 T2DM on Met + pioglitazone	52 week	Alogliptin 25 + pioglit 30 Pioglitazone 45

5.2 Review Strategy

The applicant submitted the following five completed, phase 3, placebo- or active-controlled, double-blind studies in the CR to alogliptin NDA 22-271. I previously reviewed studies OPI-001 and OPI-002 in my July 1, 2009 review of the alogliptin/pioglitazone FDC NDA.

- 01-05-TL-322OPI-001 (OPI-001): *A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of the combination of SYR-322 (SYR110322) and pioglitazone HCl (Actos) in subjects with T2DM*
- 01-06-TL-322OPI-002 (OPI-002): *A multicenter, double-blind study to determine the efficacy and safety of SYR-322 plus pioglitazone HCl (Actos), SYR-322 alone or pioglitazone HCl alone in subjects with T2DM*
- 01-06-TL-322OPI-004 (OPI-004): *A multicenter, randomized, double-blind study to determine the efficacy and safety of the addition of SYR-322 25 mg versus dose titration from 30 mg to 45 mg of Actos pioglitazone HCl in subjects with T2DM who have inadequate control on a combination of metformin and 30 mg of pioglitazone HCl therapy*
- SYR-322_301 (301): *A multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing SYR-322 alone and combination SYR-322 with pioglitazone versus placebo on postprandial lipids in subjects with T2DM*
- SYR-322_303 (303): *A multicenter, randomized, double-blind study to evaluate the efficacy and safety of alogliptin compared to glipizide in elderly subjects with T2DM*

The applicant also submitted interim results from CV study SYR-322_402 (402, EXAMINE), *A multicenter, randomized, double-blind, placebo-controlled study to evaluate CV outcomes following treatment with alogliptin in addition to standard of care in subjects with T2DM and acute coronary syndrome.*

My efficacy review focuses on the HbA1c results of studies 303 and OPI-004. My safety review focuses on the pooled controlled phase 2 and 3 data, with an emphasis on CV safety, controlled data beyond week 26, and safety in renally impaired subjects (including dose adjustment), as these deficiencies were outlined in the CR letters.

5.3 Discussion of Individual Studies/Clinical Trials

Note: Aspects pertaining to the statistical analysis of the primary endpoint (e.g., statistical population, methodology, control of type 1 error) for each trial is discussed in the context of the efficacy results in section 6.1.4 Analysis of Primary Endpoint(s).

1) SYR-322_402 (402, EXAMINE): A multicenter, randomized, double-blind, placebo-controlled study to evaluate CV outcomes following treatment with alogliptin in addition to standard of care in subjects with T2DM and acute coronary syndrome (Amendment 8)

Comments:

- *Please refer to previous clinical and statistical reviews of this protocol, as described under section 2.5 Summary of Presubmission Regulatory Activity Related to Submission.*
- *Study 402 is ongoing and therefore the interim results discussed in this review are confidential.*

Study phase and dates conducted: This phase 3 study was initiated in September 2009 and is ongoing. The cutoff date for interim data was April 29, 2011 and for SAE reports was May 31, 2011.

Objectives:

Primary: To demonstrate that no excess risk of MACE exists following treatment with alogliptin compared with placebo when given in combination with standard of care in subjects with T2DM and ACS. The primary MACE composite is CV death, nonfatal MI, and nonfatal stroke.

Secondary: To evaluate time from randomization to the first occurrence of any event in the secondary MACE composite: CV death, nonfatal MI, nonfatal stroke, and urgent revascularization due to unstable angina.

The CV events included in the primary objectives were defined in the CV Endpoints Committee (CEC) charter as follows. (For the full definition, please refer to the CV Endpoints Committee (CEC) charter for study 402 that was submitted to alogliptin IND 69,707 in serial document number [SDN] 446.)

- CV death: Sudden cardiac death, death due to acute MI, heart failure, other CV causes (i.e. deaths not included in other CV categories), and presumed CV deaths (i.e. deaths not attributed to a CV death category or a non-CV cause)
- Nonfatal MI: Clinical classification (i.e. types 1-5), spontaneous MI, percutaneous coronary intervention-related MI, and coronary artery bypass grafting (CABG)-related MI
- Stroke: The rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent nonvascular cause

Comment: I compared the CV endpoint definitions in the CEC charter and CV protocol 402 amendments to the July 22, 2009 draft Standardized Definitions for CV Outcomes Trials and communications containing the agency's comments on the protocol. The applicant followed the advice provided. The CEC charter's definitions are very similar to the July 22, 2009 draft definitions. One discrepancy I found was that, on January 4,

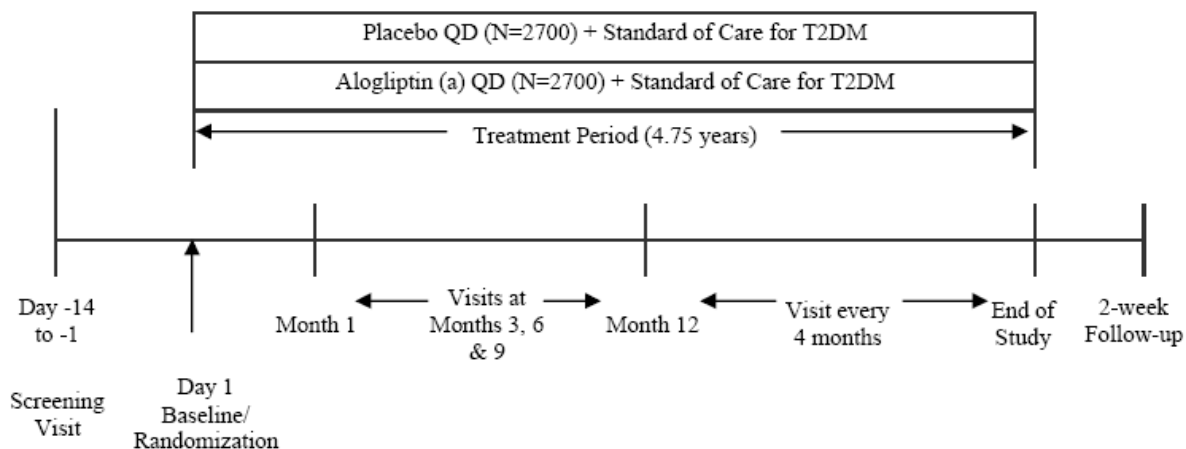
2010, the agency recommended that stent thrombosis be adjudicated using the Academic Research Consortium definitions and that the timing of the events in each treatment group be specified. Although I did not find evidence that the sponsor heeded this particular advice, in the context of the lengthy definitions provided and variety of events adjudicated, I conclude that protocol 402 and the CEC charter defined and adjudicated CV events in a manner consistent with the advice provided by the agency and our negotiations with the company. Furthermore, stent thrombosis events were few and, therefore, did not contribute meaningful data to the CV conclusions.

The July 22, 2009 draft definitions have since been revised. The most recent version is dated May 31, 2011. The two versions differ moderately. However, it can only be expected that the applicant followed the advice provided at the time, which they did. Another change to the CV safety evaluation of T2DM drugs is that applicants are now permitted to include hospitalization for unstable angina in the primary endpoint, although it should not drive the result of this endpoint.

Study design: Study 402 is a randomized, double blind, placebo controlled, two-arm study to evaluate the CV safety of alogliptin compared to placebo when added to standard of care in T2DM subjects with ACS. The study duration is dependent on the number of MACE events, but the maximum length of follow up will be ~4.75 years. The duration for each subject will vary but is estimated to be ~2 years on average.

After a screening period of up to two weeks, subjects will be randomized (1:1) to alogliptin or placebo daily. Randomization will be stratified based on country and screening renal function (using the cutpoints shown below). Study medication will be dosed as follows. Changes to the dose may be made during the study based on the subject's current renal status.

- Normal renal function or mild renal impairment (eGFR ≥ 60 ml/min using MDRD): Alogliptin 25 mg daily or placebo
- Moderate renal impairment (eGFR ≥ 30 and < 60 ml/min using MDRD): Alogliptin 12.5 mg daily or placebo
- Severe renal impairment (eGFR < 30 ml/min using MDRD): Alogliptin 6.25 mg daily or placebo



(a) At randomization, subjects will be assigned 25 mg, 12.5 mg, or 6.25 mg QD depending on renal function. Following randomization, dose adjustments will be allowed based on changes in renal function.

Figure 1. Study 402: Design

Source: Protocol 402 Amendment 8 Figure 6.a

Subjects will continue to be followed according to the protocol until the study is completed, even if they experience a nonfatal MACE composite event or if they discontinue study drug. If the subject refuses to return for study visits, telephone visits may be conducted, although this is not preferred.

When a sufficient number of events has occurred (see below), the study will conclude and subjects will return to complete the end of study and follow up visits.

The following committees will oversee the study:

- The Steering committee will oversee the study's conduct.
- The Data Monitoring Committee (DMC) will oversee the study's safety.
- The CV Endpoints Committee (CEC) will adjudicate suspected MACE events.

Comment: Subjects are monitored for pancreatitis in study 402. They are advised to make an appointment if they experienced persistent nausea and/or vomiting for ≥ 3 days with or without abdominal pain. Serum amylase and lipase are to be obtained at the visit.

Study drug should be interrupted immediately if any of the following occur:

- *If pancreatitis was suspected*
- *Serum amylase ≥ 2 ULN*
- *Serum lipase ≥ 2 ULN*

If any of the above occur, serum amylase and lipase should be repeated within seven days of the first sample and imaging performed. If pancreatitis is confirmed, the study drug should not be restarted but the subject should continue to be followed. If any of

the above circumstances occur, the investigator must complete the AE/SAE eCRF page and a Pancreatitis Adverse Event of Special Interest Form.

Table 4. Study 402: Schedule

	Screening Period	Treatment Period Visit Schedule							Follow-Up Visit (a)
Procedure	Screening / Visit 1	Baseline / Random- ization Visit 2	Month 1/ Visit 3	Month 3/ Visit 4	Month 6/ Visit 5	Month 9/ Visit 6	Month 12 & Every 4 Months until EOS	End of Study Visit/ Early Termin- ation	2 Weeks after Final Visit (a)
Day	-14 to -1	1							
Visit Window			±5	±7	±14	±14	±14	±14	±5
Informed consent/HIPAA Authorization/PGx (if required or if applicable)	X (b)								
Inclusion/exclusion	X								
Demographics, medical history (including medication history)	X	X (l)							
8-hour fast (b)	X	X	X	X	X	X	X	X	
Diabetes education	X	X	X						
Randomization		X							
Complete physical exam	X							X	
Vital signs	X	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X	X	
Height	X								
12-lead ECG (c)		X			X		X	X	
Review concomitant medications and pretreatment events/AEs and AEs of special interest (d)	X	X	X	X	X	X	X	X	X
Laboratory tests (hematology and serum chemistry) (e)	X	X	X	X	X	X	X	X	
Serum pregnancy tests (f)	X							X	
Urine pregnancy tests (f)		X					X		
HbA1c	X	X	X	X	X	X	X	X	
FPG (g)	X	X	X	X	X	X	X	X	

	Screening Period	Treatment Period Visit Schedule							Follow-Up Visit (a)
	Screening / Visit 1	Baseline / Randomization / Visit 2	Month 1 / Visit 3	Month 3 / Visit 4	Month 6 / Visit 5	Month 9 / Visit 6	Month 12 & Every 4 Months until EOS	End of Study Visit/ Early Termination	2 Weeks after Final Visit (a)
Procedure									
Day	-14 to -1	1							
Visit Window			±5	±7	±14	±14	±14	±14	±5
hsCRP (h)	X	X					X	X	
CV biomarker sample collection (i)		X			X			X	
Urinalysis and renal biomarkers (j)		X	X		X		X	X	
PGx sample collection (k)		X							
TVRS	X	X	X	X	X	X	X	X	X
Dispense study medication		X	X	X	X	X	X		
Document drug accountability		X	X	X	X	X	X	X	
Collection of unused study drug			X	X	X	X	X	X	

Source: Protocol 402 Amendment 8 Appendix A

Inclusion criteria:

1. Male or female subjects 18 years of age or older who have a diagnosis of T2DM, who either are receiving monotherapy or combination antidiabetic therapy (with the exception of a DPP-4 inhibitor or GLP-1 analogue) prior to Screening.
2. Subjects must meet the following HbA1c requirements based on the following baseline therapy. (HbA1c can be repeated during Screening.)
 - If a subject's antidiabetic regimen includes oral monotherapy or oral combination therapy, the subject must have an HbA1c level between 6.5% and 11.0%, inclusive, at Screening.
 - If the subject's antidiabetic regimen includes insulin, the subject must have an HbA1c level between 7.0% and 11.0%, inclusive, at Screening.
3. Subject has a history of ACS (acute MI or unstable angina requiring hospitalization) within 15 to 90 days prior to randomization.

Comment: The diagnosis of ACS prior to randomization was revised from within 15 – 60 days to within 15-90 days in protocol 402 amendment 4 (March 23, 2010).

4. Female subjects of childbearing potential who are sexually active who agree to routinely use adequate contraception from Screening throughout the duration of the study. Women NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy, tubal ligation) or who are

postmenopausal (defined as at least 45 years and above and at least 1 year since last regular menses).

5. Subject or the subject's legally acceptable representative is able and willing to provide written informed consent prior to the initiation of any study procedures.
6. The subject is capable of understanding and complying with protocol requirements, including scheduled clinic appointments.

Exclusion criteria:

1. Subject has signs of or is diagnosed with type 1 diabetes mellitus or latent autoimmune diabetes in adults.
2. Subject is currently receiving a GLP-1 analogue for glycemic control of T2DM at Screening.
3. Subject has received a DPP-4 inhibitor for either more than 14 days total or within the 3 months prior to Screening.
4. Subject has any hemodynamically unstable CV disorder including heart failure (NYHA Class 4), refractory angina, uncontrolled arrhythmias, critical valvular heart disease, and severe hypertension at Screening.
5. Subject has had an ACS event less than 15 days prior to Randomization.
6. Subject is hospitalized at Baseline/Randomization Visit. Subjects who have been discharged from an acute hospital to a cardiac rehabilitation center or nursing home at Baseline/Randomization Visit are not excluded.
7. Subject has received dialysis within 14 days prior to Screening.
8. Subject has a history of infection with human immunodeficiency virus.
9. Subject has a history of alcohol or substance abuse within the 6 months prior to the Screening Visit.
10. Subject has received any investigational drug within the 30 days prior to the Screening Visit or has received an investigational antidiabetic drug within the 3 months prior to the Screening Visit.
11. Subject has any major illness or debility that, in the investigator's opinion, prohibits the subject from participating in the study.

12. The subject is a study site employee, or is an immediate family member (i.e., spouse, parent, child, and sibling) of a study site employee who is involved in conduct of this study.

13. Subject is pregnant, intends to become pregnant during the study, or is lactating.

Treatments and management: Alogliptin 6.25, 12.5, or 25 mg daily (as appropriate based on renal status) or placebo, in addition to the standard of care for T2DM.

Subjects who temporarily suspend or permanently discontinue study medication may be restarted at any time at the discretion of the investigator with approval from the Medical Monitor.

Study drug should be temporarily discontinued if any of the following occur:

- Serum creatinine increases $\geq 2x$ compared to baseline
- eGFR decreases $>50\%$ compared to baseline

Study drug should also be interrupted if pancreatitis is suspected or amylase/lipase are $\geq 2x$ the upper limit of normal (ULN). If pancreatitis is confirmed, the drug should not be restarted.

Study sites including enrollment: At the time of the interim analysis, 2149 subjects were enrolled. Approximately 5,400 subjects will be enrolled at ~1,300 sites globally.

Assuming an O'Brien-Fleming-type spending function, group sequential analyses after 550, 600, and 650 adjudicated events will provide approximately 91% power to declare non-inferiority of alogliptin to placebo with a non-inferiority margin of 1.3, a true hazard ratio of 1.0, and an overall 1-sided 2.5% significance level.

Further assuming an O'Brien-Fleming-type spending function, sequential analyses after 80, 100, 125, and 150 adjudicated events will provide approximately 94% power to declare non-inferiority of alogliptin to placebo with a non-inferiority margin of 1.8 (the recommended premarketing cutoff according to the 2008 guidance), a true hazard ratio of 1.0, and an overall 1-sided 2.5% significance level.

If the true hazard ratio is 0.95, the group sequential analyses will have approximately 98% power and 97% power to declare non-inferiority of alogliptin to placebo with non-inferiority margins of 1.3 and 1.8, respectively. Conversely, if the true hazard ratio is 1.05, these group sequential analyses will have approximately 76% power and 90% power to declare non-inferiority of alogliptin to placebo with non-inferiority margins of 1.3 and 1.8, respectively.

Efficacy (exposure/response) assessments:

Primary: The time from randomization to the first occurrence of any event in the primary MACE composite (CV death, nonfatal MI, nonfatal stroke)

Secondary: The time from randomization to the first occurrence of any event in the primary MACE composite (CV death, nonfatal MI, nonfatal stroke, urgent revascularization due to unstable angina)

Safety assessments: SAEs, AEs, renal function, ECGs, vital signs, clinical laboratories

Data analysis: Study 402 was conducted in accordance with the December 2008 guidance, *Diabetes Mellitus: Evaluating CV risk in new antidiabetic therapies to treat type 2 diabetes*. As such, an independent CEC was established to prospectively adjudicate, in a blinded fashion, all deaths, nonfatal myocardial infarctions (MIs), nonfatal stroke, hospitalization for unstable angina, hospitalization due to heart failure, and definite stroke thrombosis. Potential events for adjudication were identified by the investigator (using questioning and the CV Events Checklist as per the protocol), a MedDRA preferred terms (PT) list (provided by the FDA), or an adjudicator; this was acceptable to cardiology reviewer Dr. Karen Hicks and myself. Events were adjudicated according to the process shown in Figure 2.

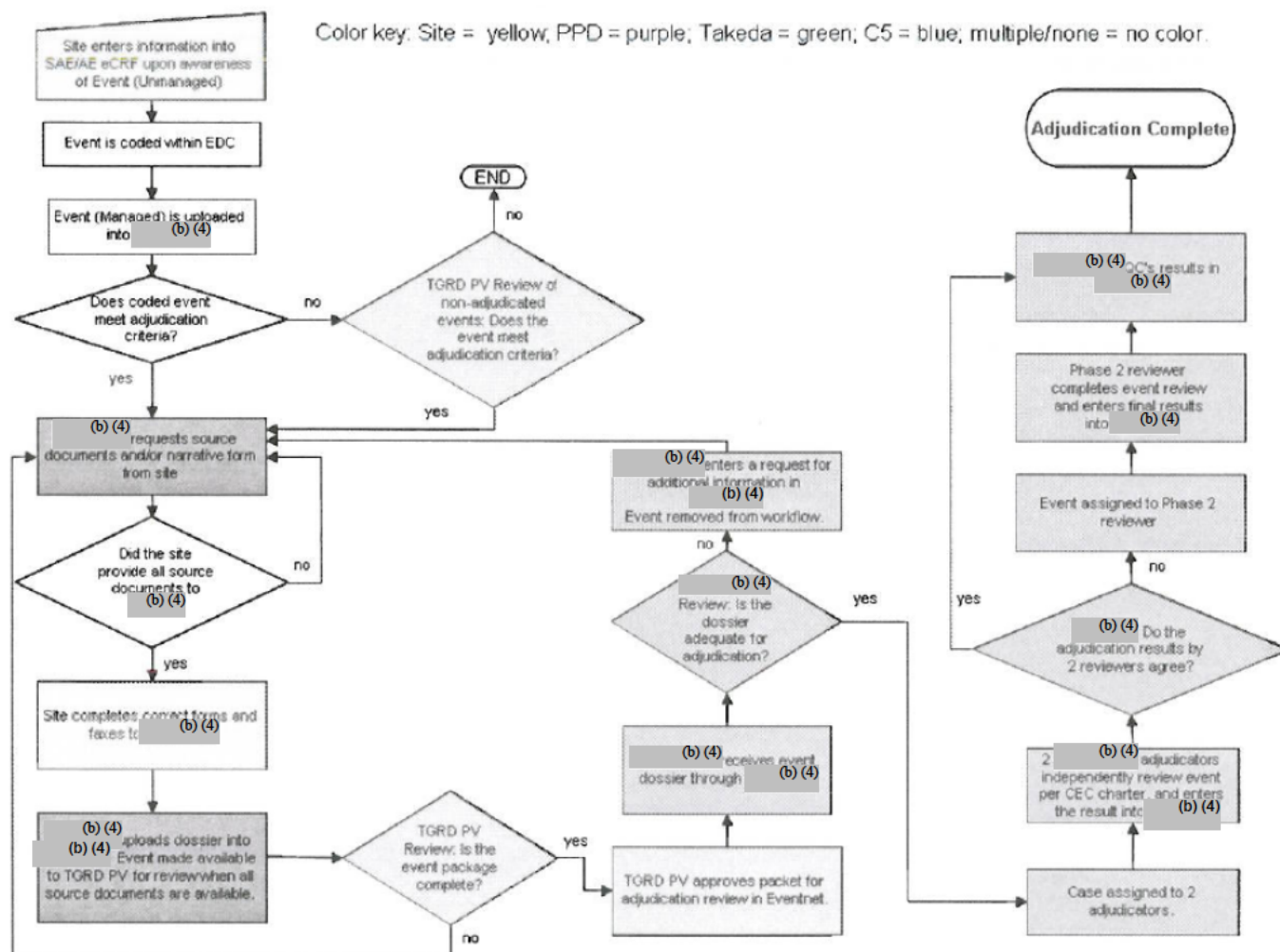


Figure 2. Study 402: CV event adjudication process

Source: CEC charter Appendix 3

Abbreviations:

eCRF=Electronic case report form; EDC=Electronic data capture;

(b) (4) (CRO); (b) (4); TGRD=Takeda Global Research & Development

CV event reviewers were as follows:

- Phase 1: Two (b) (4) cardiology fellows who are board certified in internal medicine and completed at least the first year of their cardiology fellowship
- Phase 2: CEC medical director

Neurologic event reviewers were as follows:

- Phase 1: Two board certified neurologists
- Phase 2: Senior level neurologist

The CEC medical director provided final approval of both CV and neurologic events.

As described in the guidance, prior to approval, the upper bound of the two-sided 95% CI for the estimate CV risk ratio should be less than 1.8. Prospective unblinded analyses were conducted by an independent statistician as part of a group sequential design. To protect the overall statistical validity and study integrity, individuals associated with the unblinded analyses were not involved in preparation and review of blinded data.

See also section 7.7 Additional Submissions / Safety Issues

2) SYR-322_303 (303): *A multicenter, randomized, double-blind study to evaluate the efficacy and safety of alogliptin compared to glipizide in elderly subjects with T2DM (Amendment 10)*

Study phase and dates conducted: This phase 3 study was conducted from June 25, 2008 to August 30, 2010.

Objectives:

Primary: To evaluate the efficacy of alogliptin as compared with glipizide on HbA1c change from Baseline at week 52 in adults 65 to 90 years of age with T2DM

Secondary: To evaluate the following:

- The efficacy of alogliptin as compared with glipizide on HbA1c changes from Baseline at weeks 4 through 42.
- Other measures of glycemic control after treatment with alogliptin as compared with glipizide, including FPG, incidence of marked hyperglycemia (FPG \geq 200 mg/dL), and incidence of hyperglycemic rescue.
- The incidence of hypoglycemic events as a measure of the safety of alogliptin as compared with glipizide.
- HbA1c responder rates (e.g., HbA1c \leq 6.5% or 7.0% and decrease from baseline \geq 0.5%, 1.0%, 1.5%, 2.0% at week 52) after treatment with alogliptin as compared with glipizide.
- Changes in 2-hour postprandial glucose (PPG) levels after treatment with alogliptin as compared with glipizide.
- Changes in “pancreatic function” after treatment with alogliptin as compared with glipizide, determined by changes in homeostasis model assessment (HOMA) β -cell function and proinsulin/insulin ratio.
- Changes in body weight following treatment with alogliptin as compared with glipizide.
- Serum lipids, specifically total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG).
- Inflammatory responses, specifically high-sensitivity C-reactive protein (hsCRP).

- The safety of alogliptin as compared with glipizide by evaluating AEs, clinical laboratory parameters, vital signs measurements, physical examination findings, and electrocardiogram (ECG) readings.

Study design: Study 303 was a 52-week, randomized (1:1), double blind, active-controlled, 2-treatment-arm study of alogliptin 25 mg daily versus glipizide 5 – 10 mg (titrated for inadequate control). Subjects in schedule A (those who only failed diet and exercise) did not have a washout period whereas those in schedule B (those who failed anti-diabetic monotherapy) had a four-week washout period in addition to the screening, treatment, and follow up periods (see inclusion criteria below). Subjects were stratified by HbA1c at week -1 (<8% or ≥8%), study schedule (A or B), and geographic region.

	Screening Period (Up to 2 weeks)	Washout Period 4 weeks			Treatment Period												Follow- up Period
Assessments					Baseline Visit (Day 1)	2	4	8	12	16	20	26	34	42	52 (or ET)	54 (or 2 weeks after ET visit)	
Week	-6 to -5	-4	-3	-1													

Up to 2 Weeks Screening Period	4-Week Washout Period	Alogliptin 25 mg/day	
		Glipizide 5 to 10 mg/day	
		Treatment Period (52 Weeks)	
			Follow-up Period

Figure 3. Study 303: Design (Note: There is no washout period for patients who failed only diet and exercise.)

Source: CSR 303 Figure 9.b

Table 5. Study 303: Study procedures (Note: There is no washout period for patients who failed only diet and exercise.)

Assessments	Screening Period	Washout Period (a)			Treatment Period												Follow-Up
	(Up to 2 weeks) -6 to -5	-4	-3	-1	Randomization (Day 1)	2 ±2 days	4 ±2 days	8 ±7 days	12 ±7 days	16 ±7 days	20 ±7 days	26 ±7 days	34 ±7 days	42 ±7 days	52/ ET (b) ±7 days	54 ±7 days	
Week																	
Informed consent	X																
Inclusion/exclusion	X			X													
Demographics and medical history (including medication history)	X																
Overnight fast	X			X	X	X	X	X	X	X	X	X	X	X	X		
Diabetes education (c)	X	X	X	X	X	X	X					X					
Randomization					X												
Physical exam	X				X				X			X		X	X		
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body temperature	X				X				X			X			X		
Body weight	X				X			X	X			X		X	X		
Height and BMI	X																
12-lead ECG	X				X				X			X			X		
EQ-5D with VAS and SF-12 QOL & PRO measures					X							X			X		
DTSQ QOL & PRO measures	X (d)						X (d)					X (d)			X (e)		
HypoSRQ QOL & PRO measures					X		X					X			X		
Issue subject diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Review diaries and glucometer readings			X	X	X	X	X	X	X	X	X	X	X	X	X		
Review concomitant medications and AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology and serum chemistry (including fasting plasma glucose)	X				X	X	X	X	X	X	X	X	X	X	X		
Lipid panel					X			X	X			X		X	X		
2-hour PPG (f)					X							X			X		
Urinalysis	X				X				X			X		X	X		

Assessments	Screening Period	Washout Period (a)			Treatment Period												Follow-Up
	(Up to 2 weeks) -6 to -5	-4	-3	-1	Randomization (Day 1)	2 ±2 days	4 ±2 days	8 ±7 days	12 ±7 days	16 ±7 days	20 ±7 days	26 ±7 days	34 ±7 days	42 ±7 days	52/ ET(b) ±7 days	54 ±7 days	
Week																	
Proinsulin					X				X			X		X	X		
Insulin					X				X			X		X	X		
C-peptide	X				X		X	X	X	X	X	X	X	X	X		
HbA1c	X			X(g)	X		X	X	X	X	X	X	X	X	X		
Thyroid-stimulating hormone	X																
hsCRP					X				X			X		X	X		
Calculated HOMA β-cell function					X				X			X		X	X		
Serum pregnancy test (and urine at Day 1) (h)	X				X				X			X		X	X		
Call IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Issue glucometer		X															
Issue glucometer ancillary supplies		X	X(i)	X(i)	X(i)	X(i)	X(i)	X(i)	X(i)	X(i)	X(i)	X(i)	X(i)	X(i)	X(i)		
Dispense alogliptin 25 mg or matching placebo					X	X(j)	X	X	X	X	X	X	X	X	X		
Dispense glipizide or matching placebo					X	X(j)	X(j)	X	X	X	X	X	X	X	X		
Document drug accountability						X	X	X	X	X	X	X	X	X	X		

Source: CSR 303 Table 9.b

Inclusion criteria:

- The subject is male or female, between the ages of 65 and 90, inclusive, with a diagnosis of type 2 diabetes mellitus who has either:
 - Failed diet and exercise therapy alone as demonstrated by inadequate glycemic control (defined as an HbA1c concentration between 6.5% and 9.0%, inclusive) while receiving no antidiabetic treatment (defined as less than 7 days of any

antidiabetic treatment) within the two months prior to Screening (Study Schedule A). Subjects following Schedule A may be randomized immediately upon confirmation of eligibility. OR

- Failed treatment with oral monotherapy alone (may include treatment with two or more antidiabetic agents if for less than 7 days) as demonstrated by inadequate glycemic control (defined as an HbA1c concentration between 6.5% and 8.0%, inclusive) within the two months prior to Screening (Study Schedule B). Subjects following Schedule B will undergo a 4-week washout period including an assessment at the end of washout to re-confirm eligibility prior to randomization (see additional inclusion criteria below).

Comment: Subjects with fairly low HbA1c's were enrolled in this non-inferiority trial. This may have made it easier to demonstrate non-inferiority. See also section 6.1.4 Analysis of Primary Endpoint(s).

2. Body mass index ≥ 23 kg/m² and ≤ 45 kg/m².
3. Subject is capable of understanding and complying with protocol requirements.
4. Subject or the subject's legally acceptable representative signs a written, informed consent form prior to the initiation of any study procedures.
5. If regularly using other, non-excluded medications, must be on a stable dose for at least the 4 weeks prior to Screening. However, as needed use of prescription or over-the-counter medications is allowed at the discretion of the investigator.
6. Neither pregnant (confirmed by laboratory testing in females of childbearing potential) nor lactating.
7. Female subject of childbearing potential who is sexually active agrees to use adequate contraception (as defined in the informed consent form) from screening throughout the duration of the study.
8. Able and willing to monitor their own blood glucose concentrations with a home glucose monitor.
9. No major illness or debility that in the investigator's opinion prohibits the subject from completing the study.

Additional inclusion criteria for Schedule B at week -1:

- The subject must have a HbA1c concentration between 6.5% and 9.0% inclusive.
- The subject has not received any antidiabetic medication during the entire washout period.

If a subject's HbA1c concentration value does not meet the additional inclusion criteria, then the assessment may be repeated on a weekly basis, for a maximum of 2 additional weeks.

Exclusion criteria:

1. Systolic blood pressure ≥ 160 mm Hg and/or diastolic pressure ≥ 100 mm Hg.
2. Hemoglobin ≤ 12 g/dL for males or ≤ 10 g/dL for females.
3. Alanine aminotransferase ≥ 3 x upper limit of normal.
4. Calculated creatinine clearance ≤ 50 mL/min.
5. Thyroid-stimulating hormone level outside of the normal range.
6. History of cancer, other than squamous cell or basal cell carcinoma of the skin, that has not been in full remission for at least 5 years prior to Screening. (A history of treated CIN I or CIN II [cervical intraepithelial neoplasia] is allowed.)
7. History of laser treatment for proliferative diabetic retinopathy within the 6 months prior to Screening.
8. History of treated diabetic gastroparesis, gastric banding, or gastric bypass surgery.
9. New York Heart Association Class III or IV heart failure regardless of therapy. Currently treated subjects who are stable at Class I or II are candidates for the study.
10. History of coronary angioplasty, coronary stent placement, coronary bypass surgery, or myocardial infarction within the 6 months prior to Screening.
11. History of any hemoglobinopathy that may affect determination of HbA1c.
12. History of infection with HIV.
13. History of a psychiatric disorder that will affect the subject's ability to participate in the study.
14. History of angioedema in association with use of angiotensin-converting enzyme inhibitors or angiotensin-II receptor inhibitors.
15. History of alcohol or substance abuse within the 2 years prior to Screening.
16. History of treatment with any weight-loss drugs or oral or systemically injected glucocorticoids within the 3 months prior to Screening.

17. Receipt of any investigational drug within the 30 days prior to Screening.
18. Prior treatment in an investigational study of alogliptin.
19. Clinically significant medical abnormality or disease or clinically significant abnormal findings at Screening (other than type 2 diabetes) that, in the opinion of the investigator, should exclude the subject from the study.
20. Subject is a study site employee, or is an immediate family member of a study site employee who is involved in the conduct of this study.

Treatments and management: Subjects received alogliptin 25 mg or glipizide. Patients randomized to glipizide started 5 mg once daily. The glipizide was titrated to 10 mg once daily up to week 12 if there was inadequate control (see below). The sponsor stated that the protocol limited glipizide dosing to 10 mg daily, not the maximum recommended dose of 40 mg, because the study was conducted in elderly subjects and glipizide's label warns of hypoglycemia, especially the elderly.

Hyperglycemia: Subjects with persistent hyperglycemia (FPG ≥ 250 mg/dL after at least one week of treatment and prior to week 12) will have undergone a dose titration (increase of glipizide or matching placebo from 5 to 10 mg). Following this dose titration, a subject who continues to experience hyperglycemia will be rescued per the criteria indicated below and will be assessed at an early termination visit:

- Subjects who were titrated on glipizide (or matching placebo) and following at least one week post-titration before week 12: FPG ≥ 250 mg/dL and confirmed by a repeat test within 7 days after the first sample
- Following week 12 through week 52: HbA1c $\geq 8.0\%$ and confirmed by a second sample drawn within 7 days after the first sample

COMMENT: The facts that 1) the glipizide dose was only uptitrated when FPG ≥ 250 mg/dl (rather than at a lower FPG threshold) and 2) the dose was limited to 10 mg (when the maximum recommended dose approved in the United States is 40 mg) complicate the assessment of efficacy. However, on October 11, 2011, the applicant clarified that the disposition dynamics in study 303 of up-titration of the glipizide/glipizide-placebo dose, hyperglycemic rescue, and discontinuation for other reasons were fairly similar between the alogliptin and glipizide arms. See also section 6.1.4 Analysis of Primary Endpoint(s).

Hypoglycemia: In the event that a titrated subject experiences hypoglycemia that the investigator feels warrants a dose reduction, then the investigator will be permitted to titrate down the glipizide (or matching placebo) dose. Subjects that have been down titrated will not be permitted to increase their glipizide (or matching placebo) dose following the dose titration. In the event that a non-titrated subject experiences

hypoglycemia then the investigator should use their discretion to determine if that subject should discontinue participation.

Mild to moderate hypoglycemia was defined as follows:

- Plasma glucose <70 mg/dl in the presence of symptoms OR
- Plasma glucose <70 mg without symptoms

Severe hypoglycemia was defined as any episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions, associated with a documented plasma glucose <70 mg/dL (unless the clinical situation makes obtaining a plasma glucose difficult, e.g., if it involves coma or seizure).

Renal function: If a subject developed renal impairment (CrCl \leq 50 ml/min based on Cockcroft-Gault [C-G] equation), he or she was discontinued.

Study sites including enrollment: Study 303 was conducted at 110 study sites in 15 countries.

A total of 441 subjects (219-222 per treatment group) were randomized. Using a 2-group t-test and the Per Protocol Set (PPS), inclusion of 215-235 subjects per treatment arm ensured at least 90% power to declare non-inferiority between the alogliptin 25 mg group and the glipizide group at week 52, assuming a non-inferiority margin of 0.4%, no difference between treatment groups, a standard deviation of change from baseline of 1.1%, an evaluability (i.e. meeting prespecified per-protocol criteria) rate of 75%, and a 1-sided 0.025 significance level.

Efficacy (exposure/response) assessments:

Primary: Change in hbA1c from baseline to week 52 in the PPS

Secondary: HbA1c, FPG, hypoglycemia, incidence of clinical response (e.g., HbA1c \leq 6.5% or 7.0% and decrease from baseline \geq 0.5%, 1.0%, 1.5%, 2.0% at week 52), 2-hour PPG, marked hyperglycemia (FPG \geq 200 mg/dl), incidence of hyperglycemic rescue, proinsulin, insulin, proinsulin/insulin ratio, HOMA β -cell function, weight, lipid variables, and hsCRP

Safety assessments: AEs, laboratory tests, vital signs, physical examination findings, and ECGs. AEs of special interest were CV events, hypoglycemia, hypersensitivity, skin disorders, and pancreatitis.

3) 01-06-TL-322OPI-004 (OPI-004): A multicenter, randomized, double-blind study to determine the efficacy and safety of the addition of SYR-322 25 mg versus dose titration from 30 mg to 45 mg of Actos pioglitazone HCl in subjects with T2DM who have inadequate control on a combination of metformin and 30 mg of pioglitazone HCl therapy (Version April 3, 2009)

Study phase and dates conducted: This phase 3 study was conducted between January 30, 2007 to June 5, 2009.

Objectives:

Primary: To evaluate the efficacy of the addition of alogliptin 25 mg versus the titration of pioglitazone from 30 to 45 mg on glycemic control (HbA1c) at weeks 26 and 52.

Secondary: HbA1c, FPG, proinsulin, insulin, proinsulin/insulin ratio, C-peptide, serum lipids, NMR lipid fractionation, free fatty acids, apolipoprotein A-I, A-II, B, C-III, PAI-1, and hsCRP, adiponectin, body weight, HOMA insulin resistance, HOMA β -cell function, incidence of marked hyperglycemia (FPG ≥ 200 mg/dl), incidence of rescue, and clinical response endpoints

Study design: Study OPI-004 was a randomized, double blind, two-treatment arm study in T2DM who were inadequately controlled on metformin ($\geq 1,500$ mg or maximum tolerated dose [MTD]) plus pioglitazone 30 mg. Subjects entered schedule A or B, depending upon their background antidiabetic medication (see Inclusion Criteria below). Schedule B subjects entered Pre-screening (see Inclusion Criteria below) and Switching Periods (12 weeks) during which time they were switched to metformin ($\geq 1,500$ mg or MTD) plus pioglitazone 30 mg. Eligible schedule B subjects then entered a 4-week Stabilization Period, along with Schedule A subjects. At the conclusion of the Stabilization Period, eligible Schedule A and B subjects were randomized (1:1) to alogliptin 25 mg or titration of pioglitazone from 30 to 45 mg. Randomization was stratified by HbA1c at week -1 ($< 8\%$ or $\geq 8\%$), study schedule (A or B), and region (European Union, US/Canada [although there were no Canadian sites], or the rest of the world). During the 52-week treatment period, subjects took their open label metformin and pioglitazone as well as blinded study drug (alogliptin 25 mg or pioglitazone 15 mg).

Pre-Screening Period (Up to 2 weeks)	Optional Switching Period 12 weeks	Screening Period (Up to 2 weeks)	Stabilization Phase				Treatment Period														Follow Up
-20 to -18	-18 to -6	-6 to -5	-4	-3	-2	-1	1	2	4	8	12	16	20	26	34	42	52/ ET	54			
	6 week Interim Lab Visit at Week -12	-43 to -36	-29	-22	-15	-8	1 (Base-line)	15	29	57	85	113	141	183	239	295	365	379			

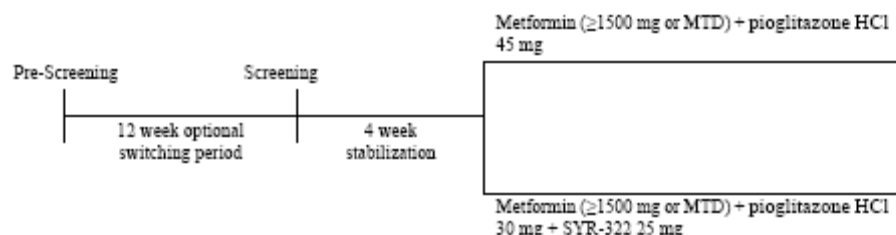


Figure 4. Study OPI-004 design (Note: The pre-screening and switching periods apply only to patients in Schedule B.)

Table 6. Study OPI-004: Schedule (Note: The pre-screening and switching periods apply only to patients in Schedule B.)

Assessments	Pre-Screening Period	Interim Lab Visit	Screening Period	Stabilization Phase				Treatment Period														Follow-Up
Week	Up to 2 weeks	6 weeks after start of Optional Switching Period	Up to 2 weeks	-4	-3	-2	-1	1	2	4	8	12	16	20	26	34	42	52 EOT/ET (a)	54			
Day				-29	-22	-15	-8	1 (Base-line)	15	29	57	85	113	141	183	239	295	365	379			
Visit Window				± 3	± 3	± 3	± 3	± 3	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 10	± 10	± 10	± 5			
Informed consent	X																					
Inclusion/exclusion	X		X																			
Additional inclusion/exclusion (e)							X															
Demographics, medical history (including medication history)	X		X																			
Overnight fast	X	X	X				X	X	X	X	X	X	X	X	X	X	X	X				
Diabetes education (b)			X	X	X	X	X	X	X	X					X							
Randomization								X														
Complete physical examination	X		X												X			X				
Brief physical examination								X				X					X					
Clinical examination of skin and digits	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Oral temperature	X		X					X	X	X	X	X			X		X	X				
Body weight	X		X					X		X	X	X			X		X	X				
Height	X																					
BMI	X		X																			

Clinical Review
Valerie S.W. Pratt, M.D.
NDAs 22-271 and 22-426
Nesina (alogliptin) and (b) (4) (alogliptin/pioglitazone FDC)

Assessments	Pre-Screening Period	Interim Lab Visit	Screening Period	Stabilization Phase				Treatment Period																Follow-Up
Week	Up to 2 weeks	6 weeks after start of Optional Switching Period	Up to 2 weeks	-4	-3	-2	-1	1	2	4	8	12	16	20	26*	34	42	52 EOT/ET (a)	54					
Day				-29	-22	-15	-8	1 (Base-line)	15	29	57	85	113	141	183	239	295	365	379					
Visit Window				± 3	± 3	± 3	± 3	± 3	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 10	± 10	± 10	± 5					
12-lead ECG			X					X							X			X						
Issue glucometer				X																				
Issue subject diary				X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Review diaries and glucometer readings					X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Review concomitant medications and AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Hematology and serum chemistry (including lipid panel and plasma glucose (e))	X	X (j)	X				X (c)	X	X	X	X	X	X	X	X	X	X	X						
Urinalysis (d)	X		X					X				X			X			X						
Proinsulin								X		X	X	X	X	X	X	X	X	X						
Insulin								X		X	X	X	X	X	X	X	X	X						
C-peptide	X		X					X		X	X	X	X	X	X	X	X	X						
HbA1c (e)	X		X				X	X		X	X	X	X	X	X	X	X	X						
Thyroid-stimulating hormone	X		X																					
hsCRP								X				X			X		X	X						
Calculated HOMA insulin resistance and HOMA beta-cell function								X				X			X		X	X						

Assessments	Pre-Screening Period	Interim Lab Visit	Screening Period	Stabilization Phase				Treatment Period														Follow-Up
Week	Up to 2 weeks	6 weeks after start of Optional Switching Period	Up to 2 weeks	-4	-3	-2	-1	1	2	4	8	12	16	20	26*	34	42	52 EOT/ET (a)	54			
Day				-29	-22	-15	-8	1 (Base-line)	15	29	57	85	113	141	183	239	295	365	379			
Visit Window				± 3	± 3	± 3	± 3	± 3	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 10	± 10	± 10	± 5			
FFA								X				X			X		X	X				
NMR lipid fractionation								X				X			X		X	X				
Apolipoprotein A-I, A-II, B, and C-III								X				X			X		X	X				
PAI-1								X				X			X		X	X				
Adiponectin								X				X			X		X	X				
Serum pregnancy test (and urine at Day 1) (f)	X		X					X		X		X			X	X	X	X				
QOL/Pharmacoeconomic assessments (g)								X							X			X				
Dispense open-label metformin (h)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Dispense open-label pioglitazone HCl 30 mg (h)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Dispense blinded study drug								X	X	X	X	X	X	X	X	X	X					
Document drug accountability (i)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Source: Protocol OPI-004 Appendix A

Inclusion criteria:

1. Male or female subjects, 18 to 80 years of age, with a historical diagnosis of type 2 diabetes mellitus.
2. The subjects must meet one of the following:
 - The subject has been inadequately controlled on a stable dose of ≥ 1500 mg (or MTD) of metformin and 30 mg of pioglitazone HCl for at least 2 months prior to Screening. Inadequate glycemic control is defined as a HbA1c concentration between 7.0 and 8.5%, inclusive. These subjects will immediately enter the 4-week stabilization period according to Study Schedule A. OR
 - The subject has been inadequately controlled (as defined by an HbA1c $\geq 7.5\%$) on combination therapy including metformin and another oral antidiabetic agent (i.e., sulfonylureas, rosiglitazone maleate, or pioglitazone HCl 15 mg, etc.). Subjects receiving combination therapy which includes a DPP-4 inhibitor should be excluded. After completing the Pre-Screening visit, these subjects will discontinue this previous combination therapy and will be switched to a stable dose of ≥ 1500 mg (or MTD) of metformin and 30 mg of pioglitazone HCl for a 12-week period according to Study Schedule B. Following this 12-week period, the subject must qualify for entry into the stabilization period by completing the Screening visit including having inadequate glycemic control defined as an HbA1c concentration between 7.0 and 10.0%, inclusive.
3. No treatment with antidiabetic agents other than metformin and pioglitazone HCl within 2 months prior to Screening (Exception: if a subject has received other antidiabetic therapy for less than 7 days within the 2 months prior to Screening).
4. Body mass index ≥ 23 kg/m² and ≤ 45 kg/m².
5. Fasting plasma C-peptide concentration ≥ 0.8 ng/mL (0.26 nmol/L).
6. Regular use of non-excluded medications is allowed; however, the subject must be on a stable dose for at least the 4 weeks prior to Screening. However, as needed use of prescription or over-the-counter medications is allowed at the discretion of the investigator.
7. Systolic blood pressure < 160 mmHg and diastolic pressure < 100 mmHg.
8. Hemoglobin ≥ 12 g/dL for males and ≥ 10 g/dL for females.
9. Alanine aminotransferase ≤ 2.5 x upper limit of normal.

10. Serum creatinine <1.5 mg/dL for males and <1.4 mg /dL for females.
11. Thyroid-stimulating hormone level \leq the upper limit of normal range and the subject is clinically euthyroid.
12. If female, must be neither pregnant (confirmed by laboratory testing in female subjects of childbearing potential) nor lactating.
13. A female subject of childbearing potential who is sexually active agrees to use adequate contraception from screening and throughout the duration of the study.
14. Able and willing to monitor their own blood glucose concentrations with a home glucose monitor.
15. No major illness or debility that in the investigator's opinion prohibits the subject from completing the study.
16. Able and willing to provide written informed consent.

Additional inclusion criteria prior to Randomization:

1. HbA1c concentration between 7.0% and 10.0%, inclusive, at the week -1 visit. (Of note, if the subject does not qualify for randomization based on this criterion, the assessment may be repeated on a weekly basis, for a maximum of 2 additional weeks.)
2. Fasting plasma glucose <275 mg/dL at week -1 visit. (Of note, if the subject does not qualify for randomization based on this criterion, the assessment may be repeated on a weekly basis, for a maximum of 2 additional weeks.)
3. At least 75% compliant with the open-label medication (metformin and pioglitazone HCl) regimen during the stabilization period, as assessed by tablet count
4. No use of oral or systemically injected glucocorticoids or use of weight-loss drugs is allowed within the 3 months prior to randomization. (Inhaled and topical corticosteroids are allowed.)

Exclusion criteria:

1. Urine albumin/creatinine ratio of >1000 μ g/mg. If elevated, the subject may be rescreened within 1 week.
2. History of cancer, other than squamous cell or basal cell carcinoma of the skin, that has not been in full remission for at least 5 years prior to Screening. (A history of treated CIN I or CIN II [cervical intraepithelial neoplasia] is allowed.).

3. History of bladder cancer.
4. History of laser treatment for proliferative diabetic retinopathy within the 6 months prior to Screening.
5. Subjects with unexplained microscopic hematuria of > +1, confirmed by repeat testing.
6. History of treated diabetic gastroparesis.
7. History of gastric bypass surgery.
8. New York Heart Association Class I-IV heart failure regardless of therapy.
9. History of coronary angioplasty, coronary stent placement, coronary bypass surgery, or myocardial infarction within the 6 months prior to Screening.
10. History of any hemoglobinopathy that may affect determination of HbA1c.
11. History of infection with hepatitis B, hepatitis C, or human immunodeficiency virus.
12. History of a psychiatric disorder that will affect the subject's ability to participate in the study.
13. History of angioedema in association with use of angiotensin-converting enzyme inhibitors or angiotensin-II receptor inhibitors.
14. History of alcohol abuse (defined as regular or daily consumption of more than 4 alcoholic drinks per day) or substance abuse (defined as illicit drug use) within the 2 years prior to Screening.
15. Receipt of any investigational drug within the 30 days prior to Screening or a history of receipt of an investigational antidiabetic drug within the 3 months prior to Screening.
16. Prior treatment in an investigational study of alogliptin.
17. Hypersensitive to pioglitazone HCl, metformin, alogliptin or other excipients.
18. The subject is a study site employee, or is an immediate family member (i.e., spouse, parent, child, sibling) of a study site employee involved in conduct of this study.
19. The subject has donated more than 400 mL of blood within the 90 days prior to Screening and Pre-Screening, if applicable.

Treatments and management: Subjects received alogliptin 25 mg or pioglitazone 15 mg (total 45 mg) daily.

Hyperglycemic rescue: Subjects who met the following criteria were rescued and completed an early termination visit:

- After more than 2 weeks (14 days) of treatment but prior to the week 4 visit: A single fasting plasma glucose ≥ 275 mg/dL as determined by the central laboratory and confirmed by a second sample drawn within 7 days after the first sample and analyzed by the central laboratory.
- From the week 4 visit but prior to the week 8 visit: A single fasting plasma glucose ≥ 250 mg/dL as determined by the central laboratory and confirmed by a second sample drawn within 7 days after the first sample and analyzed by the central laboratory.
- From the week 8 visit but prior to the week 12 visit: A single fasting plasma glucose ≥ 225 mg/dL as determined by the central laboratory and confirmed by a second sample drawn within 7 days after the first sample and analyzed by the central laboratory.
- From the week 12 visit through the end-of-treatment visit: HbA1c $\geq 8.5\%$ AND $\leq 0.5\%$ reduction in HbA1c as compared with the baseline HbA1c, confirmed by a second sample drawn within 7 days after the first sample and analyzed by the central laboratory.
- At any time point during the study. HbA1c raised to $>10\%$ as determined by the central laboratory.

Hypoglycemia: Hypoglycemia was defined as follows:

- Mild to moderate:
 - Blood glucose <60 mg/dL in the presence of symptoms OR
 - Blood glucose <50 mg/dL with or without symptoms
- Severe: Any episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions, associated with a documented blood glucose <60 mg/dL (unless the clinical situation makes obtaining a blood glucose difficult, e.g., if it involves coma or seizure).

Study sites including enrollment: According to the study report, this phase 3 study was conducted at 235 sites in 16 countries.

Comment: When the database was searched for unique site IDs that enrolled subjects, 196 sites in 17 countries were identified. Of these, 102 sites were in the US. See also Janice Derr's statistical review of the CR.

A total of 760 subjects was planned. Using a two-group t-test, a sample size of 760 subjects (380 per treatment group) in the per-protocol population provided at least 90% power to declare non-inferiority in mean change from baseline in HbA1c at either week 26 or week 52 between the alogliptin group and the pioglitazone HCl titration group,

assuming a standard deviation of 1.1%, a non-inferiority margin of 0.3%, no difference between the treatment arms, an evaluability rate (i.e., meeting prespecified per-protocol criteria) of 75%, and a 0.025 one-sided significance level. Overall, this sample size provided at least 80% power to declare non-inferiority both at week 26 and week 52. The actual number of subjects that were randomized is 821. Given the assumptions stated above, this increase in sample size increases the overall statistical power of concluding non-inferiority at week 26 and week 52 to at least 84%.

Efficacy (exposure/response) assessments:

Primary: HbA1c at weeks 26 and 52.

Secondary: HbA1c, FPG, proinsulin, insulin, proinsulin/insulin ratio, C-peptide, serum lipids, NMR lipid fractionation, free fatty acids, apolipoprotein A-I, A-II, B, C-III, PAI-1, and hsCRP, adiponectin, body weight, HOMA insulin resistance, HOMA β -cell function, incidence of hyperglycemia, incidence of rescue, and clinical response endpoints

Safety assessments: AEs, laboratory evaluations, physical examination findings, vital signs, ECGs, and occurrence of hypoglycemia. AEs of special interest included MACE, edema, weight gain, drug hypersensitivity reactions, bladder neoplasm, bone fractures, and pancreatitis.

4) SYR-322_301 (301): A multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing SYR-322 alone and combination SYR-322 with pioglitazone versus placebo on postprandial lipids in subjects with T2DM (Amendment 7)

Study phase and dates conducted: This phase 3 study was conducted from July 16, 2007 to December 17, 2009.

Objectives:

Primary: To evaluate the effects of alogliptin alone and co administered with pioglitazone hydrochloride versus placebo on postprandial triglycerides in subjects with T2DM

Secondary: To evaluate the effect of alogliptin alone and co administered with pioglitazone versus placebo on postprandial lipid parameters, postprandial lipoprotein parameters, postprandial GLP-1, postprandial glucagon, postprandial glucose, postprandial insulin, measurements of glycemic control, inflammatory markers (i.e., adiponectin and hs-CRP), cardiovascular markers (i.e., vascular cell adhesion molecule [VCAM], intercellular adhesion molecule [ICAM], and e-selectin), and endothelial function (pulse wave tonometry).

Study design: Study 301 was a randomized, double blind, placebo controlled, parallel group study in T2DM subjects who failed treatment with diet and exercise or have received at least 3 months of treatment with metformin, sulfonylurea, nateglinide, or

repaglinide. Following Screening, all eligible subjects were randomized (1:1:1) to either alogliptin 25 mg daily, coadministration of alogliptin 25 mg and pioglitazone 30 mg daily, or placebo for 16 weeks (18 weeks including follow up). Subject were stratified by statin use (no therapy in the previous 3 months vs. stable therapy) and/or ezetimibe for at least 3 months.

The secondary endpoints of postprandial GLP-1, glucagon, and glucose were evaluated after an eight hour fast and consumption of a standard mixed-meal.

Table 7. Study 301: Design

Screening	Baseline/ Randomization	Week 4	Week 8	Week 16 EOT/Early Termination	Follow-up Visit
*Day -14 to -1	Day 1	Day 29	Day 57	Day 113	Day 127

Source: Protocol 301 Amendment 7 Figure 6.a

Table 8. Study 301: Schedule

Study Phase	Screening	Baseline	Week 4	Week 8	Week 16 EOT/Early Termination	Week 18 Follow-up Visit
Day	-14 to -1	1	29±5	57±5	113±5	127±5
Informed consent	X					
Inclusion/exclusion criteria assessment	X (h)					
Demographics, medical history, and concurrent medical conditions	X					
Overnight fast (8 hours)	X	X	X	X	X	
Physical examination	X	X			X	
12-lead ECG	X	X			X	
Clinical examination of skin & digits	X	X	X	X	X	X
Vital signs	X	X	X	X	X	
Body weight and height (a)	X	X	X		X	
BMI calculation	X					
Fasting clinical laboratory tests (urinalysis, hematology, serum chemistry as required per section 9.a of the protocol)	X (i)	X (b)	X (b)	X (b,i)	X (b)	
Mixed-meal administration (c)		X	X		X	
Fasting Lipid Laboratory Tests (as per 9.1.14 of the protocol)		X	X (j)	X (j)	X	
Postprandial plasma lipid laboratory tests (as per 9.1.14 of the protocol) (d)		X	X		X	
Markers of oxidative stress and short term glycaemic control as per 9.1.14 of the protocol.		X			X	
Pulse wave tonometry (g)		X			X	
Pregnancy test (e)	X	X			X	X
Pretreatment event monitoring	X	X				
Adverse event monitoring		X	X	X	X	X
Concomitant medication		X	X	X	X	X
Administer double-blind study medication in the study clinic		X	X	X	X	
Dispense double-blind study medication (f)		X	X	X		
Drug accountability			X	X	X	

Source: Protocol 301 Amendment 7 Appendix A

Inclusion criteria:

1. The subject is male or female, with a historical diagnosis of type 2 diabetes, and must be aged 18 to 70 years, inclusive.
2. A female subject of childbearing potential who is sexually active agrees to use adequate contraception from screening throughout the duration of the study. Women NOT of child bearing potential are defined as those who have been surgically sterilized (hysterectomy, oophorectomy, tubal ligation) or who are post-menopausal (defined as at least 2 years since last regular menses).

3. The subject is capable of understanding and complying with the protocol requirements.
4. The subject has either failed treatment with diet and exercise for 3 months prior to Screening or has been receiving a stable dose of metformin, sulfonylurea, nateglinide, or repaglinide for more than 3 months prior to Screening.
5. The subject has inadequate glycemic control as defined by HbA1C concentration between 6.5 and 9.0%, inclusive.
6. The subject has a fasting plasma glucose <239 mg/dl.
7. The subject has a fasting serum triglyceride level of 150 to 443 mg/dl, inclusive.
8. The subject has not been receiving any lipid-lowering therapy within 3 months prior to Screening or is on stable statin and/or ezetimibe therapy (same drug and dose) for at least 3 months.
9. The subject has a body mass index ≥ 23 kg/m² and ≤ 45 kg/m².
10. If the subject has regular use of other, nonexcluded medications, subject must be on a stable dose for at least 4 weeks prior to Screening. Use of as needed prescription medications and over-the-counter medications is allowed at the discretion of the investigator.
11. The subject or subject's legally authorized representative signs a written informed consent prior to the initiation of any study procedures.
12. The subject is to be Apolipoprotein E 3/3 or Apolipoprotein E 3/4 phenotype positive prior to baseline.

Comment: Apolipoprotein E 3/3 and 3/4 are very common. Only 1% of the population has a different phenotype. Thus, these data are generalizable to T2DM subjects.

Exclusion criteria:

1. The subject has a history of type 1 diabetes.
2. The subject has a history of drug abuse (defined as illicit drug use) or a history of alcohol abuse (defined as regular or daily consumption of more than 4 alcoholic drinks per day) within the past 2 years.
3. The subject has a diastolic blood pressure greater than 100 mm Hg or a systolic blood pressure of greater than 160 mm Hg.

4. The subject has a previous history of cancer, other than basal cell carcinoma, that has not been in remission for at least 5 years prior to the first dose of study medication. (This criterion does not include those subjects with basal cell or Stage 1 squamous cell carcinoma of the skin.)
5. The subject has a hemoglobin <120 g/L for males and <100 g/L for females.
6. The subject has an alanine transaminase (ALT) level of greater than 2.5 times the upper limit of normal, active liver disease, or jaundice.
7. The subject has a serum creatinine level >1.5 mg/dl.
8. The subject has a fasting total cholesterol >251 mg/dl.
9. The subject has New York Heart Association heart failure of any Class (I-IV) regardless of therapy.
10. The subject has a history of coronary angioplasty, coronary stent placement, coronary bypass surgery, or myocardial infarction within 6 months prior to Screening.
11. The subject has a history of acute metabolic diabetic complications.
12. The subject has a history of any hemoglobinopathy that may affect determination of HbA1C.
13. The subject has a history of infection with human immunodeficiency virus.
14. The subject has a history of diabetic gastroparesis.
15. The subject has a history of gastric bypass surgery.
16. The subject is unwilling or unable to comply with the protocol or scheduled appointments.
17. The subject has a history of hypersensitivity or allergies to alogliptin, pioglitazone or any related compounds.
18. The subject is pregnant, intends to become pregnant during the course of the study, or is lactating.
19. The subject is currently participating in another investigational study or has participated in an investigational study within the past 30 days.

20. The subject has any other serious disease or condition at Screening or at randomization that might affect life expectancy or make it difficult to successfully manage and follow the subject according to the protocol.

Treatments and management: Subjects were randomized (1:1:1) to one of the following three treatments:

- Placebo + placebo
- Alogliptin 25 mg + placebo
- Alogliptin 25 mg + pioglitazone 30 mg

Study sites including enrollment: Study 301 was conducted at two sites in Sweden and the Netherlands.

Approximately 70 subjects were to be enrolled. For the primary efficacy variable, change from baseline in postprandial incremental AUC for triglycerides at week 16, a total of 23 or 24 subjects per treatment arm ensured at least 90% power to detect a treatment difference of 265 mg dL⁻¹ hr, assuming a standard deviation of change from baseline of 280 mg dL⁻¹ hr and a two-sided 0.05 significance level.

Efficacy (exposure/response) assessments:

Primary: Postprandial triglycerides

Secondary: Postprandial lipid parameters, postprandial lipoprotein parameters, postprandial GLP-1, postprandial glucagon, postprandial glucose, postprandial insulin, measurements of glycemic control, inflammatory markers (i.e., adiponectin and hs-CRP), cardiovascular markers (i.e., VCAM, ICAM, and e-selectin), and endothelial function (pulse wave tonometry).

Safety assessments: AEs, clinical laboratory evaluations, physical examinations, vital signs, and ECGs

6 Review of Efficacy

Efficacy Summary

The applicant proposes the following indications:

- NDA 22-271: Alogliptin for the use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM
- NDA 22-426: Alogliptin/pioglitazone FDC for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both alogliptin and pioglitazone is appropriate

The efficacy of alogliptin and alogliptin/pioglitazone FDC was demonstrated in the first NDA submission. Alogliptin 12.5 and 25 mg daily have similar efficacy in randomized clinical trials, as shown in Table 21 and discussed in Dr. Janice Derr's and Dr. Hylton

Joffe's 2008 and 2009 reviews, respectively. Therefore, if approved, I recommend 12.5 and 25 mg daily be available for subjects with normal renal function.

Before the current liver safety issue came to light, the applicant was required to further demonstrate the safety of alogliptin and the FDC as described in the June and September 2009 CR letters. The applicant therefore submitted the following five phase 3, placebo or active controlled, double blind studies in the CRs: 303, OPI-001, OPI-002, OPI-004, and 301 as well as interim results from CV safety study 402. Study reports OPI-001 and OPI-002 were previously reviewed in the original FDC NDA. Therefore, my efficacy review for the current resubmission focuses on the HbA1c results from studies 303 and OPI-004. I also briefly discuss the triglyceride and secondary endpoint results from study 301.

Studies 303 and OPI-004 randomized 441 and 803 subjects, respectively. Study 301 was smaller with 71 randomized Caucasian subjects. More subjects were rescued for hyperglycemia in studies 301 and OPI-004, which had the primary endpoint of HbA1c. The rate of discontinuation was 15.3 – 21.5% in those studies but only 1.4% in 16-week study 301, which had a triglyceride primary endpoint.

Study 303: The primary endpoint was the efficacy of alogliptin as compared with glipizide on HbA1c change from Baseline at week 52 in adults 65 to 90 years of age with T2DM. The LS mean treatment differences for the PPS and FAS populations were -0.05% and -0.02%, respectively, with both analyses yielding a 1-sided 97.5% CI upper boundary of 0.1, which is less than the prespecified non-inferiority margin of 0.4%. Therefore, per the protocol, alogliptin was non-inferior (but not superior) to glipizide in T2DM adults 65 to 90 years.

Both alogliptin 25 mg and glipizide (up to 10 mg) resulted in a maximal reduction from baseline in HbA1c of ~0.3%-0.4% by Week 12 (for alogliptin) and Week 16 (for glipizide) with a waning of effect starting around Week 20 or 26. Therefore, these therapies do not appear to have durable effects in this population. Furthermore, efficacy conclusions are limited by 1) the large non-inferiority margin (which was not justified by the sponsor), 2) the enrollment of subjects with fairly low HbA1c's which may have made it easier to demonstrate non-inferiority, and 3) the applicant's limiting the glipizide titration (for FPG ≥ 250 mg/dl and dose ≤ 10 mg). These design and enrollment flaws complicate the primary efficacy assessment of NI and limit interpretability of glipizide's and alogliptin's effectiveness in the elderly.

Regarding secondary endpoints, the alogliptin group had a numerically greater mean change in FPG from baseline and a numerically higher percentage of subjects with HbA1c $\leq 7.0\%$ or $\leq 6.5\%$ at endpoint when compared to glipizide. However, glipizide subjects were numerically less likely to have marked hyperglycemia (≥ 200 mg/dl) and be rescued. However, these differences between the two treatment groups for all four secondary endpoints were minor and not statistically significant.

Study OPI-004: The primary endpoint was to evaluate the efficacy of the addition of alogliptin 25 mg versus the titration of pioglitazone from 30 to 45 mg on HbA1c at weeks 26 and 52. The LS mean treatment difference between the Met+A25+Pio and Met+P45 groups was -0.5% and -0.4% at weeks 26 and 52, respectively (both favoring the alogliptin group). The upper bounds of the 1-sided 97.5% CI were -0.35 and -0.28 at weeks 26 and 52, respectively. As per the protocol, this demonstrated noninferiority at weeks 26 and 52 and superiority at week 52. (According to the protocol, the test for superiority at Week 26 was only exploratory because type 1 error was not controlled for that analysis.) Although subjects with fairly low HbA1c's were enrolled and the NI margin was 0.3%, making it easier to demonstrate non-inferiority, this is moot given that the trial was able to show superiority.

Regarding secondary endpoints, the Met+A25+P30 group demonstrated significantly improved glycemic control based on the secondary endpoints of the change in FPG, percentage of subjects with HbA1c $\leq 7.0\%$ and $\leq 6.5\%$, incidence of marked hyperglycemia (FPG ≥ 200 mg/dl), and incidence of hyperglycemic rescue, compared to the Met+P45 group.

Study 301: The primary endpoint was to evaluate the effects of alogliptin alone and co-administered with pioglitazone hydrochloride versus placebo on postprandial triglycerides in subjects with T2DM at 16 weeks. Both the alogliptin 25 mg and alogliptin 25 mg + pioglitazone 30 mg groups produced statistically significant ($p < 0.001$) reductions at week 16 in total triglycerides as measured by postprandial incremental AUC(0-8) change from baseline compared with placebo. (The mechanism for this change is unknown.) Although subjects in the alogliptin 25 mg group had a numerically greater LS mean change in AUC(0-8) for total triglycerides compared with the alogliptin 25 mg + pioglitazone 30 mg group (347.0 vs. 293.4 mg•hr/dL, respectively), this difference was not statistically significant ($p = 0.445$). Furthermore, the applicant does not propose labeling the triglyceride data, only postprandial glucose, glucagon, and GLP-1 in label section 12.2 Pharmacodynamics.

6.1 Indication

The applicant proposes the following indications:

- NDA 22-271: Alogliptin for the use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM
- NDA 22-426: Alogliptin/pioglitazone FDC for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both alogliptin and pioglitazone is appropriate

6.1.1 Methods

The efficacy of alogliptin and alogliptin/pioglitazone FDC was demonstrated in the first NDA submission. (Please refer to my previous reviews of NDA 22-271 and 22-426.)

In the CR letter, the applicant was required to further demonstrate the safety of alogliptin and the FDC. Thus, the applicant submitted the following five phase 3, placebo or active controlled, double blind studies in the CRs: 303, OPI-001, OPI-002, OPI-004, and 301 as well as interim results from CV safety study 402. Study reports OPI-001 and OPI-002 were previously reviewed in the original FDC NDA. Therefore, my efficacy review for the resubmission focuses on the HbA1c results from studies 303 and OPI-004. I also briefly discuss the triglyceride results from study 301.

6.1.2 Demographics

The demographics of the randomized populations in studies 303, OPI-004, and 301 are shown in Table 9. The mean age of subjects ranged from 54.3 – 70.1 years and was greater in study 303 (as expected given that this trial was conducted in the elderly) when compared to studies OPI-004 and 301. The percentage of males in each treatment group ranged from 43.8 – 83.3%; subjects tended to be leaner in study 303 and heavier in lipid study 301. The mean BMI was ~31. The mean duration of T2DM ranged from 5.0 – 7.5 years in various treatment groups. Studies 303 and OPI-004 were racially diverse, although study 301 was comprised of only Caucasian subjects.

Table 9. Demographics of studies 303, OPI-004, and 301 (Randomized)

	Study 303		Study OPI-004		Study 301		
	Alo (n=222)	Glipizide (n=219)	Met+A25+P30 (n=404)	Met+P45 (n=399)	Plb (n=24)	A25 (n=25)	A25+Pio30 (n=22)
Characteristic							
Age (mean years [SD])	70.1 (4.4)	69.8 (4.1)	54.3 (9.9)	55.9 (9.9)	59.1 (6.2)	58.7 (6.5)	59.1 (6.9)
Gender (male n [%])	102 (45.9)	96 (43.8)	210 (52.0)	204 (51.1)	20 (83.3)	15 (60.0)	16 (68.2)
BMI (mean [SD])	29.6 (4.3)	30.02 (4.5)	31.5 (5.2)	31.6 (5.2)	32.1 (4.0)	31.1 (4.1)	31.2 (3.5)
Duration of DM (years mean [SD])	6.3 (6.3)	5.9 (6.3)	7.5 (5.2)	6.9 (4.6)	5.6 (3.2)	6.4 (3.6)	5.0 (3.8)
Race (n [%])							
American Indian or Alaska Native	12 (5.4)	13 (5.9)	2 (0.5)	0	0	0	0
Asian	19 (8.6)	26 (11.9)	79 (19.6)	78 (19.5)	0	0	0
Black or African American	16 (7.2)	20 (9.1)	41 (10.1)	36 (9.0)	0	0	0
Multiracial	6 (2.7)	6 (2.7)	-	-	-	-	-
Native Hawaiian or Pacif Isl	-	-	2 (0.5)	0	0	0	0
White	169 (76.1)	154 (70.3)	242 (59.9)	256 (64.2)	24 (100.0)	25 (100.0)	22 (100.0)
Other	-	-	38 (9.4)	29 (7.3)	-	-	-
Ethnicity (Hispanic n [%])	79 (35.6)	70 (32.0)	30 (7.4)	31 (7.8)	0	0	0

Source: CSRs 303 Table 10.b, CSR OPI-004 Table 10.b, and CSR 301 Table 15.1.6

6.1.3 Subject Disposition

Studies 303 and OPI-004 randomized 441 and 803 subjects, respectively. Study 301 was smaller with 71 randomized subjects. In studies 303 and OPI-004, the completion rate was quite low, ranging from 57.1 – 70.0% across treatment groups; the low completion rate is largely due to premature withdrawal for hyperglycemic rescue. In study 301, the completion rate was 98.6%.

More subjects were rescued for hyperglycemia in studies 303 and OPI-004 (which had the primary endpoint of HbA1c) compared to study 301. The hyperglycemic rescue criteria differed for studies 303 and OPI-004 (see Section 5 above) and were not defined for study 301. For study 303, rescue for hyperglycemia was similar in the two treatment groups (25% with alogliptin vs. 22% with glipizide). A greater discrepancy between treatment groups with respect to rescue for hyperglycemia was seen in study OPI-004 (11% with alogliptin vs. 22% with uptitrated pioglitazone). The rate of discontinuation for reasons other than hyperglycemic rescue was 15.3 – 21.5% in studies 303 and OPI-004 but only 1.4% in 16-week study 301, which had a triglyceride

primary endpoint. The reasons for discontinuation in studies 303 and OPI-004 varied but were generally balanced between treatment groups.

On October 11, 2011, the applicant clarified that the disposition dynamics in study 303 of up-titration of the glipizide/glipizide-placebo dose, hyperglycemic rescue, and discontinuation for other reasons were fairly similar between the alogliptin and glipizide arms.

Table 10. Disposition of studies 303, OPI-004, and 301

	Study 303		Study OPI-004		Study 301		
Screened (n)	957		969		298		
Not randomized (n)	516		166		222		
Randomized (n)	441		803		71		
Received study medication (FAS n)	Alo 222	Glipizide 219	Met+A25+P30 404	Met+P45 399	Plb 24 NS:11 S:13	A25 25 NS:10 S:15	A25+Pio30 22 NS:10 S:12
Completed (n, % of treated)	133 (59.9)	125 (57.1)	283 (70.0)	243 (60.9)	24	25	21
Hyperglyc rescue (n, % of treated)	55 (24.8)	47 (21.5)	44 (10.9)	87 (21.8)			
Discontinued (n, % of treated)	34 (15.3)	47 (21.5)	77 (19.1)	69 (17.3)	0	0	1
Adverse event	16 (7.2)	20 (9.1)	13 (3.2)	16 (4.0)			
Lost to follow up	0	4 (1.8)	6 (1.5)	2 (0.5)			
Invest discretion	0	0	6 (1.5)	8 (2.0)			
Proto violation	4 (1.8)	7 (3.2)	25 (6.2)	20 (5.0)			
Vol withdrawal	12 (5.4)	16 (7.3)	25 (6.2)	20 (5.0)			
Other	2 (0.9)	0	2 (0.5)	3 (0.8)			

Source: CSRs 303, OPI-004, and 301 Tables 10.a

Note: NS = no statin; S = statin

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoints varied between efficacy studies as follows:

- 303: To evaluate the efficacy of alogliptin as compared with glipizide on HbA1c change from Baseline at week 52 in adults 65 to 90 years of age with T2DM
- OPI-004: To evaluate the efficacy of the addition of add-on therapy with alogliptin 25 mg versus the titration of pioglitazone from 30 to 45 mg on HbA1c at weeks 26 and 52 in patients already on metformin plus pioglitazone 30 mg.
- 301: To evaluate the effects of alogliptin alone and co administered with pioglitazone hydrochloride versus placebo on postprandial triglycerides in subjects with T2DM at 16 weeks

Study 303: The primary analysis was conducted using the PPS and an ANCOVA model with change from Baseline in HbA1c at week 52 (LOCF) as the response variable. The analysis was conducted at the 1-sided 0.025 significance level. The primary model included study treatment, the study schedule (A or B) under which the subject was randomized, and geographic region as class effects, and baseline HbA1c as a continuous covariate. The LS means and SEs were used to construct a 1-sided 97.5% CI for the LS mean difference in change from Baseline in HbA1c at Week 52 between the alogliptin group and the glipizide group. Non-inferiority was demonstrated if the upper confidence limit for the LS mean difference was less than +0.4%. If non-inferiority was declared, an additional comparison for statistical superiority of the alogliptin group relative to the glipizide group was performed using the PPS and the same ANCOVA model. The 1-sided 97.5% CI of the LS mean difference was re-evaluated and statistical superiority declared if the upper limit was less than 0%.

Although the sponsor declared the PPS population as primary for the efficacy analysis, we focus on the results for both the PPS and FAS populations when evaluating non-inferiority. Therefore, results from both populations are discussed. As shown in Table 11, the LS mean change was only -0.1% in the alogliptin and glipizide treatment groups. The LS mean differences for the PPS and FAS populations using LOCF were -0.05% and -0.02%, respectively. Based on the 1-sided 97.5% CI, alogliptin was non-inferior (but not superior) to glipizide in T2DM adults 65 to 90 years according to the protocol.

However, although Figure 5 suggests greater efficacy for both alogliptin and glipizide around weeks 12-20, the small LS mean change from baseline at week 52 suggests that both treatments may not be very efficacious in the elderly over the long-term. Furthermore, 1) the large 0.4% NI margin, 2) enrollment of subjects with fairly low HbA1c's, and 3) limited glipizide dose (≤ 10 mg and uptitration for FPG ≥ 250 mg/dl, rather than at a lower threshold) also complicate the primary efficacy assessment of NI and limit the interpretability of glipizide's and alogliptin's effectiveness in the elderly.

Table 11. Study 303: Change in HbA1c from baseline to week 52 in T2DM adults 65 to 90 years

Treatment	N	Baseline HbA1c (SD)	LS Mean Change (SE)	LS Mean Difference	1-sided 97.5% CI
PPS (LOCF)					
Alogliptin	180	7.5 (0.7)	-0.1 (0.1)		
Glipizide	163	7.5 (0.6)	-0.1 (0.1)	-0.05	(-infinity, 0.13)
FAS (LOCF)					
Alogliptin	215	7.5 (0.7)	-0.1 (0.1)		
Glipizide	214	7.5 (0.6)	-0.1 (0.1)	-0.02	(-infinity, 0.13)

Source: CSR 303 Table 11.b

Note: The format of the CI reflects the use of a one-sided CI.

Clinical Review

Valerie S.W. Pratt, M.D.

NDA 22-271 and 22-426

Nesina (alogliptin) and (b) (4) (alogliptin/pioglitazone FDC)

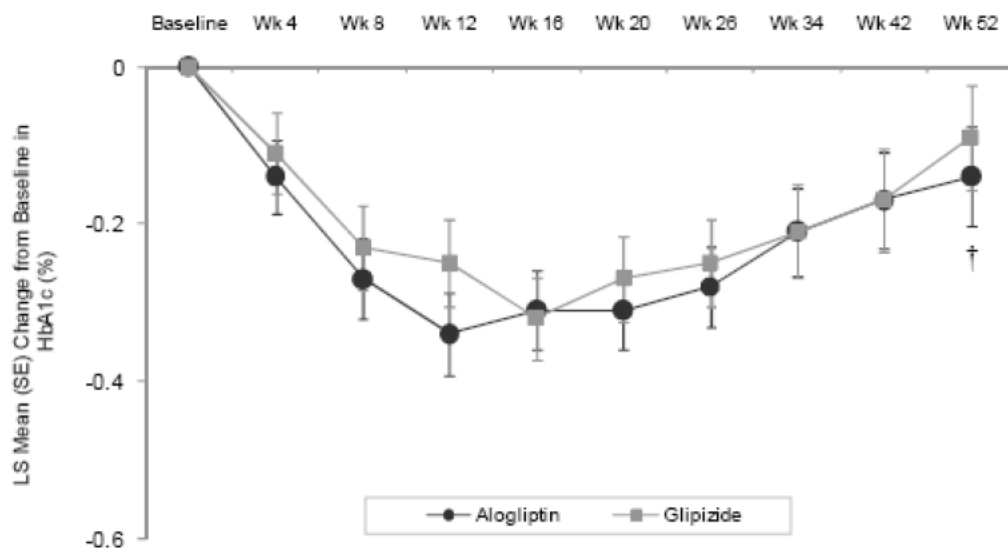


Figure 5. Study 303: LS mean change from baseline in HbA1c (%) (PPS, LOCF)

Source: CSR 303 Table 11.c

Given these concerns, the applicant-proposed labeling in Section 8.5 Geriatric Use (i.e.,

(b) (4) is not acceptable because it does not describe the study's limitations.

See also section 3.2 Compliance with Good Clinical Practices, where the data is analyzed without Dr. Pedro Lagrosa's site 3018.

Study OPI-004: The primary efficacy analysis consisted of two sequential non-inferiority analyses (margin = 0.3%) of change from baseline in HbA1c between the alogliptin group and the pioglitazone titration group conducted first at week 26 and then at week 52 using the PPS, with missing values imputed using LOCF. The primary efficacy analysis was conducted via an interim analysis at week 26 combined with a final analysis at week 52. If non-inferiority was declared at week 26, then a subsequent non-inferiority analysis was conducted for the final analysis at week 52. Each analysis was conducted at the 0.025 1-sided significance level using separate analysis of covariance models with baseline HbA1c as a covariate. At both week 26 and week 52, if non-inferiority was declared, an additional test for statistical superiority of the alogliptin group relative to the pioglitazone titration group at the 0.025 1-sided significance level also was conducted using the PPS. However, at week 26, statistical significance of the superiority test was not required to proceed to the final analysis at week 52; therefore, the test for superiority at week 26 was considered exploratory. Supportive analyses also were conducted using all subjects with both baseline and post-baseline HbA1c data

belonging to the FAS, defined as all randomized and treated subjects with both baseline and post-baseline HbA1c data.

As shown in Table 12, the LS mean difference between the Met+A25+Pio and Met+P45 groups was -0.5% and -0.4% at weeks 26 and 52, respectively. The upper bounds of the 1-sided 97.5% CI were -0.35 and -0.28 at weeks 26 and 52 (LOCF), respectively. As per the protocol, this demonstrated noninferiority at weeks 26 and 52 and superiority at week 52. Although subjects with fairly low HbA1c's were enrolled and the NI margin was 0.3%, making it easier to demonstrate non-inferiority, this is moot given that the trial was able to show superiority.

Table 12. Study OPI-004: Change in HbA1c from baseline to weeks 26 and 52

Treatment	N	Mean Baseline HbA1c (SD)	Week 26			Week 52		
			LS Mean Change (SE)	LS Mean Difference	1-sided 97.5% CI	LS Mean Change (SE)	LS Mean Difference	1-sided 97.5% CI
PPS (LOCF)								
Met+A25+Pio	303	8.3 (0.8)	-0.9 (0.0)			-0.7 (0.0)		
Met+P45	306	8.1 (0.8)	-0.4 (0.0)	-0.5	(-∞, -0.35)	-0.3 (0.0)	-0.4	(-∞, -0.28)
FAS (LOCF)								
Met+A25+Pio	397	8.3 (0.8)	-0.9 (0.0)			-0.7 (0.0)		
Met+P45	394	8.1 (0.8)	-0.4 (0.0)	-0.5	(-∞, -0.35)	-0.3 (0.0)	-0.4	(-∞, -0.29)

Source: CSR OPI-004 Table 11.b

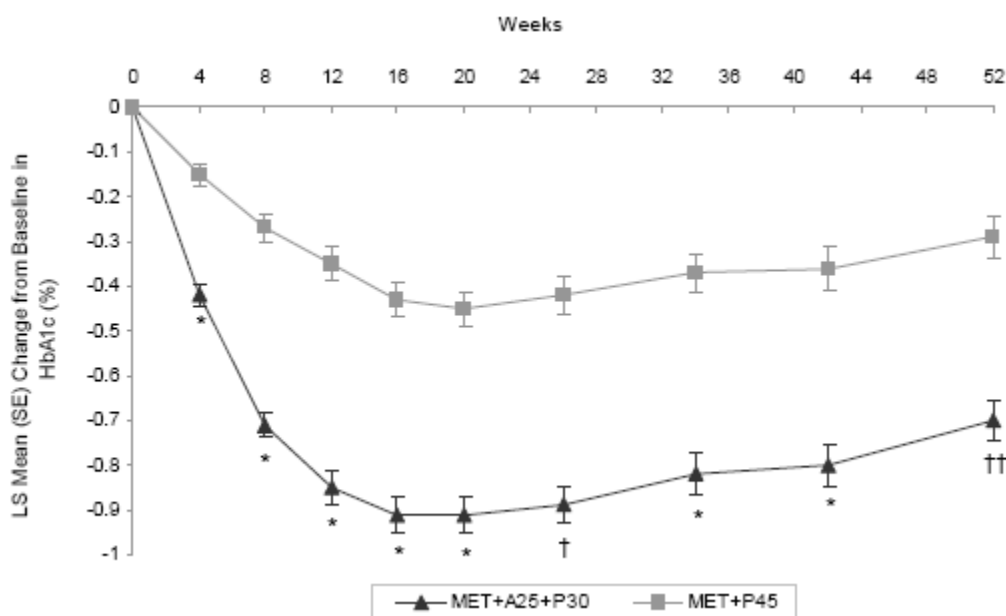


Figure 6. Study OPI-004: LS mean (SE) change from baseline in HbA1c (%) (PPS, LOCF)

Source: CSR OPI-004 Figure 11.b

I have reviewed the applicant-proposed labeling in section 14 Clinical Studies. I recommend the following changes, which will be subject to further internal discussions as well as discussions with the sponsor:

- Removal of the underlined phrase in (b) (4)
(b) (4)
as the Agency has not included similar language in other labels.
- Removal of the discussion of (b) (4)
(b) (4) Lately, we have no longer been permitting such language in diabetes labels
- Removal of the statement about a (b) (4)
(b) (4), as it was not statistically significant

Study 301: For the primary variable, the analysis was conducted using the FAS and an ANCOVA model with change from baseline in incremental AUC for triglycerides as the response variable, treatment and statin use as fixed effects, and baseline incremental AUC for triglycerides as a covariate. Comparisons between each pair of treatment arms were obtained using contrasts derived from the primary analysis model and a 2-sided 0.05 significance level. No multiplicity adjustments were used.

For the primary endpoint, both the alogliptin 25 mg and alogliptin 25 mg + pioglitazone 30 mg groups produced statistically significant ($p < 0.001$) reductions at week 16 in total triglycerides as measured by postprandial incremental AUC(0-8) change from Baseline compared with placebo. Although subjects in the alogliptin 25 mg group had a numerically greater LS mean change in AUC(0-8) for total triglycerides compared with the alogliptin 25 mg + pioglitazone 30 mg group (347.0 vs. 293.4 mg•hr/dL, respectively), this difference was not statistically significant ($p = 0.445$) compared with placebo.

Notes:

- Although a four-week, randomized, double-blind, vildagliptin study in drug-naïve patients demonstrated improved triglycerides, the mechanism for this change is unknown.²
- The applicant is not requesting labeling the triglyceride data. Therefore, these data are presented only in summary form.

2 Matikainen N, Manttari S, Schweizer A, Ulvestad A, Mills D, Dunning BE, et al. Vildagliptin therapy reduces postprandial intestinal triglyceride-rich lipoprotein particles in patients with type 2 diabetes. *Diabetologia* 2006;49(9):2049-57.

Table 13. Study 301: Change in postprandial incremental AUC(0-8) for total triglycerides (mg/hr/dl) from baseline to week 4 and 16 (FAS)

Treatment	Baseline mean (SD)	N	Week 4			N	Week 16		
			LS Mean Change (SE)	LS Mean Diff v Plb (95% CI)	LS mean diff v Alo (95% CI)		LS Mean Change (SE)	LS Mean Diff v Plb (95% CI)	LS mean diff v Alo (95% CI)
Placebo	847 (301)	24	-16 (61)			24	-40 (48)		
A25	706 (337)	25	-288	-272 (-452, -92)		25	-347 (47)	-307 (-443, -171)	
A25+Pio 30	769 (413)	22	-279	-262 (-447, -79)	9 (-180, 199)	21	-293 (51)	-254 (-394, -1131)	54 (-85, 192)

Source: CSR 301 Table 11.b

The results of a subset analysis showed that the statistically significant reductions from Baseline in postprandial incremental AUC for total triglycerides in the alogliptin 25 mg and alogliptin 25 mg + pioglitazone 30 mg groups at week 16 vs. placebo were achieved regardless of subjects' use of statins although the treatment differences were numerically smaller for the no statin subgroup.

Table 14. Study 301: Change in postprandial incremental AUC(0-8) for total triglycerides (mg/hr/dl) from baseline to week 16 by statin use (FAS)

Treatment	N	Base mean (SD)	LS Mean Δ (SE)	LS Mean Diff v Plb (95% CI)	LS mean diff v Alo (95% CI)
Statin					
Placebo	11	810	20 (73)		
A25	10	731	-360 (76)	-380 (-596, -163)	
A25+Pio30	9	691	-249 (80)	-268 (-492, -44)	111 (-115, 338)
No Statin					
Placebo	13	878	-87 (63)		
A25	15	688	-350 (59)	-263 (-440, -87)	
A25+Pio30	12	828	-314 (65)	-227 (-409, -45)	36 (-142, 214)

Source: CSR 301 Table 11.c

See also Janice Derr's November 18, 2011 statistical review of the CRs.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints related to glycemic control in studies 303 and OPI-004 were the change in FPG, percentage of subjects with HbA1c ≤7.0% and ≤6.5% at endpoint, incidence of marked hyperglycemia (FPG ≥200 mg/dl), and incidence of hyperglycemic rescue. As the applicant proposes labeling Study 301's secondary endpoints of postprandial glucose, glucagon, and GLP-1 in the Pharmacodynamics section of the label, those results are also discussed here.

Study 303:

Fasting plasma glucose: At baseline, mean FPG values were similar in the alogliptin and glipizide groups (147 and 144 mg/dL, respectively). Decreases in FPG were observed in both treatment groups at all time points, although there were no statistically significant differences between the two groups and the numerically largest decreases (approx -10 mg/dL) occurred during Weeks 12-20 of the study with waning of effect thereafter (only -2 to -4 mg/dL at Week 52). These findings are consistent with the HbA1c results.

Table 15. Study 303: Change from baseline in FPG (mg/dl) (FAS)

Time Point Statistics	Alogliptin N=222	Glipizide N=219	P-Value (a)
Baseline	n=217	n=214	
Mean (SD)	147.6 (40.03)	144.1 (34.62)	
Median (range)	140.0 (57-331)	139.0 (84-304)	---
Week 2	n=196	n=199	
LS mean (SE)	-3.8 (1.93)	-5.0 (1.91)	
LS mean difference (95% CI) (a)		1.2 (-4.2, 6.5)	0.664
Week 4	n=217	n=213	
LS mean (SE)	-7.7 (1.93)	-7.6 (1.95)	
LS mean difference (95% CI) (a)		-0.2 (-5.6, 5.2)	0.947
Week 8	n=217	n=214	
LS mean (SE)	-8.9 (1.76)	-8.7 (1.77)	
LS mean difference (95% CI) (a)		-0.3 (-5.2, 4.7)	0.919
Week 12	n=217	n=214	
LS mean (SE)	-10.2 (1.84)	-9.9 (1.86)	
LS mean difference (95% CI) (a)		-0.3 (-5.4, 4.9)	0.912
Week 16	n=217	n=214	
LS mean (SE)	-7.9 (1.85)	-11.4 (1.86)	
LS mean difference (95% CI) (a)		3.5 (-1.7, 8.6)	0.186
Week 20	n=217	n=214	
LS mean (SE)	-9.8 (1.78)	-8.7 (1.79)	
LS mean difference (95% CI) (a)		-1.1 (-6.1, 3.9)	0.661
Week 26	n=217	n=214	
LS mean (SE)	-7.9 (1.97)	-6.2 (1.99)	
LS mean difference (95% CI) (a)		-1.7 (-7.2, 3.8)	0.543
Week 34	n=217	n=214	
LS mean (SE)	-5.4 (1.98)	-5.7 (1.99)	
LS mean difference (95% CI) (a)		0.4 (-5.2, 5.9)	0.897
Week 42	n=217	n=214	
LS mean (SE)	-3.6 (2.13)	-7.4 (2.14)	
LS mean difference (95% CI) (a)		3.7 (-2.2, 9.7)	0.218
Week 52	n=217	n=214	
LS mean (SE)	-2.4 (2.24)	-4.2 (2.26)	
LS mean difference (95% CI) (a)		1.8 (-4.5, 8.1)	0.574

Source: CSR 303 Table 11.e

Percentage of subjects with HbA1c $\leq 7.0\%$ and $\leq 6.5\%$ at endpoint: A greater percentage of alogliptin subjects achieved HbA1c $\leq 7.0\%$ or $\leq 6.5\%$ at week 52 when compared to glipizide subjects, although the difference was not statistically significant. The large percentage of patients at goal in both groups (nearly 50%) at Week 52 is consistent with the low HbA1c's at study baseline, particularly given that the mean HbA1c reduction from baseline to Week 52 was only -0.1% in both treatment groups.

Table 16. Study 303: Percentage of subjects achieving HbA1c $\leq 7.0\%$ or $\leq 6.5\%$ at week 52 (FAS)

Clinical Response Measure Statistics	Alogliptin N=222	Glipizide N=219	P-Value
HbA1c $\leq 6.5\%$, n (%)	48 (22.3)	39 (18.2)	
Logistic regression, odds ratio (95% CI) (a,b)		1.424 (0.837, 2.421)	0.192
HbA1c $\leq 7.0\%$, n (%)	105 (48.8)	97 (45.3)	
Logistic regression, odds ratio (95% CI) (a,b)		1.308 (0.834, 2.052)	0.242

Source: CSR 303 Table 11.h

Incidence of marked hyperglycemia (FPG ≥ 200 mg/dl): The overall incidence of subjects who experienced FPG ≥ 200 mg/dl was higher in the alogliptin group (22.5%) compared to the glipizide group (16.9%), although the difference was not statistically significant (p=0.229).

Incidence of hyperglycemic rescue: The overall incidence of subjects who were rescued due to hyperglycemia was higher in the alogliptin group (24.9%) compared with the glipizide group (21.5%), although the difference was not statistically significant (p=0.688).

Summary: At Week 52 in study 303, the alogliptin group had a smaller mean change in FPG from baseline and a higher percentage of subjects with HbA1c $\leq 7.0\%$ or $\leq 6.5\%$ at endpoint when compared to glipizide. However, glipizide subjects were less likely to have marked hyperglycemia (≥ 200 mg/dl) and be rescued. The difference between the two treatment groups for all four of these secondary endpoints was not statistically significant.

Study OPI-004:

Change in FPG: The mean FPG at baseline was similar between treatment groups (162 mg/dl). Significantly greater decreases in FPG were observed in the Met+A25+P30 group at all time points, compared to the Met+P45 group. At week 52, the LS mean changes from baseline were -15 and -4 mg/dl, respectively (p<0.001).

Table 17. Study OPI-004: Change from baseline in FPG (mg/dl) (FAS)

Time Point Statistics	MET+A25+P30 N=404	MET+P45 N=399	P-Value (a)
Baseline	n=399	n=396	
Mean (SD)	161.8 (41.82)	162.2 (42.74)	
Median (range)	159.0 (76-327)	159.0 (52-333)	---
Week 2 CFB	n=360	n=345	
LS mean (SE)	-15.5 (1.56)	-0.5 (1.59)	
LS mean difference (95% CI) (a)		-14.9 (-19.3, -10.6)	<0.001
Week 4 CFB	n=397	n=394	
LS mean (SE)	-17.7 (1.48)	-1.4 (1.49)	
LS mean difference (95% CI) (a)		-16.3 (-20.4, -12.1)	<0.001
Week 8 CFB	n=399	n=396	
LS mean (SE)	-19.1 (1.56)	-5.7 (1.57)	
LS mean difference (95% CI) (a)		-13.4 (-17.7, -9.0)	<0.001
Week 12 CFB	n=399	n=396	
LS mean (SE)	-19.6 (1.60)	-4.8 (1.61)	
LS mean difference (95% CI) (a)		-14.8 (-19.2, -10.3)	<0.001
Week 16 CFB	n=399	n=396	
LS mean (SE)	-18.0 (1.60)	-4.5 (1.60)	
LS mean difference (95% CI) (a)		-13.6 (-18.0, -9.1)	<0.001
Week 20 CFB	n=399	n=396	
LS mean (SE)	-16.4 (1.65)	-5.8 (1.66)	
LS mean difference (95% CI) (a)		-10.6 (-15.2, -6.0)	<0.001
Week 26 CFB	n=399	n=396	
LS mean (SE)	-17.1 (1.79)	-4.9 (1.79)	
LS mean difference (95% CI) (a)		-12.2 (-17.2, -7.3)	<0.001
Week 34 CFB	n=399	n=396	
LS mean (SE)	-13.6 (1.88)	-6.2 (1.88)	
LS mean difference (95% CI) (a)		-7.5 (-12.7, -2.2)	0.005
Week 42 CFB	n=399	n=396	
LS mean (SE)	-15.9 (1.87)	-4.9 (1.88)	
LS mean difference (95% CI) (a)		-11.0 (-16.2, -5.8)	<0.001
Week 52 CFB	n=399	n=396	
LS mean (SE)	-14.6 (1.89)	-3.7 (1.89)	
LS mean difference (95% CI) (a)		-10.9 (-16.2, -5.7)	<0.001

Source: CSR OPI-004 Table 11.f

Percentage of subjects with HbA1c ≤7.0% and ≤6.5% at endpoint: At both weeks 26 and 52, significantly higher percentages of subjects in the Met+A25+P30 group achieved HbA1c ≤7.0% and ≤6.5%, compared to the Met+P45 group (see Table 18).

Table 18. OPI-004: Percentage of subjects with HbA1c ≤6.5% and ≤7% at weeks 26 and 52 (FAS)

	Met+A25+P30 (n=404)	Met+P45 (n=399)	p-value
Week 26			

HbA1c ≤6.5% (n [%])	56 (13.9)	31 (7.8)	
Odds ratio (95% CI)		2.3 (1.396, 3.739)	0.001
HbA1c ≤7 % (n [%])	156 (39.1)	103 (25.8)	
Odds ratio (95% CI)		2.7 (1.897, 3.881)	<0.001
Week 52			
HbA1c ≤6.5% (n [%])	35 (8.7)	17 (4.3)	
Odds ratio (95% CI)		2.5 (1.344, 4.644)	0.004
HbA1c ≤7 % (n [%])	134 (33.2)	85 (21.3)	
Odds ratio (95% CI)		2.4 (1.692, 3.444)	<0.001

Source: CSR OPI-004 Table 15.2.26

Incidence of marked hyperglycemia (FPG ≥200 mg/dl): The overall incidence of subjects who experienced marked hyperglycemia was significantly ($p<0.001$) lower in the Met+A25+P30 group (27.3%) compared to the Met+P45 group (36.1%).

Incidence of hyperglycemic rescue: The overall incidence of subjects who were rescued due to hyperglycemia was significantly ($p<0.001$) lower in the Met+A25+P30 group (10.9%) compared to the Met+P45 group (21.7%).

Summary: In study OPI-004, the Met+A25+P30 group demonstrated significantly improved glycemic control based on the secondary endpoints of the change in FPG, percentage of subjects with HbA1c ≤7.0% and ≤6.5%, incidence of marked hyperglycemia (FPG ≥200 mg/dl), and incidence of hyperglycemic rescue, compared to the Met+P45 group. These findings are consistent with the HbA1c results.

Study 301:

The applicant proposes labeling the secondary endpoints of postprandial glucose, glucagon, and GLP-1 in the Pharmacodynamics section of the label. These secondary endpoints were analyzed using the FAS and a model similar to the primary analysis model described in section 6.1.4 Analysis of Primary Endpoint(s).

At week 16, treatment with alogliptin 25 mg + pioglitazone 30 mg resulted in reduced postprandial glucose compared to placebo throughout the 8-hour postprandial period. However, subjects who received alogliptin probably had lower fasting glucose at week 16 than those who received placebo; this may have affected the postprandial results. Alogliptin also resulted in decreased postprandial glucagon compared to placebo at all week 16 postprandial time points (see Figure 7). Increases in postprandial GLP-1 were also seen at week 16, regardless of whether subjects took alogliptin alone or in combination with pioglitazone (see Figure 8).

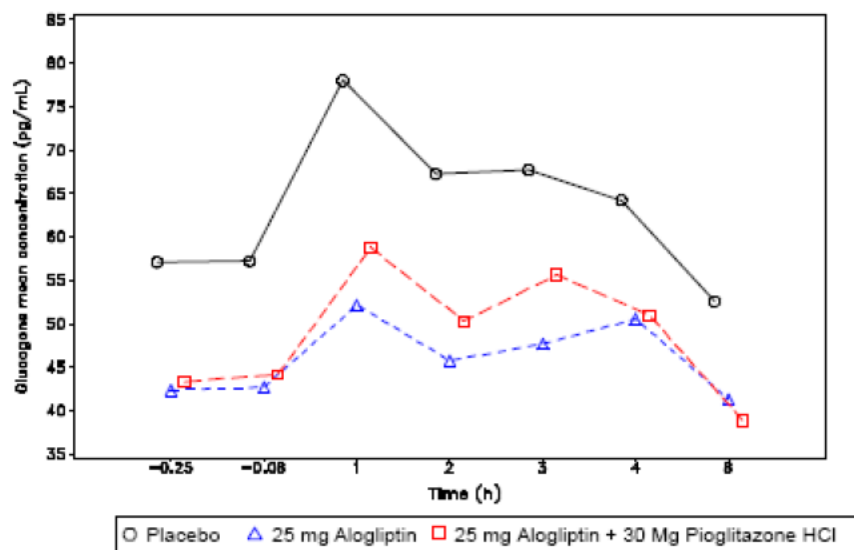


Figure 7. Study 301: Glucagon (pg/ml) postprandial concentrations by week 16 time point (FAS, LOCF)

Source: CSR 301 Figure 11.c

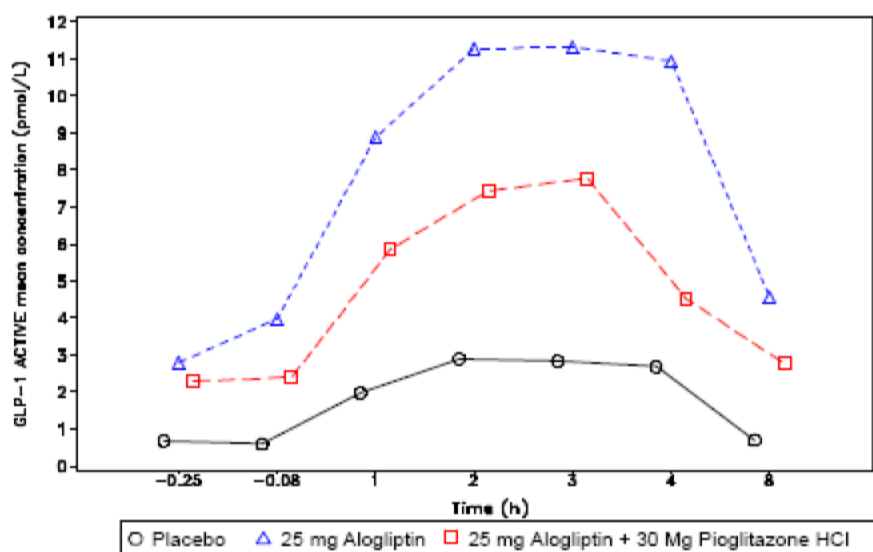


Figure 8. Study 301: Active GLP-1 (pmol/l) postprandial concentrations by week 16 time point (FAS, LOCF)

Source: CSR 301 Figure 11.b

The applicant proposed the following labeling in section 12.2 Pharmacodynamics: (b) (4)

(b) (4)
(Figures 1 and 2 below).



Figure 9. Study 301: Applicant-proposed Prescribing Information Figure 1: Postprandial change from baseline for glucose (mg/dL) and glucagon (pg/mL) at week 16 (LOCF)

Source: Applicant-proposed prescribing information Figure 1

I question the need to label these results as this information is not routinely added to antidiabetic medication labels. I am not sure it adds more clinically relevant data beyond what would be included in the mechanism of action section of the label. As discussed with Statistics, if we choose to label these results, these data should be viewed as descriptive because they lack statistical rigor. Thus, the asterisks and p-values should be removed. If the decision is to allow some or all of these data in the label, I recommend the addition of the phrase, *It is unclear how these findings relate to changes in glycemic control in patients with T2DM*, as follows similar data in the Januvia (sitagliptin) NDA 21-995 label.

6.1.6 Other Endpoints

HOMA β -cell function was assessed in studies 303 and OPI-004, although it is not a well-validated surrogate for insulin beta-cell function and does not rise to the level of evidence to support inclusion in labeling. Therefore, those data are not reviewed here.

6.1.7 Subpopulations

In studies 303 and OPI-004, the sponsor evaluated the change in HbA1c from baseline in the following subgroups: gender, age, race, ethnicity, and baseline BMI (<30 or ≥30). A summary of the LS mean changes from baseline to week 52 is shown in Table 19 and Table 20. Although no formal statistical analysis was conducted, the tables indicate that reductions in HbA1c with alogliptin relative to comparator at week 52 were generally comparable to the overall results although findings in subgroups with small sample sizes are limited.

Table 19. Study 303: Change in HbA1c from baseline to week 52 by demographic subgroup (FAS)

Subgroup	Alogliptin N=222	Glipizide N=219
	LS Mean Change From Baseline in HbA1c (%) at Week 52 (n)	
Sex		
Male	-0.11 (n=99)	-0.11 (n=94)
Female	-0.16 (n=116)	-0.11 (n=120)
Age		
<75 years	-0.11 (n=180)	-0.12 (n=189)
≥75 years	-0.27 (n=35)	-0.02 (n=25)
Race		
American Indian or Alaska Native	-0.41 (n=12)	-0.22 (n=13)
Asian	0.01 (n=19)	0.35 (n=25)
Black or African American	0.01 (n=15)	0.02 (n=20)
White	-0.15 (n=163)	-0.18 (n=150)
Multiracial	0.02 (n=6)	-0.38 (n=6)
Ethnicity		
Hispanic or Latino	-0.11 (n=77)	-0.23 (n=67)
Not Hispanic or Latino	-0.15 (n=138)	-0.06 (n=147)
Baseline BMI		
<30	-0.17 (n=132)	-0.17 (n=118)
≥30	-0.08 (n=83)	-0.04 (n=96)

Source: CSR 303 Table 11.r

Table 20. Study OPI-004: Change in HbA1c from baseline to week 52 by demographic subgroup (FAS)

Subgroup	MET+A25+P30 N=303	MET+P45 N=306
	LS Mean CFB in HbA1c (%) at Week 52 (n)	
Sex		
Male	-0.63 (n=153)	-0.23 (n=146)
Female	-0.82 (n=150)	-0.29 (n=160)
Age		
<65 years	-0.68 (n=253)	-0.22 (n=241)
≥65 years	-0.97 (n=50)	-0.40 (n=65)
≥75 years	-1.45 (n=4)	-0.25 (n=6)
Race		
American Indian/Alaska native	-1.80 (n=1)	NE (n=0)
Asian	-0.81 (n=55)	-0.21 (n=62)
Black or African American	-0.63 (n=29)	-0.02 (n=31)
Native Hawaiian/Other Pacific Islander	0.30 (n=2)	NE (n=0)
White	-0.75 (n=184)	-0.27 (n=190)
Other	-0.59 (n=32)	-0.67 (n=23)
Ethnicity		
Hispanic/Latino	-0.84 (n=21)	-0.26 (n=22)
Not Hispanic/Not Latino	-0.72 (n=282)	-0.26 (n=284)
Baseline BMI		
<30	-0.76 (n=123)	-0.21 (n=128)
≥30	-0.70 (n=180)	-0.30 (n=178)

Source: CSR OPI-004 Table 11.p

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Although alogliptin 25 mg daily offers potentially increased efficacy, alogliptin 12.5 and 25 mg daily have similar efficacy in randomized clinical trials, as shown in Table 21 and discussed in Dr. Janice Derr's and Dr. Hylton Joffe's 2008 and 2009 reviews, respectively. If approved, I therefore recommend that the 12.5 or 25 mg daily dose be used in subjects with normal renal function, although this would require changes to the Dosage and Administration section of the label.

Table 21. Primary efficacy results for the phase 2 and 3 clinical trials submitted to the original alogliptin NDA 22-271 (FAS population with LOCF)

N	Baseline mean \pm SE	Change from baseline Adj. mean \pm SE	Difference in adjusted mean change 95% CI	p-value
Study 003 (dose-ranging) – 12-week trial				
42	8.0 \pm 0.2	-0.2 \pm 0.1	Not reported	
42	7.9 \pm 0.2	-0.5 \pm 0.1	Not reported	
45	8.0 \pm 0.2	-0.6 \pm 0.1	Not reported	
43	8.1 \pm 0.2	-0.4 \pm 0.1	Not reported	
44	8.0 \pm 0.2	-0.5 \pm 0.1	Not reported	
41	8.2 \pm 0.2	0.0 \pm 0.1	Not reported	
Study 010 (monotherapy) – 26-week trial				
128	7.9 \pm 0.1	-0.6 \pm 0.1	-0.6 (-0.8, -0.4)	<0.001
131	7.9 \pm 0.1	-0.6 \pm 0.1	-0.5 (-0.8, -0.3)	<0.001
63	8.0 \pm 0.1	0.0 \pm 0.1		
Study 007 (add-on to sulfonylurea) – 26-week trial				
197	8.1 \pm 0.1	-0.5 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
201	8.1 \pm 0.1	-0.4 \pm 0.1	-0.4 (-0.6, -0.2)	<0.001
97	8.2 \pm 0.1	0.0 \pm 0.1		
Study 008 (add-on to metformin) – 26-week trial				
203	7.9 \pm 0.1	-0.6 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
210	7.9 \pm 0.1	-0.6 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
103	8.0 \pm 0.1	-0.1 \pm 0.1		
Study 009 (add-on to pioglitazone) – 26-week trial				
195	8.0 \pm 0.1	-0.8 \pm 0.1	-0.6 (-0.8, -0.4)	<0.001
195	8.1 \pm 0.1	-0.7 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
95	8.0 \pm 0.1	-0.2 \pm 0.1		
Study 011 (add-on to insulin) – 26-week trial				
126	9.3 \pm 0.1	-0.7 \pm 0.1	-0.6 (-0.8, -0.4)	<0.001
130	9.3 \pm 0.1	-0.6 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
126	9.3 \pm 0.1	-0.1 \pm 0.1		
FAS=full analyses set; LOCF=last-observation-carried-forward; SE=standard error; CI=confidence interval				

Source: Dr. Hylton Joffe.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In study 303, the change in HbA1c from baseline to weeks 2, 4, 8, 12, 16, 20, 26, 34, 42, and 52 was assessed. The mean HbA1c at baseline was similar in the alogliptin and glipizide groups (~7.5%). Both treatments resulted in decreased HbA1c from baseline at each study visit, although there were no significant differences between the

treatment groups. As illustrated in Figure 10, the maximum efficacy of glipizide (and alogliptin) was reached at week 12-16 and started to wane at week 20-26.

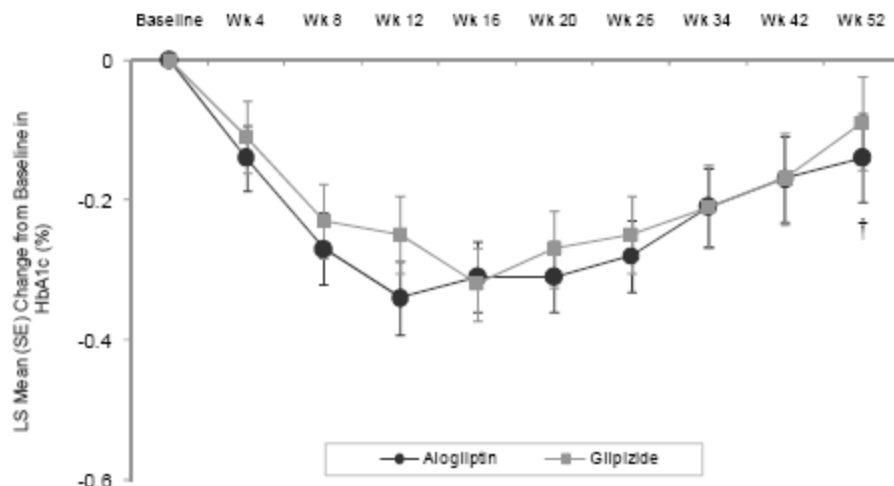


Figure 10. Study 303: Change in HbA1c from baseline (PPS)

Source: CSR 303 Figure 11.c

The primary endpoint in study OPI-004 was to evaluate the efficacy of the addition of alogliptin 25 mg versus the titration of pioglitazone from 30 to 45 mg on HbA1c at weeks 26 and 52. For a discussion of the persistence of efficacy effect in study OPI-004, please refer to 6.1.4 Analysis of Primary Endpoint(s).

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

My safety review focused on the US, pooled, controlled phase 2 and 3 alogliptin data, with an emphasis on CV safety (including interim data from study 402), controlled data beyond week 26, and the safety in renally impaired subjects (including dose adjustment), as these deficiencies were outlined in the CR letters. The 12 US, controlled, phase 2/3 studies that were pooled in the alogliptin CR were the following: 003, 007, 008, 009, 010, 011, OPI-001, OPI-002, 303, OPI-004, 301, and 402 (interim results). (See Table 3 for a description of the studies.) The following four phase 3 studies were included in the alogliptin/pioglitazone FDC CR safety database: OPI-001,

OPI-002, OPI-004, and 301. I reviewed alogliptin/pioglitazone FDC and Japanese clinical trial and postmarketing data when appropriate.

Since the original NDA, the number of subjects exposed to alogliptin has increased from 1961 to 5232. When one year is defined as 365 ± 30 days, 522 subjects were exposed to alogliptin for ≥ 1 year, as required in the CR. In long-term, Japanese phase 2 and 3 studies, 1098 subjects were exposed to alogliptin (any dose). A total of 1071 Japanese subjects completed ≥ 52 weeks of treatment.

In controlled phase 2 and 3 studies (not including Japanese studies):

- Alogliptin subjects were not at increased risk of death when compared to placebo.
- The incidence of serious adverse events (SAEs) was numerically lower in the alogliptin groups (alogliptin 25 mg 7.3% and all alogliptin 5.8%) when compared to the all comparators group (8.9%).
- Alogliptin did not increase the rate of discontinuation due to an AE when compared to placebo (alogliptin 25 mg 2.6% vs. placebo 3.0%).
- When common AEs were compared between alogliptin and all comparator subjects in the CR, incidence rates were similar. Common adverse events (AEs) included nasopharyngitis, headache, urinary tract infection, and upper respiratory tract infection.

Regarding AEs of special interest (excluding liver and renal safety, which are discussed in the laboratory section),

- CV Safety: In CV study 402, the upper bounds of the 95% CI for the risk ratios for both primary and secondary MACE analyses was <1.8 . This was also true when the primary MACE was analyzed according to the timing of the index ACS event (≤ 2 months or >2 months). Future analyses should include subgroup analysis by gender, baseline RI, and country of randomization.
- Hypersensitivity: Narrow Anaphylactic Reaction, Angioedema, and SCAR SMQ searches do not suggest alogliptin subjects are at increased risk for hypersensitivity events. However, there have potentially been two angioedema, four Stevens-Johnson syndrome (SJS), and five erythema multiforma serious Japanese postmarketing reports, in addition to the Skin Lesion findings described below. I therefore recommend that use of alogliptin be contraindicated in subjects with a history of serious hypersensitivity reaction to alogliptin. I also recommend a warning and description of the postmarketing events. Hypersensitivity should be monitored as an AE of special interest in the controlled CV study 402 and the PSURs.
- Skin lesions: The percentage of subjects reporting at least one potential cutaneous drug reaction (PCDR) AE in the completed clinical trials was numerically greater in the alogliptin groups (8.1% and 8.4%) than all comparators (6.6%). (The list of preferred terms comprising PCDRs was agreed upon with the sponsor prior to resubmission.) The incidence of rash, pruritis, dermatitis, rash

popular, and rash macular was numerically greater in the alogliptin groups than all comparator group. Although these skin reactions are not likely related to the necrotic lesions seen with other DPP4 inhibitors, they suggest that sensitive individuals may be hypersensitive to alogliptin. However, the incidence of PCDR SAEs and AEs leading to discontinuation were low (0.1-0.3%).

- Pancreatitis: Pancreatitis events have been observed in alogliptin subjects in clinical trials and postmarketing in Japan. I therefore recommend that the labeling contain an acute pancreatitis warning consistent with that of other DPP4 inhibitors. I also recommend that the applicant analyze pancreatitis events as an AE of special interest in controlled CV safety study 402 (as planned) and in the PSURs until this potential safety risk is better understood.
- Infection: The pooled clinical trial safety data was searched for events in the infections and infestations SOC. AEs occurred at similar incidence in the three treatment groups (22.4-25.2%). Events that occurred at >1% incidence in the alogliptin 25 mg group and more commonly than the all comparator group were the following: nasopharyngitis (3.9% vs. 3.3%), upper respiratory tract infection (3.5% vs. 2.4%), bronchitis (1.9% vs. 1.8%), and pharyngitis (1.2% vs. 1.1%). This is consistent with other DPP-4 inhibitors.
- Malignancy (including bladder, thyroid, and pancreatic cancer): The incidence of AEs of malignancy was similar in the alogliptin 25 mg, all alogliptin, and all comparator groups (0.4-0.5%), although pioglitazone is associated with a potential risk for bladder cancer and relatively short-term trials with limited exposures are not the best way to assess this safety risk.
- Fractures: In the limited clinical database, the use of alogliptin with pioglitazone does not increase the risk of fracture significantly more than the use of pioglitazone alone (FDC 0.8% vs. pioglitazone 0.5%).
- Hypoglycemia: Alogliptin does not appear to increase one's risk of hypoglycemia when compared to placebo. However, a lower dose of insulin or sulfonylurea may be required to reduce the risk of hypoglycemia when used with alogliptin.

In controlled, phase 2 and 3 studies, laboratory samples for hematology and chemistry tests were collected at every visit under fasted conditions. Urinalysis tests were collected at protocol-specified visits. My review of the laboratory findings focused on 10 of the 12 US, controlled, phase 2/3 studies that were pooled in the CR (studies 003, 007, 008, 009, 010, 011, 303, OPI-001, OPI-002, and OPI-004). Sixteen-week, postprandial lipid study 301 was not included in the laboratory analysis; this is acceptable due to its different duration and primary endpoint. The interim results of CV study 402 are discussed only when relevant, as this study is still ongoing. In addition to measures of central tendency, outliers, and dropouts, I reviewed renal data described in the CR letters and liver-safety submissions.

In controlled phase 2 and 3 study group, the mean changes from baseline to endpoint in chemistry and hematology values were minor, generally similar between treatment groups, and not clinically meaningful. There were also no clinically significant outliers or

dropouts when hematology and chemistry values (excluding liver and renal data) were reviewed.

Regarding renal safety, the sponsor's proposed alogliptin dosage adjustment for RI is acceptable. No consistent, clinically relevant changes were noted in the following CR data:

- Number and percentage of subjects with abnormal renal function parameters in the alogliptin and alogliptin/pioglitazone FDC NDAs
- Incidence of abnormal urine albumin:creatinine ratio in the FDC NDA
- Shifts in renal function (CG and MDRD formulas) in the alogliptin NDA
- Renal function-related discontinuations and SAEs in the alogliptin and alogliptin/pioglitazone FDC NDAs

Regarding liver safety, as shown in Table 58, there is an imbalance in the number and percentage of subjects with markedly abnormal ALT values, including ALT >10x and 20x ULN in the controlled clinical trials. As described in the July 2009 guidance, *Drug-Induced Liver Injury: Premarketing Clinical Evaluation*, ALT is generally considered more liver-specific than AST. The finding of a higher rate of ALT elevation in drug-treated subjects than in a control group is a sensitive signal of the potential for drug induced liver injury (DILI). Greater, unexplained aminotransferase increases (e.g., 10x-, 15xULN) in clinical trials, such as those shown in Table 58 are a more specific signal for DILI, but not as specific as Hy's Law cases.

On December 7, 2011, the applicant submitted a response to our liver-safety information request. The submission described 23 serious liver-related cases and 8 biochemical Hy's Law (i.e., ALT >3x ULN and total bilirubin >2x ULN) cases (see Table 60). Consults were placed to OSE to review this information and subsequent liver safety submissions to the IND and NDAs.

I am also concerned by Hy's law cases TC12011A04573 and TC12011A06837 which describe moderate to severe liver disorders and a probable or highly likely association to alogliptin. I am concerned that two moderate to severe cases of liver injury associated with alogliptin have potentially been identified after only 117,359 patient-years exposure in Japan (see 8 Postmarket Experience). Additional significant cases of alogliptin-associated liver dysfunction may occur if the drug is used more widely. There are also four clinical trial cases of biochemical Hy's law (303/3128-003, 012/961-3006, 012/961-2501, and 305/5304-005) that appear to have alternative explanations. These four cases as well as cases of ALT elevation >10x ULN in the clinical trial database are undergoing review by Dr. Leonard Seeff, a hepatologist within OSE, and will be further addressed in the CDTL memorandum. However, based on even the 2 postmarketing cases of moderate/severe liver injury, unless the pending OSE consult demonstrates a similar propensity for serious liver safety reports with other DPP-4 inhibitors, I recommend a complete response to this application and require the applicant to more clearly demonstrate the liver safety of alogliptin. Specifically, I

recommend the applicant analyze serious liver events in postmarketing data and ongoing controlled, double-blind clinical studies 305, 402, and 308, which were described in their December 2011 annual report (IND 69,707 SDN 691).

The applicant requested a waiver of alogliptin studies in T2DM subjects 0-9 years and deferral in T2DM subjects 10-17 years. It plans to conduct PK study SYR-322_104 (104) and phase 3 studies SYR-311_307 (307) and SYR-322_309 (309).

No additional safety signals were detected in the Japanese clinical trial data. Review of the Japanese postmarketing data generally supported the hypersensitivity (particularly, skin and subcutaneous tissue disorders), liver disorders, and pancreatitis signals previously described.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

My safety review focused on the US, pooled, controlled phase 2 and 3 alogliptin data, with an emphasis on CV safety (including interim data from study 402), controlled data beyond week 26, and the safety in renally impaired subjects (including dose adjustment), as these deficiencies were outlined in the CR letters. As alogliptin 25 mg is the recommended dose, my safety review focused on comparing the alogliptin 25 mg and all comparators groups in the pooled studies. It also focused on the following AEs of special interest: CV safety (including CHF), renal safety, hypersensitivity, pancreatitis, skin lesions, infections, malignancy (including bladder, thyroid, and pancreatic cancer), fractures, hepatotoxicity, and hypoglycemia. When appropriate, I included information specific to the safety of the alogliptin/pioglitazone FDC.

Although over one thousand subjects were exposed to alogliptin in phase 2 and 3 studies in Japan, these studies were not included in the pooled safety database. Therefore, I selectively reviewed this data as it pertains to SAEs and AEs of special interest. I also comment on Japanese postmarketing data in section 8.

7.1.2 Categorization of Adverse Events

The pooled safety analysis used MedDRA version 13.0. I generally agreed with the categorization of AEs.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The following 12 US, controlled, phase 2/3 studies were pooled in the alogliptin CR: 003, 007, 008, 009, 010, 011, OPI-001, OPI-002, 303, OPI-004, 301, and 402 (interim results). (See Table 3 for a description of the studies.) I agree with the pooling strategy, which we discussed with the sponsor prior to submission of the CR, and used it as my primary source for reporting safety events. Please note, however, study 402 enrolled a different study population (i.e. acute coronary syndrome). When appropriate, I report results from the controlled phase 2 and 3 studies without study 402 and study 402 separately.

In the pooled analysis, subjects were placed in one of the following three groups: all comparators (n=2934, received placebo, glipizide, or pioglitazone), alogliptin 25 mg (n=3500), or all alogliptin (n=5232, received 6.25-100 mg).

The safety database for the alogliptin/pioglitazone FDC CR included four phase 3 studies (OPI-001, OPI-002, OPI-004, and 301). Treatment groups included alogliptin (n=446), pioglitazone (n=949), and alogliptin+pioglitazone (n=1533).

Please see section 5.1 Tables of Studies/Clinical Trials for a full description of the US pooled trials.

Although it would have been ideal to include the Japanese phase 2 and 3 data in the pooled analysis, it is not known if this data is fully applicable to the American population. Thus, it and the associated Japanese postmarketing data were reviewed separately.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As discussed in section 2.5 Summary of Presubmission Regulatory Activity Related to Submission, the following agreements were made regarding exposure in certain populations:

- In the CR:
 - 500 subjects should be exposed to alogliptin in controlled trials for ≥ 1 year
- In completed CV study 402:
 - 300 subjects should be on background pioglitazone
 - 200 moderate RI subjects and 100 severe RI subjects should be exposed to alogliptin for ≥ 1 year

Since the original NDA, the number of subjects exposed to alogliptin has increased from 1961 to 5232. When one year is defined as ≥ 365 days, only 265 subjects have been exposed to alogliptin for ≥ 1 year. However, as previously agreed with the sponsor ≥ 500 subjects (n=522) have been exposed to alogliptin for ≥ 1 year (defined, on February 23, 2010, as 365 ± 30 days, which takes into account the acceptable time windows for the one-year visit). See also section 2.5 Summary of Presubmission Regulatory Activity Related to Submission.

Table 22. Exposure by dose and duration (controlled phase 2 and 3 studies)

Exposure	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232
Duration in days (c)			
Mean (SD)	179.4 (107.68)	185.0 (99.78)	174.4 (88.27)
Median (min, max)	181.0 (1-533)	182.0 (1-550)	182.0 (1-550)
Cumulative exposure (subjects-years) (d)	1441.16	1773.17	2497.89
Number (%) of subjects exposed for (c)			
1 day	5 (0.2)	5 (0.1)	7 (0.1)
>1 to <7 days	26 (0.9)	18 (0.5)	22 (0.4)
≥ 7 to <30 days	162 (5.5)	157 (4.5)	247 (4.7)
≥ 30 to <166 days (<6 months)	1044 (35.6)	989 (28.3)	1378 (26.3)
≥ 6 months to <12 months	1225 (41.8)	1805 (51.6)	3052 (58.3)
≥ 12 months to <18 months	469 (16.0)	522 (14.9)	522 (10.0)
≥ 18 months	3 (0.1)	4 (0.1)	4 (0.1)
≥ 335 days	472 (16.1)	526 (15.0)	526 (10.1)
≥ 351 days	451 (15.4)	503 (14.4)	503 (9.6)
≥ 365 days	242 (8.2)	265 (7.6)	265 (5.1)

Source: IAS Table 8.1.1.1Ra and 8.1.2.1Ra.

Note: For exposure, 6 months is defined as 166 days, 12 months is defined as 335 days, and 18 months is defined as 518 days.

(a) The All Comparators Grouping combines placebo and active comparator groups, which are not shown in the table.

(b) The All Alogliptin Grouping combines 25 mg with the 6.25, 12.5, 50, and 100 mg groups, which are not shown in the table.

(c) Duration of exposure in days is calculated as date of last dose - date of first dose + 1. Last dose date is estimated for subjects ongoing in Study 402 using the earlier of the interim data cut date and the last study drug dispensing date plus the number of days in the dosing interval.

(d) Cumulative exposure in subject-years is defined as the sum of days for all subjects within a grouping divided by 365.25.

Source: SCS Table 1.f

The breakdown of cumulative exposure (subject-years) by controlled study is shown in Table 23. Study 402 contributed most to the cumulative exposure.

Table 23. Cumulative exposure (subject-years) by study (Controlled phase 2 and 3 studies)

Study	All Comparators (n=2934)	Alogliptin 25 mg (n=3500)	All Alogliptin (n=5232)
Phase 2/3 controlled	1441	1773	2498
003	6	9	40
SULF-007	41	89	179
MET -008	44	93	190

TZD-009	41	89	176
PLC-010	26	59	117
INS-011	47	53	108
301	7	15	15
303	162	173	173
402	475	475	475
OPI-001	218	237	475
OPI-002	70	148	218
OPI-004	304	334	334

Source: IAS Table 8.1.2.1Ra

In the controlled phase 2 and 3 study group that excludes the Japanese data, a total of 4162 subjects were exposed to alogliptin (6.25 – 100 mg) and 2430 were exposed to alogliptin 25 mg. More alogliptin subjects completed the studies, when compared to comparator subjects (77.0% vs. 64.2%), although these completion rates are generally lower than is seen for diabetes development programs (driven by the high incidence of hyperglycemic rescue). More comparator subjects (which included placebo-treated subjects) received hyperglycemic rescue when compared to alogliptin subjects (21.0% vs. 10.5%). A similar percentage of subjects were discontinued (10.9-11.7%). The reasons for discontinuation were generally similar between groups (see Table 24).

Table 24. Disposition of subjects (Controlled phase 2 and 3 studies)

Disposition Category	n/N (%) of Subjects		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232
Completed (c)	1190/1855 (64.2)	1851/2430 (76.2)	3204/4162 (77.0)
Hyperglycemic Rescue (d)	385/1831 (21.0)	259/2383 (10.9)	433/4115 (10.5)
Ongoing (c)	1016/1079 (94.2)	1006/1070 (94.0)	1006/1070 (94.0)
Discontinued	343/2934 (11.7)	382/3500 (10.9)	585/5232 (11.2)
Missing	0/2934	1/3500 (<0.1)	4/5232 (0.1)
Primary Reason for Discontinuation (e)			
Adverse Event	100/2934 (3.4)	98/3500 (2.8)	143/5232 (2.7)
Major Protocol Deviation	59/2934 (2.0)	59/3500 (1.7)	97/5232 (1.9)
Lost to Follow-Up	36/2934 (1.2)	38/3500 (1.1)	63/5232 (1.2)
Voluntary Withdrawal	90/2934 (3.1)	142/3500 (4.1)	205/5232 (3.9)
Pregnancy	0/2934	0/3500	1/5232 (<0.1)
Investigator Discretion (f)	45/2691 (1.7)	35/3231 (1.1)	61/4963 (1.2)
Other	13/2934 (0.4)	10/3500 (0.3)	15/5232 (0.3)

Source: IAS Table 8.2Ra.

n=number of subjects with completion status, N=number of applicable subjects in population, %=(n/N)*100.

(a) The All Comparators Grouping combines placebo and active comparator groups, which are not shown in the table.

(b) The All Alogliptin Grouping combines 25 mg with the 6.25, 12.5, 50, and 100 mg groups, which are not shown in the table.

(c) Subjects continuing study drug dosing in Study 402 are summarized as ongoing. The denominator is number of subjects treated in Study 402 (placebo=1079; alogliptin 25 mg=1070). These subjects are excluded from the denominator for the calculation of percentage of subjects who completed study drug dosing.

(d) Subjects who met the hyperglycemic rescue criteria defined for the study protocol. These subjects are not included in the discontinuation summary. As Studies 301 and 402 did have not defined rescue criteria, percentages are based on the number of subjects in each grouping.

(e) Percentages are based on the number of subjects in each grouping for which the discontinuation reason was an available option.

(f) Studies 301 and 303 did not include 'Investigator Discretion' as a possible reason for discontinuation.

Source: SCS Table 1.d

In long-term, Japanese phase 2 and 3 studies, 1098 subjects were exposed to alogliptin (any dose). A total of 1071 Japanese subjects completed ≥52 weeks of treatment.

Study 402: In CV study 402, a total of 1042 subjects have been exposed to alogliptin for a mean duration of 5.4 months. When the disposition for ongoing study 402 was reviewed, the placebo and alogliptin 25 mg groups were similar, especially in regards to the incidence of premature discontinuations.

Table 25. Study 402: Exposure by duration

Exposure	Placebo (n=1076)	Alogliptin (n=1058)
Number of subjects exposed	1061	1042
Mean (SD) duration (months)	5.4 (3.7)	5.4 (3.7)
Number (%) subjects exposed for ≥1y (≥335 d)	96 (8.9)	99 (9.4)

Source: SCS Table 1.g

Table 26. Study 402: Disposition of subjects

Disposition Category	Number (%) of Subjects	
	Placebo N=1076	Alogliptin 25 mg N=1058
Randomized	1076	1058
Randomized but not treated	15 (1.4)	16 (1.5)
Completed study drug (a)	0	1 (0.1)
Prematurely discontinued study drug	65 (6.0)	62 (5.9)
Primary Reason for Discontinuation		
Adverse Event	31 (2.9)	27 (2.6)
Major Protocol Deviation	1 (0.1)	0
Lost to Follow-Up	4 (0.4)	3 (0.3)
Voluntary Withdrawal	22 (2.0)	25 (2.4)
Investigator Discretion	2 (0.2)	3 (0.3)
Other	5 (0.5)	4 (0.4)

Source: Study 402 Table 15.1.2.

Note: Subjects who were treated but not counted as randomized, due to incomplete records in the CRF at the time of the data cut, are excluded from Study 402 data tables but included in IAS data tables.

n=number of subjects with completion status, N=number of randomized subjects, %=(n/N)*100.

(a) Subject 402/8478-005 was reported as having completed the study due to a CRF documentation error.

Source: SCS Table 1.e

Renal function: Although it was agreed on September 30, 2010 (see Section 2.5) that the completed CV study 402 would expose 200 moderate RI subjects and 100 severe RI subjects to alogliptin for ≥1 year, Table 27 and Table 28 show the number of subjects exposed to alogliptin by baseline renal function (calculated by C-G and MDRD) in study 402 and the safety pool, respectively. Few subjects with severe RI have been exposed to alogliptin (n=24-32).

Table 27. Study 402: Baseline renal function

Characteristic	Number (%) of Subjects	
	Placebo N=1076	Alogliptin 25 mg N=1058
Renal Function (C-G)		
Normal	393 (36.5)	411 (38.8)
Mild Impairment	397 (36.9)	386 (36.5)
Moderate Impairment	217 (20.2)	213 (20.1)
Severe Impairment	24 (2.2)	24 (2.3)
Renal Function (MDRD)		
Normal	128 (11.9)	113 (10.7)
Mild Impairment	566 (52.6)	614 (58.0)
Moderate Impairment	306 (28.4)	280 (26.5)
Severe Impairment	31 (2.9)	27 (2.6)

Source: Study 402 Table 15.1.3.

Source: SCS Table 1.k

Table 28. Baseline renal function (Controlled phase 2 and 3 studies excluding study 301)

Characteristic	All Comparators (a) N=2910	Alogliptin 25 mg N=3453	All Alogliptin (b) N=5185
Serum Creatinine (mg/dL) (c)			
Mean (SD)	0.98 (0.331)	0.97 (0.276)	0.96 (0.255)
Median	0.90	0.90	0.90
Min, Max	0.4, 8.1	0.5, 4.3	0.4, 4.3
Renal Function (C-G), n (%) (c)			
Normal	1520 (52.2)	1895 (54.9)	3000 (57.9)
Mild Impairment	995 (34.2)	1149 (33.3)	1685 (32.5)
Moderate Impairment	328 (11.3)	357 (10.3)	447 (8.6)
Severe Impairment	24 (0.8)	24 (0.7)	25 (0.5)
Renal Function (MDRD), n (%) (c)			
Normal	501 (17.2)	609 (17.6)	979 (18.9)
Mild Impairment	1805 (62.0)	2235 (64.7)	3397 (65.5)
Moderate Impairment	532 (18.3)	550 (15.9)	749 (14.4)
Severe Impairment	30 (1.0)	31 (0.9)	32 (0.6)

Source: IAS Table 8.3.1Ra.

Note: Actual number of evaluable subjects may vary slightly from treatment group Ns, as presented in source table.

(a) The All Comparators Grouping combines placebo and active comparator groups, which are not shown in the table.

(b) The All Alogliptin Grouping combines 25 mg with the 6.25, 12.5, 50, and 100 mg groups, which are not shown in the table.

(c) Laboratory results were not obtained from a central laboratory for Study 301, so this study is excluded from this summary.

Source: SCS Table 1.i

7.2.2 Explorations for Dose Response

See section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations and my previous NDA reviews.

7.2.3 Special Animal and/or In Vitro Testing

Data from the alogliptin/metformin rat embryofetal development study indicated there was no interaction. Please refer to David Carlson's January 18, 2012 review of the CR.

7.2.4 Routine Clinical Testing

The Sponsor obtained laboratory tests, vital signs, and ECGs at reasonable time points during the studies and under consistent settings, where applicable. I have reviewed the timing of these assessments in section 5.3 Discussion of Individual Studies/Clinical Trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to section 7.5.4 Drug-Disease Interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As described in section 2.4 Important Safety Issues With Consideration to Related Drugs, AEs of special interest include the following: CV safety (including CHF), renal safety, hypersensitivity, pancreatitis, skin lesions, infections, malignancy (including bladder, thyroid, and pancreatic cancer), fractures, hepatotoxicity, and hypoglycemia.

The applicant analyzed CV events, hypersensitivity reactions, acute pancreatitis, malignancies, and infections and infestations as AEs of interest in the Summary of Clinical Safety (SCS). Renal safety was specifically addressed by the requirements outlined in the CR letters. I reviewed fractures, hepatotoxicity, and hypoglycemia using the documents and data submitted.

7.3 Major Safety Results

7.3.1 Deaths

In controlled phase 2 and 3 studies, the incidence of death was low and similar between treatment groups (1.0% placebo, 0.4% alogliptin 25 mg, 0.2% alogliptin 12.5 mg, and 0.1% active comparator). The higher rates on the placebo and alogliptin 25 mg groups is driven by CV study 402, which contributed the majority of subjects and enrolled subjects at high CV risk.

A total of 51 deaths were reported by May 31, 2011. Of these, four deaths were previously reported in the original NDA or safety update. Fifteen deaths occurred >14 days after the last dose of study drug or were reported after the clinical database cutoff (April 29, 2011). Of the remaining 36 deaths, 18 (50.0%) subjects received placebo, 1 (2.8%) received pioglitazone 45 mg, and 17 (47.2%) received alogliptin (3 received 12.5 mg and 14 received 25 mg).

Subjects who died had risk factor(s) or concomitant illness(es) associated with their cause of death. Alogliptin subjects were not at increased risk of death when compared to placebo. See also section 7.3.5 Submission Specific Primary Safety Concerns, which discusses MACE.

Table 29. Deaths (controlled phase 2 and 3 studies)

Study/Site-Subject Age (yr)/Sex/Race	Treatment	Study Day at Time of Death	Cause of Death	Relevant Medical History	Circumstances of Death Autopsy Findings
Completed Studies in the Controlled Phase 2 and 3 Study Group					
008/520-8010 (a) 49/Female/White	Alogliptin 12.5 mg	45	Hypertensive heart disease	Hypertension, obesity, smoker	Ambulance called when subject developed shallow breathing following acute illness with GI symptoms; pronounced dead on arrival at hospital. Autopsy: hypertensive heart disease
009/463-9003 (a) 62/Male/White	Alogliptin 12.5 mg	42	Sudden death	Hyperlipidemia, ex-smoker	Died suddenly at home; attempts at resuscitation unsuccessful. Autopsy: none
011/464-5005 (a) 72/Male/White	Alogliptin 12.5 mg	71	Sudden death	MI, ischemic heart disease, CAD, hypertension arterial, hyperlipoproteinemia, CHF, cerebral infarction, smoker	Died suddenly at home. Autopsy: none
008/448-8001 (a) 56/Male/White	Alogliptin 25 mg	63	MI (b)	Hypercholesterolemia, smoker	Died in postoperative recovery after cholecystectomy. Autopsy: MI
011/404-5006 56/Female/White	Alogliptin 25 mg	230	Myelofibrosis (b)	Anemia, obesity, hypertension, chronic gastritis, dyslipidemia, thrombocytopenia, smoker (35 years)	Hospitalized with UTI, diagnosis of myelofibrosis confirmed, with secondary diagnosis of acute myeloblastic leukemia; the subject developed upper GI bleeding, evolved poorly, and died. Autopsy: unknown
322OPI-004/ 1230-4515 70/Female/White	Alogliptin 25 mg + pioglitazone 30 mg	62	MI	Hypertension, unstable and stable angina, MI, mixed dyslipidemia, arteriosclerosis obliterans of the lower extremities, cerebrovascular arteriosclerosis, arteriosclerosis of the aorta	Attempts to resuscitate at hospital unsuccessful. Autopsy: none
322OPI-001/ 907-3016 62/Female/White	Pioglitazone 45 mg	156	Sudden cardiac death	Obesity, asthma, chronic bronchitis, arterial hypertension, ventricular hypertrophy, smoker	Found unconscious at work; attempts to resuscitate unsuccessful. Cause of death per medical/legal report was acute coronary insufficiency. Autopsy: unavailable
Study 402					
402/1194-003 48/Male/Asian	Blinded	9	Head injury (c,d)	Hypertension, CAD, non-smoker	Presented with severe head injury. Autopsy: none
402/8062-003 66/Male/White	Placebo	187	Multi-organ failure (b)	Angina, MI, CABG, renal dysfunction, exertional dyspnea, obesity (BMI=41), gout, ulnar neuropathy, anemia, retinal bleed, PCI, cardiac arrhythmia, hypertension, CVA, cardiomegaly, ex-smoker (25 years)	Hospitalized with continued dizziness, nausea and hypotension post pacemaker insertion. Progressed poorly in ICU, and died from multiple organ failure. Autopsy: severe atherosclerotic CAD, massive cardiomegaly, bilateral myocardial hypertrophy, chronic CHF with bilateral pulmonary edema and congestion, hepatic cardiac sclerosis, bilateral pleural effusions, ascites, atherosclerosis of aorta, and saddle pulmonary embolism.
402/8227-001 70/Male/White	Placebo	344	Cardiac arrest (b)	COPD, MI, arrhythmia, hypertension, respiratory failure, hyperlipidemia, smoker (35 years),	Found dead on nursing home bed. Death certificate illegible. Autopsy: none

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402/8247-018 78/Female/Black	Placebo	76	MI	MI, hypertension, CHF, nonsmoker	Presented with cold sweats, clammy skin, dyspnea and difficulty speaking. Assessed as having acute respiratory failure, severe bronchial spasm, possible inflammatory acute pulmonary edema (secondary to ischemia). Experienced bradyarrhythmia and cardiac arrest with pulseless electrical activity. The direct cause of death per site was septic shock that occurred 2 weeks after hospital admission for recurrent MI. Autopsy: none
402/8259-003 64/Male/White	Placebo	51	Coma	Hypertension, stroke, chronic renal failure, ex-smoker (49 years)	Initially hospitalized with ischemia of the right hallux foot, which progressed to septic shock and coma. Death occurred a few weeks after initial admission. Cause of death per death certificate was multiple organ failure, cardiac insufficiency, respiratory infection, diabetes mellitus, and acute renal insufficiency. Autopsy: none
402/8304-005 70/Male/White	Placebo	14	Septic shock	MI, arrhythmia, hypertension, CHF, peripheral artery disease diabetic foot, anemia, diabetic nephropathy, ex-smoker (20 years)	Hospitalized due to worsening of diabetic foot, which progressed poorly; the subject became hemodynamically unstable, and subsequently went into cardiorespiratory arrest and died. Cause of death per death certificate was septic shock and renal failure. Autopsy: none
402/8369-004 76/Female/White	Placebo	37	Cardiac failure congestive	Pulmonary edema, CABG, CHF, cardiac arrhythmia, chronic renal failure, diabetic retinopathy, MI, PCI, hypertension, aortic valve stenosis, nonsmoker	Hospitalized with dyspnea and abdominal pain, and diagnosed with CHF. Died in hospital 5 days later. Autopsy: none
402/8388-001 70/Female/Asian	Placebo	24	Acute MI	MI and hypertension, nonsmoker	Died at home after developing crushing chest pain during fight with family member; resuscitative efforts were unsuccessful and subject was dead-on-arrival at hospital. Autopsy: none
402/8388-022 54/Male/Asian	Placebo	115	Sudden cardiac death (b)	MI, pneumonia, CVA, anemia, hypertension, ex-smoker (29 years),	Died following sudden loss of consciousness; resuscitative efforts in ER were unsuccessful. Autopsy: none
402/8392-012 61/Male/White	Placebo	22	Cardiac arrest (c)	CHF class IV, MI	Cardiac arrest; resuscitative efforts failed. Autopsy: none
402/8418-001 50/Male/White	Placebo	162	ACS (b)	MI, unstable angina, CHF, hypertension, nonsmoker	Died following hospitalization due to ACS Autopsy: none
402/8429-004 77/Male/White	Placebo	17	Cardiac failure chronic	Hypertension, COPD, pulmonary hypertension, MI, ischaemic, cardiopathy, ex-smoker (43 years)	Died at home from CHF secondary to MI Autopsy: none
402/8461-006 52/Female/White	Placebo	268	Cardiac failure (c)	Hypertension, multiple MIs, non-smoker	Multiple MIs in the past year. Hospitalized with heart failure, and died 3 days later. Autopsy: none
402/8503-007 55/Male/Asian	Placebo	97	Hepatic neoplasm malignant	MI, PCI, ex-smoker (10 years)	Refused hospitalization and treatment for advanced liver cancer. Died at home after increasing abdominal discomfort and confusion. Autopsy: none

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402/8552-015 59/Female/White	Placebo	37	Cardiac failure	Hypertension, MI, cardiac failure, PCI, peptic ulcer, nonsmoker	Hospitalized with worsening CHF after stopping carvedilol and clopidogrel on her own. Readmitted with decompensated heart failure IV (worsened from III-IV), and subsequently died due to sepsis. Cause of death per death certificate was multiple organ failure, severe sepsis, pneumonia, and cardiac insufficiency. Autopsy: none
402/8598-005 59/Female/White	Placebo	97	ACS	COPD, MI, CHF, unstable angina, hypertension, ex-smoker	Developed abdominal pain and dyspnea, and subsequently cardiac arrest. Resuscitative efforts by EMT were not successful. Autopsy: none
402/8646-001 70/Male/White	Placebo	293	Pulmonary edema	TB, DVT, MI, pulmonary edema, ex-smoker (15 years)	Prolonged hospitalization due to complications after DHS osteosynthesis, which progressed poorly. Died in hospital without any alarming signs. Autopsy: high grade sclerosis of coronary arteries, acute myocardial ischemia, and pulmonary edema.
402/8656-003 66/Female/Asian	Placebo	26	Acute MI	Hypertension, MI, CHF, dyslipidemia, chronic kidney disease, nonsmoker	Following MI, developed V-Fib and died. Autopsy: none
402/8681-007 69/Female/White	Placebo	168	Sudden cardiac death	CHF, hypertension, bilateral pneumonia, MI, diabetic nephropathy, obesity, CVA, nonsmoker	Died suddenly at home. Cause of death per death certificate was decompensation of cardiac activity and postinfarction cardiosclerosis. Autopsy: none
402/8697-011 73/Female/White	Placebo	55	Cardiac failure acute	High cholesterol, CAD, hypertension, CHF nephropathy, PCI, unstable angina, peripheral artery disease, left ventricular hypertrophy, partial left bundle branch block, retinopathy, nonsmoker	Died in the ER. Autopsy: not provided
402/8729-006 67/Female/Asian	Placebo	281	Cardiac arrest	Unstable angina, hypertension	Hospitalized with chest pain, palpitations and breathlessness. Autopsy: none
402/8758-003 67/Female/White	Placebo	2	Cardiac failure acute	Hypertension, ischemic heart disease	Died suddenly. Autopsy: none
402/8786-001 72/Male/White	Placebo	104	Hemorrhagic stroke	MI, CABG, hypertension	Presented with intense headache and vomiting followed by coma and respiratory arrest. Autopsy: none
402/8807-001 84/Male/White	Placebo	12	Sudden death	CHF, CVA, hypertension	Died on bed without any warning. Autopsy: none
402/8929-007 61/Female/Asian	Placebo	55	Sudden cardiac death	Acute MI, hypertension	Developed dyspnea then went into cardiac arrest. Autopsy: none
402/8933-001 68/Female/Asian	Placebo	116	Acute MI (b,c)	MI, severe pulmonary hypertension, thalassemia, CHF, ischemic cardiomyopathy, smoker (53 years)	Developed sudden angina pain with dyspnea and respiratory failure. Cause of death per death certificate was cardiac muscle deprived of blood. Autopsy: none
402/8948-001 55/Male/White	Placebo	65	CAD (b)	MI, CABG, unstable angina, hypertension	Experienced chest pains prior to death. Autopsy: none

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402/8214-001 64/Male/White	Alogliptin 25 mg	123	CVA	Hypertension, MI, COPD, CVA, A-fib	Hospitalized with left hemiparesis and dysarthria; diagnosed with stroke and died 11 days later. Autopsy: none
402/8225-006 79/Female/White	Alogliptin 25 mg	127	Cardiac failure congestive	CHF, asthma, MI, unstable angina	Hospitalized with progressive shortness of breath, dyspnea and orthopnea, diagnosed with CHF and acute on chronic kidney injury. Discharged to hospice in guarded condition and died in hospice 31 days after the last dose of study therapy. Autopsy: not provided.
402/8276-003 85/Female/White	Alogliptin 25 mg	233	MI	MI, unstable angina, CHF, hypertension	Hospitalized with sudden onset of palpitations and dyspnea with confirmed troponin elevation, leading to diagnosis of recurrent MI. Died 2 days later in ICU. Autopsy: none
402/8360-001 82/Male/White	Alogliptin 25 mg	158	Sepsis (b)	MI, CABG, hypertension, CHF	Hospitalized for bilateral pneumonia, and died from sepsis. Death occurred 3.5 months after the last dose of study medication. Autopsy: none
402/8364-001 63/Male/White	Alogliptin 25 mg	184	Cardiac arrest	MI, CABG, CAD, unstable angina, hypertension	GP reported that the subject died at home due to cardiac arrest. Cause of death per death certificate was V-fib. Autopsy: none
402/8364-020 80/Male/White	Alogliptin 25 mg	18	Cardiac arrest	MI, hyperlipidemia, CABG, unstable angina, hypertension, CAD	Collapsed on the street and died; confirmed by EMT. Autopsy: none
402/8411-002 64/Female/White	Alogliptin 25 mg	3	MI	Hypertension, CHF, CAD, MI	Hospitalized with intense chest pains with severe and repeated cardiac arrhythmia and died the next day. Autopsy: ischemic heart disease, recurrent transmural MI, acute CV failure and multi-organ failure.
402/8475-003 60/Male/White	Alogliptin 25 mg	129	MI	MI	Died suddenly while having conversation. Autopsy: none
402/8476-004 75/Male/White	Alogliptin 25 mg	39	Acute MI	Hypertension, MI, non-smoker	Hospitalized with severe chest pain and died without warning while in treatment. Autopsy: none
402/8476-005 74/Male/White	Alogliptin 25 mg	62	Acute MI	Hypertension, MI	Hospitalized with acute chest pain with ST depression, and died the following day due to cardiogenic shock. Autopsy: none
402/8478-019 62/Female/White	Alogliptin 25 mg	64	Cardiogenic shock (c)	MI, hypertension	Hospitalized with unstable angina, and developed troponin elevation 4 days later while under treatment for unstable angina. Died due to cardiogenic shock 6 days after MI onset. Autopsy: none
402/8485-001 57/Female/Multiracial	Alogliptin 25 mg	79	Septic shock	CHF, hypertension, ischemic heart disease, unstable angina	Developed post-surgical Pseudomonas infection; subsequently died from septic shock. Autopsy: none
402/8504-002 56/Female/Asian	Alogliptin 25 mg	16	Cardiac failure	Hypertension, ischemic cardiomyopathy	Hospitalized with statin-induced rhabdomyolysis, and progressed to renal failure and cardiac arrest. Autopsy: not provided.

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402/8534-002 49/Male/White	Alogliptin 25 mg	238	MI (b)	MI, CABG, unstable angina, hypertension	Passed out while getting ready to go fishing, and then went into cardiac arrest. Autopsy: none
402/8566-003 67/Male/White	Alogliptin 25 mg	104	Arrhythmia (c)	MI, hypertension, CHF	Per PI, subject experienced arrhythmia at home during the night and died. Autopsy: none
402/8611-007 71/Male/White	Alogliptin 25 mg	68	Death	CABG, hypertension, CHF, CVA, MI, unstable angina	Died in sleep. Autopsy: none
402/8861-002 87/Female/White	Alogliptin 25 mg	124	Acute MI	MI, hypertension	Felt sudden dyspnea, and fainted while going to the rest room; transferred to his bed by family and died. Death was certified by a physician at home on the same day. Autopsy: none

Source: IAS Table 8.4.8Ra and Pharmacovigilance database.

A-fib=atrial fibrillation, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHF=congestive heart failure, COPD=chronic obstructive pulmonary disease, CPR=cardiopulmonary resuscitation, CVA=cerebrovascular accident, DHS=dynamic hip screw, DVT=deep venous thrombosis, EMT=emergency medical technician, ER=emergency room, GI=gastrointestinal, GP=general practitioner, ICU=intensive care unit, PCI=percutaneous coronary intervention, PE=pleural effusion, PI=principal investigator, TB=tuberculosis, UTI=urinary tract infection, V-fib=ventricular fibrillation

(a) Reported in original NDA or 120-Day Safety Update.

(b) Not considered treatment-emergent (ie, occurred >14 days after last dose of study drug).

(c) Reported after clinical database cut date (29 April 2011).

(d) Subject was randomized and died after clinical database cut date (29 April 2011).

Source: SCS Table 2.f

Note: Subject 402/8485-001 died of septic shock two weeks after cardiac revascularization surgery.

7.3.2 Nonfatal Serious Adverse Events

A summary of SAEs reported by ≥5 subjects in the original and resubmitted NDAs is shown in Table 30. As expected with the increased exposure, the incidence of any SAE was greater in the CR. There was a numeric imbalance in pancreatitis events (all alogliptin 5/5232 or 0.096% vs. all comparators 1/2934 or 0.034%). However, the incidence of SAEs was lower in the alogliptin groups (alogliptin 25 mg 7.3% and all alogliptin 5.8%) when compared to the all comparators group (8.9%).

Review of the complete list of SAEs (i.e., including those reported in <5 subjects) did not reveal additional noteworthy findings, especially in light of the list of AEs of special interest described in Section 7.3.4.

Table 30. SAEs reported by ≥5 subjects in the original or resubmitted NDA

SOC Preferred Term	Number (%) of Subjects					
	Original NDA			NDA Resubmission		
	Placebo N=534	Alogliptin 25 mg N=910	All Alogliptin (a) N=1961	All Comparators (b) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (a) N=5232
Any SAE	20 (3.7)	42 (4.6)	80 (4.1)	260 (8.9)	255 (7.3)	306 (5.8)
Blood and lymphatic system disorders	0	0	0	6 (0.2)	6 (0.2)	6 (0.1)
Anemia	0	0	0	5 (0.2)	5 (0.1)	5 (0.1)
Cardiac disorders	2 (0.4)	11 (1.2)	23 (1.2)	119 (4.1)	100 (2.9)	113 (2.2)
Acute coronary syndrome	0	0	0	5 (0.2)	2 (0.1)	2 (<0.1)
Acute myocardial infarction	0	0	0	29 (1.0)	18 (0.5)	18 (0.3)
Angina pectoris	0	5 (0.5)	7 (0.4)	14 (0.5)	14 (0.4)	16 (0.3)
Angina unstable	2 (0.4)	1 (0.1)	1 (0.1)	28 (1.0)	22 (0.6)	23 (0.4)
Cardiac failure	0	0	0	11 (0.4)	11 (0.3)	11 (0.2)
Cardiac failure congestive	0	3 (0.3)	4 (0.2)	9 (0.3)	13 (0.4)	14 (0.3)
Coronary artery disease	0	0	2 (0.1)	8 (0.3)	5 (0.1)	7 (0.1)
Myocardial infarction	0	2 (0.2)	4 (0.2)	7 (0.2)	10 (0.3)	12 (0.2)
Gastrointestinal disorders	1 (0.2)	2 (0.2)	4 (0.2)	17 (0.6)	17 (0.5)	22 (0.4)
Pancreatitis	0	0	1 (0.1)	1 (<0.1)	3 (0.1)	5 (0.1)
General disorders and administration site conditions	0	3 (0.3)	8 (0.4)	21 (0.7)	17 (0.5)	22 (0.4)
Non-cardiac chest pain	0	3 (0.3)	6 (0.3)	11 (0.4)	11 (0.3)	14 (0.3)
Hepatobiliary disorders	1 (0.2)	1 (0.1)	3 (0.2)	6 (0.2)	8 (0.2)	12 (0.2)
Cholecystitis	0	0	2 (0.1)	0	3 (0.1)	5 (0.1)
Infections and infestations	5 (0.9)	11 (1.2)	17 (0.9)	41 (1.4)	37 (1.1)	46 (0.9)
Appendicitis	1 (0.2)	1 (0.1)	2 (0.1)	1 (<0.1)	4 (0.1)	5 (0.1)
Pneumonia	1 (0.2)	1 (0.1)	1 (0.1)	9 (0.3)	6 (0.2)	6 (0.1)
Metabolism and nutrition disorders	1 (0.2)	0	1 (0.1)	14 (0.5)	9 (0.3)	10 (0.2)
Hypoglycemia	0	0	1 (0.1)	2 (0.1)	5 (0.1)	6 (0.1)
Musculoskeletal and connective tissue disorders	1 (0.2)	2 (0.2)	5 (0.3)	11 (0.4)	14 (0.4)	17 (0.3)
Musculoskeletal chest pain	0	0	0	4 (0.1)	8 (0.2)	8 (0.2)
Nervous system disorders	2 (0.4)	3 (0.3)	4 (0.2)	25 (0.9)	26 (0.7)	28 (0.5)
Cerebrovascular accident	0	0	0	4 (0.1)	5 (0.1)	5 (0.1)
Syncope	0	0	0	2 (0.1)	5 (0.1)	5 (0.1)
Renal and urinary disorders	1 (0.2)	1 (0.1)	2 (0.1)	15 (0.5)	19 (0.5)	21 (0.4)
Renal failure acute	0	0	0	7 (0.2)	6 (0.2)	6 (0.1)
Respiratory, thoracic and mediastinal disorders	0	3 (0.3)	3 (0.2)	17 (0.6)	21 (0.6)	22 (0.4)
Chronic obstructive pulmonary disease	0	0	0	5 (0.2)	5 (0.1)	5 (0.1)

Source: SCS Table 2.g

More SAEs in the cardiac disorders SOC were observed in the NDA resubmission than in the original NDA (alogliptin 25 mg: 2.9% vs. 1.2%, respectively; comparators 4.1% vs. 0.4%). This is explained by the cardiac events contributed by CV study 402

(alogliptin 25 mg n=81, placebo n=113). When these events are removed from the NDA resubmission totals, there were 6 (0.2%) placebo events and 19 (0.5%) alogliptin 25 mg events.

7.3.3 Dropouts and/or Discontinuations

A summary of AEs which led to discontinuation and were reported by ≥ 3 subjects in the original and resubmitted NDAs is shown in Table 31. Despite the increased exposure, the incidence of study discontinuation due to AEs did not change substantially between the original and resubmitted NDAs (e.g. alogliptin 25 mg: 2.4% vs. 2.6%). Similarly, there was not a substantial change in the rate of discontinuation due to cardiac disorders (alogliptin 25 mg: 0.3% vs. 0.4%). Alogliptin did not increase one's rate of discontinuation due to an AE when compared to all comparator (alogliptin 25 mg 2.6% vs. placebo 3.0%). The alogliptin-treated patients who discontinued due to liver function test abnormal are discussed in the liver subsection of the laboratory results section.

When dropouts due to AEs that occurred in <3 subjects were reviewed in all alogliptin subjects (n=1961), there was one event each of pancreatitis acute, serum sickness, and alanine aminotransferase increased as well as several individual cases under the Skin and Subcutaneous Tissue Disorders SOC.

Table 31. AEs leading to discontinuation reported by ≥3 subjects in the original and resubmitted NDAs

SOC Preferred Term	Number (%) of Subjects					
	Original NDA			NDA Resubmission		
	Placebo N=534	Alogliptin 25 mg N=910	All Alogliptin (a) N=1961	All Comparators (b) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (c) N=5232
Any AE leading to study discontinuation	11 (2.1)	22 (2.4)	48 (2.4)	87 (3.0)	90 (2.6)	131 (2.5)
Cardiac disorders	1 (0.2)	3 (0.3)	5 (0.3)	13 (0.4)	14 (0.4)	18 (0.3)
Acute myocardial infarction	0	0	0	4 (0.1)	2 (0.1)	2 (<0.1)
Cardiac failure congestive	0	2 (0.2)	2 (0.1)	1 (<0.1)	3 (0.1)	3 (0.1)
Myocardial infarction	0	1 (0.1)	1 (0.1)	3 (0.1)	5 (0.1)	5 (0.1)
Gastrointestinal disorders	2 (0.4)	1 (0.1)	2 (0.1)	8 (0.3)	9 (0.3)	13 (0.2)
Diarrhea	0	0	0	4 (0.1)	1 (<0.1)	2 (<0.1)
Nausea	1 (0.2)	0	0	2 (0.1)	1 (<0.1)	3 (0.1)
General disorders and administration site conditions	0	2 (0.2)	5 (0.3)	7 (0.2)	10 (0.3)	14 (0.3)
Edema	0	0	1 (0.1)	4 (0.1)	0	1 (<0.1)
Edema peripheral	0	0	0	2 (0.1)	4 (0.1)	4 (0.1)
Investigations	0	3 (0.3)	7 (0.4)	9 (0.3)	11 (0.3)	17 (0.3)
Lipase increased	0	0	0	3 (0.1)	2 (0.1)	2 (<0.1)
Liver function test abnormal	0	1 (0.1)	3 (0.2)	1 (<0.1)	1 (<0.1)	4 (0.1)
Metabolism and nutrition disorders	2 (0.4)	0	1 (0.1)	12 (0.4)	4 (0.1)	5 (0.1)
Hyperglycemia	0	0	0	1 (<0.1)	3 (0.1)	3 (0.1)
Hypoglycemia	0	0	1 (0.1)	8 (0.3)	0	1 (<0.1)
Nervous system disorders	2 (0.4)	2 (0.2)	8 (0.4)	8 (0.3)	5 (0.1)	13 (0.2)
Headache	1 (0.2)	1 (0.1)	4 (0.2)	1 (<0.1)	1 (<0.1)	5 (0.1)

Source: SCS Table 2.i

7.3.4 Significant Adverse Events

AEs of special interest include the following: CV safety (including CHF), hepatotoxicity, renal safety, hypersensitivity, skin lesions, pancreatitis, infections, malignancy (including bladder, thyroid, and pancreatic cancer), fractures, and hypoglycemia.

See also section 8 Postmarket Experience.

CV safety (including CHF): See section 7.3.5 Submission Specific Primary Safety Concerns.

Hepatotoxicity: See section 7.4.2 Laboratory Findings.

Renal Safety: See section 7.4.2 Laboratory Findings.

Hypersensitivity: Hypersensitivity has been associated with other DPP4 inhibitors, such as sitagliptin, saxagliptin, and vildagliptin. Serious hypersensitivity events were observed under the alogliptin IND and NDA. The applicant was therefore asked to search the clinical trials included in the CR (including controlled Japanese trials and uncontrolled open-label study 012) and the postmarketing database using the following SMQs: Anaphylactic Reaction, Angioedema, and Severe Cutaneous Adverse Reactions (SCAR). The applicant responded to this information request on November 17, 2011.

The results of the search of controlled phase 2 and 3 studies are shown in Table 32 and summarized in Table 33. Although data from SMQ searches suggest that subjects taking alogliptin 25 mg are at increased risk of angioedema and severe cutaneous events when compared to placebo (angioedema SMQ: 3.4% vs. 1.8%; severe cutaneous reactions SMQ: 1.4% vs. 0.9%, see Table 32), the difference is driven mainly by nonserious events that were identified by broad search terms, which may overestimate the frequency of events, compared to more specific, narrow search terms.

For example, according to the broad Anaphylactic Reaction and Angioedema SMQ search, two alogliptin 25 mg subjects experienced a serious hypersensitivity reaction in a clinical trial. However, subject 402/8364-001 did not experience an anaphylactic reaction, and subject 011/370-5013's angioedema was likely not alogliptin-related. There was also one serious case of serum sickness which led to discontinuation.

- Subject 402/8364-001 (CIOMS Report TPG2010A00693): 63 year old male with history of T2DM, significant cardiac history including MI and coronary artery bypass graft, and asthma started alogliptin on May 14, 2010. On (b) (6) he was admitted for anterior chest wall pain with sweating, nausea, and dyspnea. ECG and troponin levels ruled out cardiac pain. Musculoskeletal chest pain was diagnosed. *Comment: This is not a case of anaphylactic reaction. It was detected on broad SMQ search due to dyspnea and cardiac arrest, which occurred three months apart.*
- Subject 011/370-5013: 34 year old male with a history of T2DM, appendectomy, and arterial hypertension was admitted to the hospital on day 4 for hypersensitivity. According to the narrative, relevant concomitant medications at the time of the event included losartan, candesartan, hydrochlorothiazide, and insulin. He experienced difficulty breathing, trouble talking, and swallowing difficulties. Examination revealed edema of the uvula, face, and neck; blood pressure 160/100 mm Hg, and normal oxygen saturation. He was treated with chlorpheniramine. The event resolved. Study medication was interrupted and then resumed on day 4. The subject was discontinued on day 167 due to lack of efficacy. *Comment: The concomitant use of losartan, which is associated with angioedema, and the fact that he was able to resume alogliptin suggest the angioedema was not related to alogliptin.*
- Subject 009/226-9002: 59 year old male with T2DM, benign prostatic hypertrophy, hyperlipidemia, and HTN experienced serum sickness on day 32.

In addition to alogliptin, he was also taking pioglitazone 45 mg/d and glyburide 15 mg/d. On day 25, he had pruritis which progressed to diffuse papular, erythematous rash followed by periorbital edema, nausea, diarrhea, and arthralgia. Serum sickness was diagnosed on day 32. Alogliptin was discontinued. He was withdrawn from the study on day 50. He improved with the sequelae of scaly palms which resolved on day 115.

Table 32. Hypersensitivity adverse events (Controlled phase 2 and 3 studies)

MedDRA SMQ	Number (%) of Subjects [Events per 100 Subject-Years]			
	Placebo N=2234	All Comparators (a) N=3485	Alogliptin 25 mg N=3972	All Alogliptin (b) N=6330
Serious and Nonserious Events				
Anaphylactic Reaction SMQ	4 (0.2%)	7 (0.2%)	7 (0.2%)	11 (0.2%)
Narrow Scope Terms (A)	1 (<0.1%)	1 (<0.1%)	0	0
B and C	2 (0.1%)	4 (0.1%)	5 (0.1%)	9 (0.1%)
D and (B or C)	1 (<0.1%)	2 (0.1%)	2 (0.1%)	2 (<0.1%)
Angioedema SMQ	40 (1.8%) [5.1]	96 (2.8%) [7.0]	136 (3.4%) [8.1]	210 (3.3%) [8.8]
Narrow Scope Terms	8 (0.4%) [1.1]	19 (0.5%) [1.4]	20 (0.5%) [1.1]	35 (0.6%) [1.3]
Broad Scope Terms	32 (1.4%) [4.0]	80 (2.3%) [5.6]	119 (3.0%) [7.0]	182 (2.9%) [7.5]
Severe Cutaneous Adverse Reactions SMQ	19 (0.9%) [2.3]	36 (1.0%) [2.3]	54 (1.4%) [3.0]	82 (1.3%) [3.2]
Narrow Scope Terms	3 (0.1%) [0.4]	6 (0.2%) [0.4]	3 (0.1%) [0.2]	6 (0.1%) [0.3]
Broad Scope Terms	16 (0.7%) [1.9]	30 (0.9%) [1.9]	51 (1.3%) [2.8]	77 (1.2%) [3.0]
Serious Events				
Anaphylactic Reaction SMQ	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Narrow Scope Terms (A)	1 (<0.1%)	1 (<0.1%)	0	0
B and C	0	0	0	0
D and (B or C)	0	0	1 (<0.1%)	1 (<0.1%)
Angioedema SMQ	0	0	1 (<0.1%) [0.1]	1 (<0.1%) [0.0]
Narrow Scope Terms	0	0	0	0
Broad Scope Terms	0	0	1 (<0.1%) [0.1]	1 (<0.1%) [0.0]
Severe Cutaneous Adverse Reactions SMQ	0	0	0	0
Nonserious Events				
Anaphylactic Reaction SMQ	3 (0.1%)	6 (0.2%)	6 (0.2%)	10 (0.2%)
Narrow Scope Terms (A)	0	0	0	0
B and C	2 (0.1%)	4 (0.1%)	5 (0.1%)	9 (0.1%)
D and (B or C)	1 (<0.1%)	2 (0.1%)	1 (<0.1%)	1 (<0.1%)
Angioedema SMQ	40 (1.8%) [5.1]	96 (2.8%) [7.0]	135 (3.4%) [8.0]	209 (3.3%) [8.8]
Narrow Scope Terms	8 (0.4%) [1.1]	19 (0.5%) [1.4]	20 (0.5%) [1.1]	35 (0.6%) [1.3]
Broad Scope Terms	32 (1.4%) [4.0]	80 (2.3%) [5.6]	118 (3.0%) [6.9]	181 (2.9%) [7.4]
Severe Cutaneous Adverse Reactions SMQ	19 (0.9%) [2.3]	36 (1.0%) [2.3]	54 (1.4%) [3.0]	82 (1.3%) [3.2]
Narrow Scope Terms	3 (0.1%) [0.4]	6 (0.2%) [0.4]	3 (0.1%) [0.2]	6 (0.1%) [0.3]
Broad Scope Terms	16 (0.7%) [1.9]	30 (0.9%) [1.9]	51 (1.3%) [2.8]	77 (1.2%) [3.0]

Source: Appendix 3, Tables 2.2.1, 2.3.1, and 2.4.1.

B = respiratory distress; C = pruritus, generalized flush, and urticaria; D = vascular collapse.

(a) The All Comparators Grouping includes the active comparator dose group, which is not shown in the table.

(b) The All Alogliptin Grouping includes the alogliptin 6.25, 12.5, 50, and 100 mg dose groups, which are not shown in the table.

Source: November 17, 2011 submission (SDN 56) Table 4

As shown in Table 33, a search for hypersensitivity events using narrow SMQ search terms suggests Alogliptin subjects are not at increased risk for these events compared to the All Comparator group.

Table 33. Summary of hypersensitivity adverse events identified using narrow search terms for the Anaphylactic Reaction, Angioedema, and Severe Cutaneous Adverse Reactions SMQs (Controlled phase 2 and 3 studies)

	Number (%) of Subjects [Events per 100 Subject-Years]			
	Placebo N=2234	All Comparators (a) N=3485	Alogliptin 25 mg N=3972	All Alogliptin (b) N=6330
All hypersensitivity events	11 (0.5%) [1.5]	25 (0.7%) [1.9]	23 (0.6%) [1.3]	41 (0.6%) [1.6]
Serious hypersensitivity events	1 (<0.1%) [0.1]	1 (<0.1%) [0.1]	0	0
Nonserious hypersensitivity events	10 (0.4%) [1.4]	24 (0.7%) [1.8]	23 (0.6%) [1.3]	41 (0.6%) [1.6]

Source: Appendix 3, Table 2.1.1.

(a) The All Comparators Grouping includes the active comparator dose group, which is not shown in the table.

(b) The All Alogliptin Grouping includes the alogliptin 6.25, 12.5, 50, and 100 mg dose groups, which are not shown in the table.

Source: November 17, 2011 submission (SDN 56) Table 3

There have also been Japanese postmarketing safety reports of anaphylactic reaction, angioedema, and SCAR events (see Table 34). Although many of these were nonserious or were identified using broad search terms, there were two angioedema (the third patient listed in Table 34 with serious angioedema appears to rather have had congestive heart failure), four Stevens-Johnson syndrome (SJS), and five erythema multiforme serious Japanese postmarketing events.

Table 34. Summary of postmarketing hypersensitivity events (Cutoff October 27, 2011) identified by SMQ

SMQ	Serious	Nonserious	Total
Anaphylactic reaction	0	2	2
Angioedema	3	32	35
Severe cutaneous adverse reaction (SCAR)	11	44	55

Source: November 17, 2011 submission (SDN 56)

Table 35. Serious postmarketing cases of angioedema (cutoff date October 27, 2011)

Case Number	Treatment	Criteria	Preferred Term
TCI2010A06345	Nesina 25 mg	Narrow	Urticaria
TCI2011A05420	Nesina 25 mg	Narrow	Urticaria
TCI2011A04779	Nesina 25 mg	Broad	Edema

Source: November 17, 2011 submission (SDN 5) Table 7

Serious Japanese postmarketing angioedema events:

- TCI2010A06345: 52 year old Japanese female started alogliptin on November 20, 2010. On (b) (6) red wheals, itching, and urticaria developed in the lumbar region. On (b) (6) this extended over the whole body. Due to swelling of the face and head, she visited the hospital and was admitted. BP was 110/40 mmHg, temperature 37.7° C, SpO2 94%, CRP 15.7 mg/dl, WBC 9,640/mcL, and platelets 82,000/mcL. She also had signs of vasculitis. She was medically managed. Alogliptin was discontinued. The event resolved on (b) (6) when she was discharged.
- TCI2011A05420: 74 year old Japanese female started alogliptin on September 16, 2011. On (b) (6) she had a generalized rash (urticaria) and alogliptin was discontinued. On (b) (6) she visited the hospital. On October 6, the event was resolving and a drug-induced lymphocyte stimulation test (DLST) was to be performed.
- TCI2011A04779: 63 year old male started alogliptin around (b) (6). Three days later, he went to the hospital for edema of the face and lower extremities. Increased cardiothoracic ratio was also noted. He was diagnosed with cardiac failure. Alogliptin was discontinued. Furosemide and digoxin were started. A week later, he was improved. *Comment: This event was detected with broad SMQ search terms and does not represent a case of angioedema.*

Table 36. Serious postmarketing cases of severe cutaneous adverse reactions (Cutoff date October 27, 2011)

Case Number	Treatment	Criteria	Preferred Term
TCI2011A04457	Nesina 25 mg	Narrow and Broad	Stevens-Johnson syndrome
TCI2011A02510	Nesina 25 mg	Narrow and Broad	Stevens-Johnson syndrome
TCI2011A04420	Nesina (dose unknown)	Narrow and Broad	Stevens-Johnson syndrome
TCI2011A04343	Nesina 25 mg	Narrow and Broad	Erythema multiforme
TCI2011A04366	Nesina 25 mg	Narrow and Broad	Erythema multiforme
TCI2011A05092	Nesina (dose unknown)	Narrow and Broad	Erythema multiforme
TCI2011A05698	Nesina 25 mg	Narrow and Broad	Erythema multiforme
TCI2011A02481	Nesina 25 mg	Broad	Drug eruption
TCI2011A02922	Nesina 25 mg	Broad	Drug eruption
TCI2011A03960	Nesina 25 mg	Broad	Drug eruption
TCI2011A02219	Nesina 25 mg	Broad	Drug eruption, edema

Source: November 17, 2011 submission (SDN 56) Table 8

Three serious SCAR events were cases of Stevens-Johnson syndrome (SJS), although one lacked supporting information. Another case of SJS (TCI2012A00131) was submitted to the IND on January 24, 2012. There were four serious reports of erythema multiforme and another (TCI2011A06360) submitted to the IND on February 9, 2012.

Japanese postmarketing SJS events:

- TCI2011A04457: 78 year old female started alogliptin on August 1, 2011. Glimepiride, which is associated with allergic skin reactions, was also used. On August 9, she developed itching. Alogliptin was discontinued August 10. On (b) (6) after seeing dermatology, she was hospitalized for a severe drug eruption and possible SJS. Oral antidiabetic drugs were changed to insulin. Steroid treatment was begun. DLST gave a positive reaction for glimepiride and negative result for alogliptin. The event resolved. *Comment: Although the DLST gave a positive test for glimepiride, it is not approved for use in the US nor suitable to diagnose an allergy in a given individual. SJS began after starting alogliptin.*
- TCI2011A02510: 80 year old female on multiple medications was changed from vildagliptin to alogliptin on April 1, 2011. On (b) (6) she had redness around the eyes, generalized erythema, lower leg edema, impaired appetite, conjunctival redness, and fever (38.9 C). CRP 1.26, WBC 6400, neutrophils 85%, HbA1c 6.9%. She was admitted for suspicion of SJS after a discussion with dermatology. Alogliptin was discontinued on April 11. Medical management, including steroids, was begun. The event resolved.
- TCI2011A04420: Event reported by pharmacist. No details provided.
- TCI2012A00131: 83 year old female was switched from vildagliptin to alogliptin on December 28, 2011. On January 7, wheals appeared on the body and extremities. Severe oral mucosal erosion and desquamation was noted. Her appetite was “markedly” impaired. Symptoms were “almost intolerable”. Medical management was begun on January 10. The event resolved.

Japanese postmarketing erythema multiforme events:

- TCI2011A04343: 82 year old female on multiple medications was seen by dermatology on July 7, 2011 for diffuse erythematous lesions on her head, that were felt to be due to hair dye. Topical steroid was started. The condition improved. On July 9, glimepiride was replaced with alogliptin and metformin. She developed dizziness. On July 18, erythema with itching developed. She used topical dexamethasone. Only July 19, she was seen by dermatology; diffuse lesions of erythema (erythema exudativum multiforme) with infiltration were noted on the trunk. Prednisolone was prescribed. On (b) (6) facial erythema developed and she was hospitalized. Recently prescribed medications, including alogliptin, were discontinued. Topical and oral steroids were begun. DLST results were as follows: alogliptin SI 162%, tolterodine tartrate SI 180%, and levocetirizine hydrochloride SI 159%. No drugs were assessed as positive (SI \geq 181%), although results were in the upper range of normal. Patch tests were negative. Symptoms improved. She was discharged on (b) (6). *Comment: Again, DLST is not approved for use in the US nor suitable to diagnose an allergy in a given individual.*
- TCI2011A04366: 70 year old female was switched from sitagliptin to alogliptin on July 9, 2011. On July 26, she developed fever, skin itching, and generalized redness. She was hospitalized and alogliptin discontinued on (b) (6). Medical

treatment, including steroid, was begun. On (b) (6) she had oliguria, increased serum creatinine, and decreased blood pressure for which dopamine was begun. The eruption resolved on (b) (6)

- TC12011A05092: A middle-aged female was switched from vildagliptin to alogliptin. Ten days later, erythema exudativum multiforme developed on her whole body. Alogliptin was discontinued. The event resolved. Vildagliptin was restarted without any problems. Lymphocyte transformation test was positive for alogliptin.
- TC12011A05698: 60 year old female started alogliptin on October 6, 2011. On October 18, she had a whole body rash and fever (38.9 C). She discontinued alogliptin on October 18 and saw dermatology the next day, when a diagnosis of drug-induced erythema multiforme due to alogliptin was made. CRP was increased (4.2). The event resolved.
- TC12011A06360: 76 year old male started alogliptin on November 11, 2011. On (b) (6) he had generalized itchy skin and a hot feeling, so he went to the hospital. He was treated with IV steroids and oral fexofenadine, but symptoms worsened. He went to another hospital on (b) (6). He was diagnosed with erythema multiforme exudativum by dermatology. Alogliptin was discontinued. He was medically managed. Symptoms improved in 2 weeks.

In summary, narrow Anaphylactic Reaction, Angioedema, and SCAR SMQ searches of controlled phase 2 and 3 studies do not suggest alogliptin subjects are at increased risk for hypersensitivity events. However, there have been two angioedema, four SJS, and five erythema multiforma serious Japanese postmarketing reports, in addition to the Skin Lesion findings described below.

With regard to the label, I therefore recommend that use of alogliptin be contraindicated in subjects with a history of serious hypersensitivity reaction to alogliptin. I also recommend a warning and description of the postmarketing events. Hypersensitivity should be monitored as an AE of special interest in the controlled CV study 402 and the PSURs.

Skin lesions: As described in section 2.4 Important Safety Issues With Consideration to Related Drugs, necrotizing skin lesions, which have been observed in monkeys given other DDP4 inhibitors, were not seen in alogliptin studies in mice, rats, dogs, or monkeys. Nonetheless, examination of the skin and digits was performed at every visit in most of the phase 3 studies. On February 23, 2010, the skin-related AE search terms were discussed with the sponsor. An updated search of the database was conducted for the CR; the results are shown in Table 37. In addition to that list, multiple other events potentially related to alogliptin were also reported in <3 subjects (e.g. serum sickness [see above], erythema, hypersensitivity, dermatitis, drug eruption, and facial edema).

Table 37. Potential cutaneous drug reaction (PCDR) AEs by PT reported by ≥3 subjects in any group (controlled phase 2 and 3 studies)

Preferred Term	Number (%) of Subjects		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232
Any PCDR AE	194 (6.6)	282 (8.1)	437 (8.4)
Rash	27 (0.9)	46 (1.3)	66 (1.3)
Pruritus	12 (0.4)	43 (1.2)	60 (1.1)
Dry skin	14 (0.5)	21 (0.6)	30 (0.6)
Dermatitis	2 (0.1)	15 (0.4)	22 (0.4)
Dermatitis contact	7 (0.2)	12 (0.3)	21 (0.4)
Eczema	13 (0.4)	13 (0.4)	21 (0.4)
Skin lesion	10 (0.3)	10 (0.3)	20 (0.4)
Blister	7 (0.2)	11 (0.3)	19 (0.4)
Skin ulcer	10 (0.3)	12 (0.3)	17 (0.3)
Skin exfoliation	5 (0.2)	7 (0.2)	16 (0.3)
Rash papular	4 (0.1)	10 (0.3)	15 (0.3)
Asthma	5 (0.2)	11 (0.3)	14 (0.3)
Dermatitis allergic	5 (0.2)	5 (0.1)	14 (0.3)
Rash macular	2 (0.1)	10 (0.3)	14 (0.3)
Urticaria	8 (0.3)	9 (0.3)	13 (0.2)
Erythema	2 (0.1)	9 (0.3)	11 (0.2)
Hypersensitivity	2 (0.1)	6 (0.2)	9 (0.2)
Skin discoloration	1 (<0.1)	4 (0.1)	7 (0.1)
Drug hypersensitivity	1 (<0.1)	3 (0.1)	6 (0.1)
Pruritus generalized	5 (0.2)	3 (0.1)	6 (0.1)
Rash pruritic	4 (0.1)	4 (0.1)	6 (0.1)
Face edema	1 (<0.1)	2 (0.1)	5 (0.1)
Skin fissures	4 (0.1)	3 (0.1)	5 (0.1)
Bronchospasm	2 (0.1)	3 (0.1)	4 (0.1)
Rash erythematous	3 (0.1)	2 (0.1)	4 (0.1)
Seborrheic dermatitis	3 (0.1)	2 (0.1)	4 (0.1)
Acrodermatitis	2 (0.1)	2 (0.1)	3 (0.1)
Campbell de Morgan spots	0	2 (0.1)	3 (0.1)
Dermatitis atopic	1 (<0.1)	2 (0.1)	3 (0.1)
Drug eruption	1 (<0.1)	2 (0.1)	3 (0.1)
Intertrigo	0	1 (<0.1)	3 (0.1)
Rash maculo-papular	3 (0.1)	2 (0.1)	3 (0.1)
Skin disorder	1 (<0.1)	1 (<0.1)	3 (0.1)
Swelling face	2 (0.1)	3 (0.1)	3 (0.1)
Diabetic foot	4 (0.1)	2 (0.1)	2 (<0.1)
Vulvovaginal pruritus	3 (0.1)	1 (<0.1)	2 (<0.1)
Angioedema	3 (0.1)	1 (<0.1)	1 (<0.1)

Source: IAS Table 8.4.9.2Ra.

Note: Events are arranged by descending frequency in the "All Alogliptin" grouping.

(a) The All Comparators Grouping combines placebo and active comparator groups, which are not shown in the table.

(b) The All Alogliptin Grouping combines 25 mg with the 6.25, 12.5, 50, and 100 mg groups, which are not shown in the table.

Source: SCS Table 2.o

The percentage of subjects reporting at least one potential cutaneous drug reaction (PCDR) AE was greater in the alogliptin groups (8.1% and 8.4%) than all comparators (6.6%). (Note, the list of preferred terms comprising the PCDRs was agreed upon with the sponsor prior to resubmission.) The incidence of rash, pruritus, dermatitis, rash papular, blister, and rash macular was numerically greater in the alogliptin groups than all comparator group. Although these skin reactions are not likely related to the necrotic lesions seen with other DPP4 inhibitors, they suggest that sensitive individuals may be

hypersensitive to alogliptin. This idea is supported by nonclinical findings in dogs, as described in David Carlson's August 27, 2008 review.

The incidence of PCDR SAEs and AEs leading to discontinuation, however, was low in both groups.

Table 38. PCDR SAEs and AEs leading to discontinuation (controlled phase 2 and 3 studies)

Type of AE	All comparators (n=2934)	Alogliptin 25 mg (n=3500)	All alogliptin (n=5232)
SAE	4 (0.1%)	6 (0.2%)	6 (0.1%)
AEs leading to discontinuation	5 (0.2%)	11 (0.3%)	18 (0.3%)

Source: IAS Tables 8.4.9.3Ra and 8.4.9.4Ra

Pancreatitis: On November 17, 2011, the applicant responded to our request for pancreatitis information. Specifically, it clarified the search technique (MedDRA SMQ acute pancreatitis [category A]) and databases used for the IND Analysis of Similar Events Summary (ASE) and NDA Integrated Summary of Clinical Safety (IAS). The ASE search uses the global safety database of completed and ongoing clinical studies, literature reports, postmarketing studies, and spontaneous reports. The IAS search uses a database of completed, controlled phase 2/3 IND studies. The results of the search for both the ASE and IAS are shown in Table 39. Using both the ASE and IAS database, ten (71.4%) of 14 pancreatitis events occurred in alogliptin subjects, although one event occurred before the first dose. Seven (70.0%) of 10 serious events occurred in alogliptin subjects. All subjects had risk factors for pancreatitis (see Table 39). I generally agree with the table's proposed risk factors as shown except for the following cases:

- Subject 001/256-5004: 45 year old female with history of T2DM, hyperlipidemia, and neuropathy experienced acute pancreatitis which led to study drug withdrawal on day 73. Concomitant medications included acetaminophen, naproxen, metformin, glargine insulin, atorvastatin, diphenhydramine, evening primrose, black cohosh, and clotrimazole cream. After diagnosis on day 73, she was medically managed and the event resolved with sequelae on day 89.
Comment: The report provided does not describe cholecystitis.
- OCT-001/0013-114: 60 year old Japanese male started alogliptin 25 mg daily on August 10, 2007. On (b) (6) he had fever, nausea, abdominal distention, and abdominal pain, so he went to the hospital. Amylase was 836 IU/L. CT showed swelling of the pancreatic head/body, increased opacities of the surrounding area, and body fluid retention. Gastroscopy revealed reduced gastrointestinal motion due to stomach irritation. MRI showed pancreatitis without pathologic dilation/blocking of the main pancreatic duct or space occupying lesions. He was medically managed, and alogliptin was discontinued. He was discharged on (b) (6) and alogliptin was resumed. *Comment:*

Although page three of the narrative states “Alcohol use (unk.) (Continuing: Yes)”, the main narrative does not describe alcohol use. There is also no blockage of the main pancreatic duct.

- 402/8211-008: 47 year old female with history of T2DM, hyperlipidemia, and previous tobacco use started alogliptin on September 21, 2010. On April 7, 2011, she had pain radiating to the back, abdominal pain, nausea, diarrhea, and vomiting which led her to be hospitalized on (b) (6). Ultrasounds showed mild steatosis. Gastrosocopy was unremarkable. Amylase was 150 U/L (normal 30-110) and lipase 1168 U/L (normal 23-300). Study drug was interrupted (b) (6) and resumed May 17. She was discharged (b) (6). *Comment: The applicant changed this case to “abdominal pain syndrome”. Given the patient’s symptoms and lipase >3x ULN, I believe this is a case of pancreatitis.*

Table 39. Acute pancreatitis events identified in the IND ASE and NDA IAS using MedDRA SMQ acute pancreatitis (category A)

Study	Subject Number	Treatment	Serious (Yes/No)	Included in IAS (Yes/No)	Included in IND ASE (Yes/No)	Alternative Etiology
OPI-001	436-3004	Alogliptin 12.5 mg	Yes	Yes	Yes	History of pancreatitis. Cholecystectomy.
OPI-002	750-2501	Alogliptin 25 mg	Yes	Yes	Yes	Associated with acalculous cholecystitis.
011	269-5004	Alogliptin 12.5 mg	Yes	Yes	Yes	Coincident with cholecystitis.
402	8552-010	Placebo	Yes	Yes	Yes	Associated with cholelithiasis. History of smoking and alcohol use.
402	8746-007	Alogliptin 25 mg	Yes	Yes	No (a)	Event occurred before 1 st dose of study drug.
402	8093-001	Alogliptin 25 mg	Yes	Yes	No (b)	Exacerbation of chronic pancreatitis. History of fatty liver and alcoholism.
011	256-5004	Alogliptin 25 mg	No	Yes	No (c)	Associated with cholecystitis.
OCT-001	0013-114	Alogliptin 25 mg	Yes	No (d)	Yes	Alcohol use.
MET-302	5166-007	Alogliptin 25 mg	No	No (e)	Yes	History of chronic pancreatitis, cholecystectomy.
MET-302	5082-004	Alogliptin 25 mg	No	No (e)	Yes	Alcohol use. Hyperlipidemia.
308	4011-003	Blinded	Yes	No (e)	Yes	History of pancreatitis. Symptoms following alcohol intake. Considered not related.
402	8521-002	Alogliptin 25 mg	Yes	No (f)	Yes	History of cholelithiasis.
402	8231-003	Placebo	No	No (g)	Yes	History of gall stones, cholecystitis, hyperlipidemia.
402	8211-008	Placebo	Yes	No (g)	Yes	History of steatosis. Diagnosis not confirmed. Event changed to abdominal pain syndrome.

(a) Event occurred on day of randomization but prior to dosing.

(b) Case coded to the preferred term “pancreatitis chronic” in the safety database, which was not included in the SMQ used in the IND ASE.

(c) Nonserious case was not included in IND ASE.

(d) Japanese studies were not included in the integrated dataset for the NDA resubmission.

(e) Study was ongoing at the time of the NDA resubmission (July 2011).

(f) Event was not treatment-emergent because it occurred greater than 14 days after last dose of study drug.

(g) Event occurred after the cut-off date (29 April 2011) for the IAS.

Source: November 17, 2011 submission (SDN 56) Table 1

In controlled phase 2 and 3 studies included in the IAS, six alogliptin subjects and one comparator subject had pancreatitis. However, given the number of subjects exposed, the percentage of alogliptin and comparator subjects with pancreatitis events was similar.

Table 40. Acute pancreatitis AEs (narrow scope) (Controlled phase 2 and 3 studies)

Preferred Term	Number (%) of Subjects		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232
Any Pancreatitis AE	1 (<0.1)	4 (0.1)	6 (0.1)
Pancreatitis	1 (<0.1)	3 (0.1)	5 (0.1)
Pancreatitis acute	0	1 (<0.1)	1 (<0.1)

Source: SCS Table 2.q

There were no pancreatitis events in the controlled, phase 2 or 3 Japanese studies. The applicant searched the Japanese postmarketing data (cutoff October 27, 2011) and identified six serious cases of pancreatitis (see Table 41), including one fatal case (TCI2010A0463) which are described below:

- TCI2010A04635: 81 year old Japanese female with T2DM, hyperlipidemia, six 6 mm gallstones, and osteoporosis. Two months after starting alogliptin 25 mg, she had abdominal pain and AST and ALT were 88 and 122, respectively. Days later, she had abdominal pain, nausea, vomiting, diarrhea, and increased bowel sounds and was hospitalized. BP was 128/70 mm Hg, HR 81 bpm, temperature 35.7 C, and SpO2 99%. At midnight, amylase was 2581. CT showed grade 2 pancreatitis, including enlarged pancreas, edematous hepatoduodenal ligament and pericholecystic tissues, gallstones, dilated common bile duct which “could be explained by age”, no choledocholithiasis, and no dilation of the main pancreatic duct. She was medically managed. The next day, her vital signs became unstable and she died of severe pancreatitis. Autopsy revealed necrotizing pancreatitis.
- TCI2011A02785: 70 year old Japanese male with T2DM and hyperlipidemia started alogliptin on January 24, 2011. On (b) (6) he had abdominal pain and tenderness, back pain, nausea, and vomiting. Ultrasound and CT were performed and suggested acute pancreatitis without gallstones. Triglycerides were 118, amylase 3470, and lipase 7825. He was hospitalized and medically managed. He was not a heavy drinker (<180 ml/). *Comment: As, per the report, dyslipidemia was “adequately controlled”, alogliptin-related pancreatitis should be considered.*
- TCI2011A03338: 85 year old Japanese female was started on alogliptin on May 2, 2011. On (b) (6) she had nausea, vomiting, anorexia, and abnormal labs.

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Acute pancreatitis and acute hepatitis were diagnosed. Alogliptin was discontinued. She was medically managed. On (b) (6) she had acute respiratory failure and was given oxygen. Although blood work improved and she ate meals, as of (b) (6) the events were unresolved. Rehabilitation was required.

- TCI2011A04401: 61 year old Japanese male with history of cholecystectomy started alogliptin on July 9, 2011. On (b) (6) “hypochondrial” pain developed and the patient was hospitalized. CT showed enlargement of the pancreas and fatty infiltration consistent with pancreatitis, enlarged liver, and kidney stones. History did not support alcohol-related pancreatitis. Alogliptin was discontinued. He was discharged.
- TCI2011A04813: 48 year old Japanese male with history of hepatic steatosis, “gall bladder enlargement”, and renal calculus/calcification on CT was started on alogliptin on November 6, 2010. On July 23, 2011, amylase was 158 U/L (normal 37-125). On (b) (6) he had abdominal pain and went to the hospital where he was admitted and stayed for pancreatitis through (b) (6).
- TCI2011A04936: 58 year old male with T2DM, HTN, hyperuricemia, gall bladder stone, and alcohol use experienced abdominal pain 16 days after starting alogliptin. After two days, he had hyperbilirubinemia, jaundice, and was in a “shocked state” due to severe pancreatitis. He also developed acute renal failure and disseminated intravascular coagulation (DIC). Continuous hemodiafiltration (CHDF) was performed for three days. Antibiotics were given. The patient improved over two weeks. *Comment: While this case is noteworthy for its severity, the presence of hyperbilirubinemia and jaundice on day 2 suggests another cause (e.g. gallstone pancreatitis) independent of or in conjunction with alogliptin.*

Table 41. Serious pancreatitis postmarketing cases (Cutoff date October 27, 2011)

Case number	Treatment	Preferred Term	Outcome	Etiology
TCI2010A04635	Nesina 25 mg	Pancreatitis necrotizing Liver disorder	Fatal	Multiple gallbladder stones as evidenced by dilation of extrahepatic common bile duct on autopsy.
TCI2011A02785	Nesina 25 mg	Pancreatitis acute Decreased appetite Abdominal dissention	Resolving	Dyslipidemia.
TCI2011A03338	Nesina 25 mg	Pancreatitis acute Hepatitis acute Acute respiratory failure Nausea Vomiting Decreased appetite Pyrexia	Ongoing	Undetermined.
TCI2011A04401	Nesina 25 mg	Pancreatitis acute	Resolved	Post-cholecystectomy. Hepatic steatosis.
TCI2011A04813	Nesina 25 mg	Pancreatitis acute	Resolved	Hyperlipidemia, Suspected bile duct calculus based on gall bladder enlargement on CT.
TCI2011A04936	Nesina 25 mg	Pancreatitis acute Renal failure acute Disseminated intravascular coagulation	Resolving	Gallstone.

Source: November 17, 2011 submission (SDN 56) Table 2

Pancreatitis events have been observed in alogliptin subjects in clinical studies and postmarketing in Japan. I therefore recommend that the labeling contain an acute pancreatitis warning consistent with that for other DPP4 inhibitors. I also recommend that the applicant analyze pancreatitis events as an AE of special interest in controlled CV safety study 402 (as is planned) and summarize pancreatitis events in the PSURs until this potential safety risk is better understood.

Infections: DPP4 has many substrates other than GIP and GLP-1, including chemokines involved in immune development and function. DPP-4 is expressed on a subset of CD4+ and CD8+ T-cells and natural killer cells. Thus, there is a theoretical concern that DPP-4 inhibition may increase the risk for infections.

Therefore, the pooled phase 2/3 controlled safety data was searched for events in the infections and infestations SOC. (See Table 42.) AEs occurred at a similar incidence in the three treatment groups (22.4-25.2%), although events, driven by nasopharyngitis and upper respiratory infection, were numerically greater with alogliptin. Events that occurred at >1% incidence in the alogliptin 25 mg group and more commonly than the all comparator group were the following: nasopharyngitis (3.9% vs. 3.3%), upper respiratory tract infection (3.5% vs. 2.4%), bronchitis (1.9% vs. 1.8%), and pharyngitis (1.2% vs. 1.1%).

The incidence of infection SAEs was similar in the alogliptin 25 mg and all comparators groups (1.1% vs. 1.4%, respectively). The incidence of infection AEs that lead to discontinuation was also similar (0.2% vs. 0.3%).

Table 42. AEs from the infections and infestations SOC reported by ≥5 subjects in any group (Controlled phase 2 and 3 studies)

Preferred Term	Number (%) of Subjects		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232
Any Infections and Infestations AE	656 (22.4)	833 (23.8)	1319 (25.2)
Nasopharyngitis	98 (3.3)	137 (3.9)	213 (4.1)
Urinary tract infection	108 (3.7)	130 (3.7)	212 (4.1)
Upper respiratory tract infection	70 (2.4)	122 (3.5)	180 (3.4)
Influenza	71 (2.4)	84 (2.4)	122 (2.3)
Bronchitis	53 (1.8)	65 (1.9)	103 (2.0)
Pharyngitis	31 (1.1)	43 (1.2)	71 (1.4)
Sinusitis	34 (1.2)	39 (1.1)	58 (1.1)
Gastroenteritis	25 (0.9)	35 (1.0)	51 (1.0)
Rhinitis	13 (0.4)	16 (0.5)	29 (0.6)
Cellulitis	15 (0.5)	21 (0.6)	26 (0.5)
Tinea pedis	18 (0.6)	16 (0.5)	25 (0.5)
Fungal skin infection	7 (0.2)	19 (0.5)	24 (0.5)
Respiratory tract infection	7 (0.2)	15 (0.4)	24 (0.5)
Viral infection	8 (0.3)	12 (0.3)	24 (0.5)
Pneumonia	20 (0.7)	17 (0.5)	19 (0.4)
Gastroenteritis viral	8 (0.3)	11 (0.3)	18 (0.3)
Onychomycosis	11 (0.4)	10 (0.3)	17 (0.3)
Ear infection	9 (0.3)	11 (0.3)	16 (0.3)
Tooth abscess	10 (0.3)	12 (0.3)	16 (0.3)
Furuncle	3 (0.1)	7 (0.2)	15 (0.3)
Laryngitis	3 (0.1)	8 (0.2)	14 (0.3)
Respiratory tract infection viral	13 (0.4)	9 (0.3)	14 (0.3)
Tooth infection	8 (0.3)	6 (0.2)	14 (0.3)
Herpes zoster	6 (0.2)	11 (0.3)	13 (0.2)
Paronychia	2 (0.1)	8 (0.2)	13 (0.2)
Pharyngotonsillitis	3 (0.1)	6 (0.2)	13 (0.2)
Tonsillitis	5 (0.2)	10 (0.3)	13 (0.2)
Cystitis	12 (0.4)	4 (0.1)	12 (0.2)
Lower respiratory tract infection	11 (0.4)	6 (0.2)	12 (0.2)
Otitis media	2 (0.1)	10 (0.3)	12 (0.2)
Oral herpes	7 (0.2)	6 (0.2)	11 (0.2)
Viral upper respiratory tract infection	3 (0.1)	7 (0.2)	9 (0.2)
Acute sinusitis	5 (0.2)	1 (<0.1)	8 (0.2)
Folliculitis	11 (0.4)	4 (0.1)	8 (0.2)
Tinea versicolor	3 (0.1)	5 (0.1)	8 (0.2)
Vaginal infection	5 (0.2)	5 (0.1)	8 (0.2)
Body tinea	2 (0.1)	2 (0.1)	7 (0.1)

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Vulvovaginal candidiasis	4 (0.1)	5 (0.1)	7 (0.1)
Fungal infection	8 (0.3)	4 (0.1)	6 (0.1)
Impetigo	1 (<0.1)	5 (0.1)	6 (0.1)
Amebiasis	0	3 (0.1)	5 (0.1)
Appendicitis	1 (<0.1)	4 (0.1)	5 (0.1)
Herpes simplex	1 (<0.1)	4 (0.1)	5 (0.1)
Labyrinthitis	0	4 (0.1)	5 (0.1)
Otitis externa	0	5 (0.1)	5 (0.1)
Tinea cruris	0	3 (0.1)	5 (0.1)
Erysipelas	5 (0.2)	4 (0.1)	4 (0.1)

Source: SCS Table 2.t

Malignancy (including bladder, thyroid, and pancreatic cancer): In the pooled phase 2/3 controlled safety database, the incidence of AEs of malignancy was similar in the alogliptin 25 mg, all alogliptin, and all comparator groups (0.4-0.5%). The incidence of AEs of malignancy which lead to discontinuation was also similar between the treatment groups (0.1-0.2%). Therefore, in the population and for the duration studied, alogliptin does not appear to increase the risk of malignancy.

Table 43. AEs in the Narrow-scope Malignancy SMQ (Controlled phase 2 and 3 studies)

Preferred Term	Number (%) of Subjects		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232
Any malignancy AE	15 (0.5)	13 (0.4)	25 (0.5)
Basal cell carcinoma	2 (0.1)	1 (<0.1)	5 (0.1)
Prostate cancer	0	0	2 (<0.1)
Biliary neoplasm	0	1 (<0.1)	1 (<0.1)
Bladder transitional cell carcinoma	0	1 (<0.1)	1 (<0.1)
Breast cancer	0	1 (<0.1)	1 (<0.1)
Breast cancer stage III	0	1 (<0.1)	1 (<0.1)
Cervix carcinoma	1 (<0.1)	1 (<0.1)	1 (<0.1)
Colon cancer	3 (0.1)	1 (<0.1)	1 (<0.1)
Colon polypectomy	0	0	1 (<0.1)
Endometrial cancer	0	0	1 (<0.1)
Gastric cancer	0	1 (<0.1)	1 (<0.1)
Lentigo maligna stage unspecified	0	1 (<0.1)	1 (<0.1)
Malignant melanoma	0	1 (<0.1)	1 (<0.1)
Myeloma recurrence	0	1 (<0.1)	1 (<0.1)
Non-Hodgkin's lymphoma	0	1 (<0.1)	1 (<0.1)
Non-secretory adenoma of pituitary	0	0	1 (<0.1)
Rectal cancer	0	1 (<0.1)	1 (<0.1)
Skin neoplasm excision	0	0	1 (<0.1)
Squamous cell carcinoma	0	0	1 (<0.1)
Squamous cell carcinoma of skin	2 (0.1)	0	1 (<0.1)
Tendon neoplasm	0	0	1 (<0.1)
Thyroid neoplasm	2 (0.1)	1 (<0.1)	1 (<0.1)
Bladder neoplasm	1 (<0.1)	0	0
Breast neoplasm	1 (<0.1)	0	0
Hepatic neoplasm malignant	1 (<0.1)	0	0
Lung neoplasm	1 (<0.1)	0	0
Rectosigmoid cancer	1 (<0.1)	0	0

Source: SCS Table 2.s

Fractures: The applicant searched the alogliptin/pioglitazone controlled phase 2/3 study pool for fracture-related events, using all PTs that mapped to the high level group term “fractures” or “bone and joint injuries” in MedDRA through a primary or non-primary SOC. The results of this search are shown in Table 44. However, not all of the PT’s refer to a fracture. It does not appear as if the use of alogliptin with pioglitazone increases the risk of fracture more than the use of pioglitazone alone.

Table 44. NDA 22-426: Bone fracture AEs (Alogliptin/pioglitazone controlled phase 3 studies)

Preferred Term (a)	Number of Subjects (%)		
	ALO (N=446)	PIO (N=949)	ALO+PIO (N=1533)
Any Bone Fracture AE	5 (1.1)	17 (1.8)	30 (2.0)
Limb injury	1 (0.2)	6 (0.6)	6 (0.4)
Joint sprain	1 (0.2)	4 (0.4)	5 (0.3)
Joint injury	0	1 (0.1)	5 (0.3)
Foot fracture	1 (0.2)	0	4 (0.3)
Radius fracture	0	0	4 (0.3)
Joint dislocation	0	0	2 (0.1)
Rib fracture	0	0	2 (0.1)
Rotator cuff syndrome	1 (0.2)	2 (0.2)	2 (0.1)
Ankle fracture	0	2 (0.2)	1 (0.1)
Tibia fracture	0	0	1 (0.1)
Wrist fracture	0	0	1 (0.1)
Hand fracture	1 (0.2)	1 (0.1)	0
Lower limb fracture	0	1 (0.1)	0
Traumatic fracture	0	1 (0.1)	0

Source: Alogliptin/pioglitazone SCS Table 2.t

Hypoglycemia: In all studies except 301 and 402, hypoglycemic events were collected on designated case report forms (CRFs), instead of the AE CRF, and were not summarized as AEs unless they were SAEs. As the definitions of hypoglycemia (shown in Table 45) differed between study 303 and the other studies, study 303 was analyzed separately.

In the controlled phase 2 and 3 study group excluding studies 301, 303, and 402, the rate of hypoglycemia was similar in the alogliptin 25 mg and all comparators groups (4.4% vs. 4.0%). The majority of events were mild to moderate intensity, although there was a difference in the frequency of symptomatic events associated with a blood glucose <60 mg/dL (alogliptin 25 mg 2.9% vs. all comparators 1.8%).

Table 45. Hypoglycemia events (Controlled phase 2 and 3 studies, excluding 301, 303, and 402)

Event Category	Number (%) of Subjects		
	All Comparators (a) N=1612	Alogliptin 25 mg N=2161	All Alogliptin (b) N=3893
Any Hypoglycemic Event	64 (4.0)	95 (4.4)	210 (5.4)
Symptomatic event and blood glucose <60 mg/dL (Mild to Moderate)	29 (1.8)	62 (2.9)	117 (3.0)
Symptomatic or asymptomatic event and blood glucose <50 mg/dL (Mild to Moderate)	22 (1.4)	41 (1.9)	77 (2.0)
Any event that requires assistance, associated with a documented blood glucose <60 mg/dL (Severe)	5 (0.3)	4 (0.2)	6 (0.2)

Source: SCS Table 3.s

Note: Protocols stated that blood glucose did not need to be documented if the clinical situation (e.g. coma or seizure) prohibited its measurement.

In elderly study 303, significantly more glipizide subjects experienced hypoglycemia when compared to alogliptin subjects. This is expected given the risk of hypoglycemia with sulfonylureas.

Table 46. Study 303: Hypoglycemia events

Hypoglycemia Episodes	Alogliptin N=222		Glipizide N=219	
	Episodes	n (%)	Episodes	n (%)
Total number (a)	31	12 (5.4)	232	57 (26.0)
Mild to moderate (b)				
Symptomatic and blood glucose <70 mg/dL	10	2 (0.9)	120	35 (16.0)
Symptomatic or asymptomatic and blood glucose <70 mg/dL	25	9 (4.1)	187	52 (23.7)
Severe				
Any episode that required assistance, associated with a documented blood glucose <70 mg/dL	0	0	3	3 (1.4)

Source: SCS Table 3.t

In add-on to pioglitazone and metformin trial OPI-004, the total percentages of subjects reporting hypoglycemia was 4.5% and 1.5% in the MET+A25+P30 and MET+P45 groups, respectively. Two MET+A25+P30 subject had severe hypoglycemia.

Table 47. Study OPI-004: Hypoglycemia events

Hypoglycemic events	MET+A25+P30 N=404		MET+P45 N=399		Total N=803	
	Events	n (%)	Events	n (%)	Events	n (%)
Total	57	18 (4.5)	7	6 (1.5)	64	24 (3.0)
Mild to Moderate (a)						
Symptomatic and blood glucose <60 mg/dL	20	8 (2.0)	3	2 (0.5)	23	10 (1.2)
Symptomatic or asymptomatic and blood glucose <50 mg/dL	11	7 (1.7)	2	2 (0.5)	13	9 (1.1)
Severe						
Any episode that required assistance associated with a documented blood glucose <60 mg/dL	2	2 (0.5)	0	0	2	2 (0.2)
Additional categories:						
Symptomatic and no blood glucose collected	5	4 (1.0)	3	3 (0.8)	8	7 (0.9)
Asymptomatic and blood glucose ≥50 mg/dL and ≤60 mg/dL	1	1 (0.2)	0	0	1	1 (0.1)
Symptomatic and blood glucose ≥60 mg/dL	24	4 (1.0)	1	1 (0.3)	25	5 (0.6)

Source: CSR OPI-004 Table 12.s

In lipid study 301, subjects were taught to recognize the signs and symptoms of hypoglycemia although it was not defined or graded as mild to severe. Three

alogliptin/pioglitazone subjects experienced hypoglycemia. This was numerically higher than in the placebo and alogliptin groups. However, the small sample size limits the conclusions that can be drawn.

Table 48. Study 301: AEs of hypoglycemia

Preferred term	Placebo (n=24)	Alogliptin 25 mg (n=25)	Alo 25 mg + Pio 30 mg (n=22)
Hypoglycemia	0	0	3 (13.6)

Source: CSR 301 Table 12.c

See also my original NDA 22-271 and 22-426 reviews.

7.3.5 Submission Specific Primary Safety Concerns

My original review of alogliptin revealed a numerical imbalance in serious CV AEs, not favoring alogliptin therapy. Event rates were low, which limited conclusions. As discussed in the 2008 guidance *Diabetes Mellitus: Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes*, the upper bound of the 95% CI for the risk ratios comparing the incidence of MACE with investigational agent to the incidence of MACE with placebo must be <1.8 to support approvability. To address this deficiency, the applicant worked with the agency to design CV study 402.

As discussed in section 2.5 Summary of Presubmission Regulatory Activity Related to Submission, the following agreements were made regarding CV study 402:

- The results of CV study 402 should stand alone for assessing CV safety, although a pooled analysis of controlled data from phase 2/3 trials will be considered supportive.
- The applicant may keep the inclusion criterion that subjects have an ACS event 15-60 days prior to randomization. However, if there are many early events after randomization, the adequacy of the findings would be a review issue.
- Approximately 300 subjects in completed study 402 will be on background pioglitazone.
- If ≥25% of subjects in study 402 experience a change in renal severity status, the applicant should conduct a secondary analysis by renal severity status at study endpoint.
- The applicant anticipates sufficient alogliptin-exposure (i.e. ≥1 year) in the moderate RI population (i.e. 200 subjects) in the CV trial, but not for the severe RI population. Because there are no concerning clinically relevant renal safety signals based on nonclinical pharmacology/toxicology data, the agency agreed that conduct of an additional postmarketing study in the severe RI population is acceptable if sufficient exposure (i.e. 100 subjects) is not obtained in the CV trial.
- Final decision about inclusion in the label of selected information from the interim results of CV study 402 will be made after the submissions have been reviewed.

Note: As the deaths, SAEs, AEs leading to discontinuation, and AEs of special interest for study 402 were discussed in the sections above, I will only address the CV-safety issues of study 402 here.

In CV study 402, the primary MACE consisted of CV death, nonfatal MI, and nonfatal stroke. The secondary MACE also included urgent revascularization due to unstable angina.

A summary of the adjudication outcome is shown in Table 49. (b) (4)

(b) (4). Although there was variation between the treatment groups in the incidence of hospitalization for heart failure, this event was not included in the primary MACE analysis. Overall, the adjudication appears fair and equal between the treatment groups.

Table 49. Study 402: Summary of CV events and adjudication outcomes (FAS)

(b) (4)



Source: Study 402 Table 15.3.3.4.1

According to the sponsor's analysis, as shown in Table 50, the upper bounds of the 95% CI for the risk ratios for both primary and secondary MACE analyses were <1.8. This was also true when the primary MACE was analyzed by the index ACS event (≤ 2 months or > 2 months) (see Table 51).

In Eugenio Andraca-Carrera's January 6, 2012 safety statistics review, he concurred that the upper bound of the 95% CI for the risk ratios comparing the incidence of MACE with alogliptin to the incidence of MACE with placebo is <1.8 and supports approvability. Subgroup analyses and sensitivity analyses were consistent with the primary results, except for subgroups defined by gender, baseline RI, and country of randomization.



However, these analyses were exploratory in nature and need replication to be confirmed or disproved. Therefore, future analyses of study 402 should include subgroup analysis by gender, baseline RI, and country of randomization. (The protocol already states that analyses will be stratified by country and RI, and subgroup analyses will be conducted by RI.)

He also analyzed MACE events excluding those which occurred in the first 15 or 30 days of the trial, thus offsetting the earlier than recommended ACS inclusion criteria. As expected, this resulted in wider CI's, although the upper bound was still <1.8.

Table 50. Study 402: Cox proportional hazards model for adjudicated MACE composites (FAS)

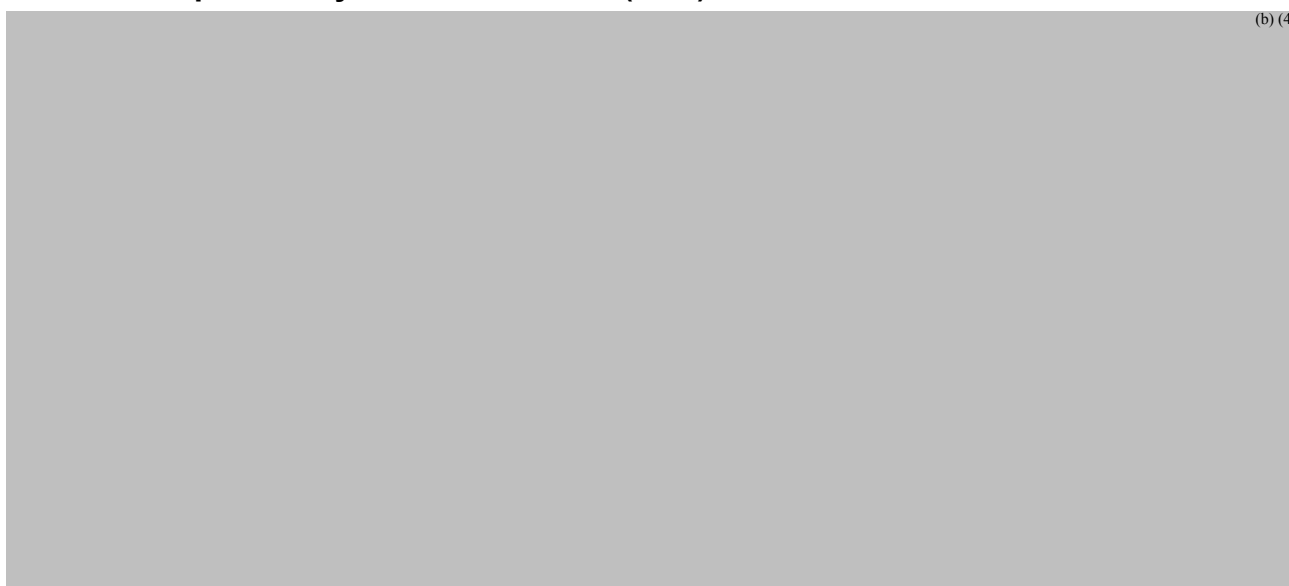
(b) (4)

A large rectangular area of the document is completely redacted with a solid gray fill, obscuring the data for Table 50.

Source: Study 402 Tables 15.3.3.1.1 and 15.3.3.2

Table 51. Study 402: Cox proportional hazards model for adjudicated primary MACE composites by index ACS event (FAS)

(b) (4)

A large rectangular area of the document is completely redacted with a solid gray fill, obscuring the data for Table 51.

Source: August 25, 2011 information response Tables 2.1 and 2.2

Regarding the recommendation that, in the completed study, ~300 alogliptin subjects be on background pioglitazone, ~200 alogliptin subjects have moderate RI, and ~100 alogliptin subjects have severe RI, the baseline totals at the time of submission for these subgroups in the ongoing study are shown in Table 52.

Table 52. Study 402: Pioglitazone use and renal function at baseline (FAS)

	Alogliptin (n=1058)	Placebo (n=1-76)	Total (n=2134)
Pioglitazone	27 (2.6)	38 (3.5)	65 (3.0)
Renal function (MDRD)			
Normal	113 (10.7)	128 (11.9)	241 (11.3)
Mild RI	614 (58.0)	566 (52.6)	1180 (55.3)
Moderate RI	280 (26.5)	306 (28.4)	586 (27.5)
Severe RI/ESRD	27 (2.6)	31 (2.9)	58 (2.7)
Renal function (CG)			
Normal	411 (38.8)	393 (36.5)	804 (37.7)
Mild RI	386 (36.5)	397 (36.9)	783 (36.7)
Moderate RI	213 (20.1)	217 (20.2)	430 (20.1)
Severe RI/ESRD	24 (2.3)	24 (2.2)	28 (2.2)

Source: Study 402 Table 15.1.6.1 and 15.1.3

Regarding the requirement that if $\geq 25\%$ of subjects experience a change in renal severity status the applicant should conduct a secondary analysis by renal severity status at study endpoint, one can see from Table 53 that this was not the case. Using the CG formula, 40 alogliptin-treated subjects worsened from normal renal function, 27 worsened from mild RI, and 6 worsened from moderate RI. Thus, 73 of 1058 (7%) of alogliptin-treated subjects' renal status worsened. Using the MDRD formula, 11% of alogliptin-treated subjects had worsened renal status. Therefore, a secondary analysis by renal severity status was not necessary.

Table 53. Study 402: Shifts from baseline renal function to last visit as measured by MDRD and CG (FAS)

	Alogliptin (n=1058)				Placebo (n=1076)			
MDRD	Baseline				Baseline			
Last Visit	Normal	Mild	Moderate	Severe/ESRD	Normal	Mild	Moderate	Severe/ESRD
Normal	63	32	0	0	73	45	2	0
Mild	40	457	27	0	43	435	65	0
Moderate	0	73	220	7	1	43	203	7
Severe/ESRD	0	0	8	17	0	0	9	18
CG								
Last Visit								
Normal	304	40	0	0	283	42	1	0
Mild	39	252	22	0	40	257	34	0
Moderate	1	27	138	4	0	27	125	4

Severe/ESRD	0	0	6	14	0	0	3	13
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Source: Study 402 Tables 15.3.4.8.3 and 15.3.4.9.3

Regarding the alogliptin and alogliptin/pioglitazone FDC labels, the applicant proposed the following in section 6.1 Clinical Studies Experience: (b) (4)

As discussed with the applicant on June 20, 2011, the agency does not support including CV outcomes data that meet the 1.8 cutpoint in approved labeling. Approval of a new treatment for T2DM implies that the 1.8 cutpoint has been met because the guidance states it must be prior to approval. For this reason, I do not support inclusion of the above italicized text in the label.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events which occurred in $\geq 3\%$ of subjects in any treatment group were analyzed in the original NDA and CR. There was a slightly lower incidence of AEs in alogliptin 25 mg subjects in the CR when compared to the original NDA (58.6% vs. 64.4%). However, the most common AEs were similar between the NDAs and were as follows (percentages are for CR vs. Original NDA):

- Nasopharyngitis (3.9% vs. 5.4%)
- Headache (3.9% vs. 4.4%)
- Urinary tract infection (3.7% vs. 4.1%)
- Upper respiratory tract infection (3.5% vs. 3.5%)

Note: In the original NDA, edema peripheral and hypertension also occurred in 3.5% of alogliptin 25 mg subjects.

In the pooled controlled phase 2/3 database, when common AEs were compared between alogliptin and all comparator subjects in the CR, incidence rates were similar. (See Table 54.) Alogliptin does not appear to increase the incidence of common AEs in this pooled database, which, I believe, is representative of the various add-on scenarios.

For example, pioglitazone has been associated with peripheral edema. The risk of peripheral edema is similar between the all comparators (2.2%) and all alogliptin (2.5%) groups in the pooled database. In add-on to pioglitazone study TZD-009, no difference was seen in the incidence of peripheral edema across treatment groups (7.2%, 6.1%, and 5.5% in the placebo, alogliptin 12.5 mg, and alogliptin 25 mg, respectively).

Table 54. Common AEs (≥3% in any group)

SOC Preferred Term	Number (%) of Subjects					
	Original NDA			NDA Resubmission		
	Placebo N=534	Alogliptin 25 mg N=910	All Alogliptin (a) N=1961	All Comparators (b) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (a) N=5232
Any AE	347 (65.0)	586 (64.4)	1260 (64.3)	1651 (56.3)	2052 (58.6)	3146 (60.1)
Gastrointestinal disorders	78 (14.6)	135 (14.8)	280 (14.3)	336 (11.5)	436 (12.5)	664 (12.7)
Diarrhea	18 (3.4)	30 (3.3)	58 (3.0)	105 (3.6)	94 (2.7)	138 (2.6)
General disorders and administration site conditions	39 (7.3)	85 (9.3)	163 (8.3)	201 (6.9)	255 (7.3)	381 (7.3)
Edema peripheral	14 (2.6)	32 (3.5)	59 (3.0)	64 (2.2)	88 (2.5)	129 (2.5)
Infections and infestations	167 (31.3)	254 (27.9)	565 (28.8)	656 (22.4)	833 (23.8)	1319 (25.2)
Nasopharyngitis	27 (5.1)	49 (5.4)	97 (4.9)	98 (3.3)	137 (3.9)	213 (4.1)
Upper respiratory tract infection	28 (5.2)	32 (3.5)	71 (3.6)	70 (2.4)	122 (3.5)	180 (3.4)
Urinary tract infection	25 (4.7)	37 (4.1)	93 (4.7)	108 (3.7)	130 (3.7)	212 (4.1)
Musculoskeletal and connective tissue disorders	70 (13.1)	120 (13.2)	267 (13.6)	304 (10.4)	410 (11.7)	640 (12.2)
Back pain	13 (2.4)	27 (3.0)	54 (2.8)	65 (2.2)	92 (2.6)	143 (2.7)
Nervous system disorders	52 (9.7)	114 (12.5)	254 (13.0)	277 (9.4)	368 (10.5)	587 (11.2)
Headache	21 (3.9)	40 (4.4)	86 (4.4)	103 (3.5)	136 (3.9)	214 (4.1)
Vascular disorders	22 (4.1)	40 (4.4)	78 (4.0)	130 (4.4)	165 (4.7)	235 (4.5)
Hypertension	16 (3.0)	32 (3.5)	61 (3.1)	85 (2.9)	101 (2.9)	159 (3.0)

Source: SCS Table 2.b

7.4.2 Laboratory Findings

Overview of Laboratory Testing in Development Program:

In controlled, phase 2 and 3 studies, laboratory samples for hematology and chemistry test were collected at every visit under fasted conditions. Urinalysis tests were collected at protocol-specified visits. The normal ranges and markedly abnormal criteria for laboratory tests are show in Table 55; they are acceptable. The sponsor did not analyze lipid levels in the studies, although interim results from CV safety study 402 were submitted.

Table 55. Normal ranges and markedly abnormal criteria for laboratory tests*

Laboratory test	Normal range	Markedly abnormal low criterion	Markedly abnormal high criterion
Albumin (g/dl)	3.5 – 5.5	<2/5 g/dl	
Alkaline phosphatase (mu/ml)	Study 303: 43.0 – 115.0 Other studies: 32.0 – 72.0		>3 xULN
BUN (mg/dl)	5.0 – 20.0		>3 xULN
Basophils (%)	0.0 – 3.0		
Bicarbonate (meq/l)	21.0 – 33.0		
Calcium (mg/dl)	8.5 – 10.5	<0.8 xLLN	>1.2 xULN
Chloride (meq/l)	95.0 – 110.0		
Creatinine (mg/dl)	0.7 – 1.4		>1.5 x baseline; >1.5 x baseline & >ULN
Eosinophils (%)	0.0 – 7.0		
Gamma GT (mu/ml)	Study 303: 10.0 – 49.0 Other studies: 5.0 – 29.0		>3 xULN
Hematocrit/PCV (%)	M: 37.0 – 51.0 F: 33.0 – 47.0	<0.8 x baseline	
Hemoglobin (g/dl)	M: 12.5-17.0 F: 11.0-15.5	<Baseline – 3 g/dl	
Lactic dehydrogenase (mu/ml)	10.0 – 100.0		>3 xULN
Lymphocytes (%)	12-46		
Microalbumin/Cr ratio	0.0 – 20.0		
MCH (pg)	27.0-34.0		
MCV (fl)	M: 78.0 – 100.0 F: 82.0 – 102.0		
Monocytes (%)	0.0 – 11.0		
Neutrophils (%)	Study 003: 42.0 – 80.0 Other studies: 46.0 – 72.0		
Phosphorus (mg/dl)	2.5 – 4.5		
Platelet count (k/cu mm)	125.0 – 375.0	<50 x10 ³ /mm ³	>600 x10 ³ /mm ³
Potassium (meq/l)	3.5 – 5.0	<3 meq/l	>5.8 meq/l
Red blood cells (10 ⁶ /cu mm)	M: 4.0 – 5.6 F: 3.7 – 5.2	<0.8 x baseline	
SGOT (AST) (mu/ml)	8.0 – 22.0		> 3, 5, 8, or 10x ULN; >3 xULN & T bili >2 mg/dl
SGPT (ALT) (mu/ml)	5.0 – 25.0		> 3, 5, 8, or 10x ULN; >3 xULN & T bili >2 mg/dl
Sodium (meq/l)	133.0 – 145.0	<130	>150
Total bilirubin (mg/dl)	0.1 – 1.1		>2 mg/dl
Total protein (g/dl)	6.0 – 8.0	<0.8 xLLN	>1.2 xULN
Uric acid (mg/dl)	M: 4.0 – 8.0 F: 2.0 – 6.0		>10.5 >8.5
Urinary microalb/Cr (mcg/mg)	Study 402: <14.0		

	Other studies: 0.0 – 20.0		
Urinary pH	5.0 – 8.0		
Urinary specific gravity	1.002 – 1.035		
White blood cells (k/cu mm)	3.7 – 11.0	<2 x10 ³ /mm ³	>20 x 10 ³ /mm ³

*Includes studies 003, 007, 008, 009, 010, 011, 303, 402, OPI-001, OPI-002, and OPI-004

Source: IAS Table 8.5.0Ra

Selection of Studies and Analyses for Drug-Controlled Comparisons of Laboratory Values:

My review of the laboratory findings focused on 10 of the 12 US, controlled, phase 2/3 studies that were pooled in the CR (studies 003, 007, 008, 009, 010, 011, 303, OPI-001, OPI-002, and OPI-004). Sixteen-week, postprandial lipid study 301 was not included in the laboratory analysis; this is acceptable due to its different duration and primary endpoint. The interim results of CV study 402 were included only when relevant, as this study is still ongoing.

I analyzed measures of central tendency, outliers or shifts from normal to abnormal, and marked outliers and dropouts for laboratory abnormalities (excluding hypo- and hyperglycemia) for the liver, renal, other chemistry, and hematology data. I also discuss the November 2011 – January 2012 liver-safety submissions as well as the blood urea nitrogen (BUN), serum creatinine, and urinary albumin/creatinine ratios in alogliptin/pioglitazone FDC NDA 22-426, as these were described in the CR letter.

Analyses Focused on Measures of Central Tendency:

In controlled phase 2 and 3 study group, the mean changes from baseline to endpoint in chemistry and hematology values were minor, generally similar between treatment groups, and not clinically meaningful (see Table 56). However, small differences in treatment effect were noted for the following laboratory parameters:

- Alkaline phosphatase (Comparators -1.1 versus alogliptin 25 mg -2.8)
- Lymphocytes (Comparators 0.1 versus alogliptin 25 mg -1.6)
- Platelet count (Comparators -4.6 versus alogliptin 25 mg -6.2)
- Total neutrophils (Comparators -0.2 versus 1.7)
- Uric acid (Comparators -0.03 versus 0.12)

Table 56. Mean change from baseline to endpoint for laboratory parameters (Controlled phase 2 and 3 study group)

	All comparators (n=2910)	Alogliptin 25 mg (n=3453)	All alogliptin (n=5185)
Chemistry			
Albumin (g/dl)	-0.04 (0.28)	-0.04 (0.27)	-0.04 (0.26)
ALT (mU/ml)	-1.0 (11.5)	-1.0 (32.38)	-1.2 (26.80)
AST(mU/ml)	-0.2 (7.24)	-0.2 (24.50)	-0.2 (20.25)
Alkaline phosphatase (mU/ml)	-1.1 (14.13)	-2.8 (14.45)	-3.0 (13.36)

Bicarbonate (meq/l)	0.2 (2.98)	0.2 (2.86)	0.1 (2.89)
BUN (mg/dl)	0.4 (5.30)	0.5 (4.77)	0.6 (4.56)
Calcium (mg/dl)	0.01 (0.40)	0.02 (0.40)	0.03 (0.39)
Chloride (meq/l)	0.3 (3.22)	0.8 (3.02)	0.9 (3.02)
Creatinine (mg/dl)	0.01 (0.16)	0.02 (0.17)	0.02 (0.15)
GGT (mu/ml)	-2.0 (20.63)	-1.4 (15.19)	-1.6 (15.96)
LDH (mu/ml)	3.6 (15.51)	2.6 (15.48)	3.0 (15.38)
Magnesium (meq/l)	0.03 (0.15)	0.05 (0.15)	0.05 (0.15)
Phosphorus (mg/dl)	0.03 (0.52)	0.02 (0.56)	0.03 (0.54)
Potassium (meq/l)	0.00 (0.47)	-0.01 (0.45)	-0.01 (0.46)
Sodium (meq/l)	0.0 (2.80)	0.3 (2.72)	0.4 (2.73)
Total bilirubin (mg/dl)	-0.01 (0.18)	-0.02 (0.18)	-0.02 (0.18)
Total Protein (g/dl)	-0.04 (0.40)	-0.03 (0.39)	-0.03 (0.39)
Uric acid (mg/dl)	-0.03 (0.91)	0.12 (0.93)	0.10 (0.94)
Hematology			
Basophils (%)	-0.1 (0.57)	-0.1 (0.60)	-0.1 (0.64)
Eosinophils (%)	-0.1 (2.72)	-0.3 (2.66)	-0.3 (2.65)
Hematocrit (%)	-0.47 (2.91)	-0.50 (2.82)	-0.55 (2.78)
Hemoglobin (g/dl)	-0.12 (0.92)	-0.13 (0.88)	-0.14 (0.86)
Lymphocytes (%)	0.1 (8.99)	-1.6 (9.34)	-1.5 (9.14)
Mean corpuscular volume (fl)	-0.23 (2.96)	-0.43 (3.10)	-0.32 (3.11)
Monocytes	0.2 (4.15)	0.3 (3.85)	0.32 (3.11)
Platelet count (10 ³ /mm ³)	-4.6 (43.90)	-6.2 (41.70)	-5.3 (40.00)
Red blood cell count (x10 ⁶ /mm ³)	-0.04 (0.31)	-0.03 (0.30)	-0.04 (0.30)
Total neutrophils (%)	-0.2 (11.48)	1.7 (11.75)	1.6 (11.63)
WBCs (10 ³ /mm ³)	-0.04 (1.52)	0.12 (1.55)	0.09 (1.56)
Urinalysis*			
Mean (SD) albumin:Cr ratio	21.9 (359.62)	20.2 (617.58)	18.8 (556.61)
Mean (SD) pH	0.06 (0.58)	0.11 (0.59)	0.10 (0.59)
Mean (SD) specific gravity	-0.0003 (0.008)	-0.0009 (0.007)	-0.0009 (0.007)

*Urinalysis samples sizes were smaller than stated at the top of the columns.

Source: SCS Tables 3.a, 3.e, 3.k, 3.o, and 3.u

As also described in the September 9, 2009 CR letter for alogliptin/pioglitazone FDC NDA 22-426, a greater mean increase in BUN and mean urinary albumin:creatinine ratio (but not creatinine, which is a better measure of renal function than BUN) was seen in the NDA 22-426 safety pool. See Table 57. However, the median changes in the albumin:creatinine ratio were more comparable between treatment groups.

Table 57. NDA 22-426: Summary of change from baseline for key renal results

	Alogliptin (n=407)	Pioglitazone (n=930)	Alo+Pio (n=1490)
BUN (mg/dl)	0.7 (3.46)	0.7 (3.99)	1.1 (4.16)
Creatinine (mg/dl)	0.02 (0.11)	0.02 (0.10)	0.03 (0.13)
Mean (SD) urinary albumin:creatinine ratio/N	-2.6 (132)/171	-0.2 (156)/392	13.5 (467)/609
Median (min, max) albumin:creatinine ratio/N	-4.0 (-702, 933)/171	-5.0 (-902, 1506)/392	-6.0 (-1051, 9608)/609

Source: NDA 22-426 SCS Tables 3.c and 3.j

Liver Data:

Outliers or Shifts from Normal to Abnormal: On November 7, 2011, the applicant responded to the first of several liver-safety information requests that were triggered by receipt of liver disorder safety report TC12011A04573 (described below) under alogliptin IND 69-707. In the November information request response, the applicant provided an updated analysis (based on an October 26, 2011 search) showing the number and percentage of individuals with serum ALT greater than normal based on all completed, controlled, phase 2 and 3 clinical studies. This analysis included data from study 402 (as of September 11, 2011) and non-IND studies. Specifically, studies 003, 007, 008, 009, 010, 011, 301, 303, CCT-001, CCCT-003, CCT-004, CCT-005, CCT-006, OPI-001, OPI-002, OPI-004, and MET-302 were included.

As shown in Table 58 and Table 59, there is an imbalance in the number and percentage of subjects with markedly abnormal ALT values, including ALT >10x and 20x ULN. As described in the July 2009 guidance, *Drug-Induced Liver Injury: Premarketing Clinical Evaluation*, ALT is generally considered more liver-specific than AST. The finding of a higher rate of ALT elevation in drug-treated subjects than in a control group is a sensitive signal of the potential for drug induced liver injury (DILI). Greater aminotransferase increases (e.g., 10x-, 15xULN), such as those shown in Table 58 are a specific signal for DILI.

Table 58. Number and percentage of subjects with markedly abnormal ALT values (All completed, controlled phase 2 and 3, studies)

Parameter (Criterion)	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline			During Treatment		
	All Comparators (a) N=4215	Alogliptin 25 mg N=4829	All Alogliptin (b) N=7187	All Comparators (a) N=4074	Alogliptin 25 mg N=4680	All Alogliptin (b) N=7011
ALT (>20xULN)	0	0	0	0	1 (<0.1%) [0.0]	2 (<0.1%) [0.1]
ALT (>10xULN)	2 (<0.1%)	3 (0.1%)	3 (<0.1%)	0	6 (0.1%) [0.2]	8 (0.1%) [0.2]
ALT (>8xULN)	2 (<0.1%)	3 (0.1%)	3 (<0.1%)	1 (<0.1%) [0.0]	9 (0.2%) [0.4]	11 (0.2%) [0.3]
ALT (>5xULN)	2 (<0.1%)	4 (0.1%)	6 (0.1%)	6 (0.1%) [0.3]	17 (0.4%) [0.7]	21 (0.3%) [0.6]
ALT (>3xULN)	10 (0.2%)	23 (0.5%)	30 (0.4%)	39 (1.0%) [1.8]	52 (1.1%) [2.1]	71 (1.0%) [2.1]

Source: November 7, 2011 liver-safety submission Table 8

Table 59. Subjects with ALT >5xULN during treatment* (All completed, controlled, phase 2/3 studies)

Maximum ALT Value	All Comparators	All Alogliptin
>20x ULN	Total = 0	Total = 2
		OPI-002/831-2508 (1771)

		009/311-9003 (646)
>10x ULN and ≤20x ULN	Total = 0	Total = 6
		009/307-9019 (357)
		402/8521-002 (312)
		303/3128-003 (300)
		402/8260-010 (293)
		402/8070-002 (267)
		OPI-001/395-3054 (257)
>8x ULN and ≤10x ULN	Total = 1	Total = 3
	OPI-001/413-3020 (229)	009/452-9003 (247)
		402/8635-004 (237)
		007/413-7007 (213)
>5x ULN and ≤8x ULN	Total = 5	Total = 10
	CCT-001/0052-103 (320)	008/464-8006 (199)
	MET-302/5057-011 (186)	402/8568-008 (195)
	303/3603-010 (162)	007/449-7007 (192)
	402/8290-002 (153)	OPI-001/387-3007 (184)
	007/381-7019 (129)	303/3212-010 (160)
		402/8107-004 (150)
		402/8284-008 (142)
		402/8411-006 (142)
		402/8262-002 (141)
		009/452-9009 (138)

*The maximum observed ALT value is listed in parentheses.

Source: February 22, 2012 submission Table 1

Marked outliers and dropouts for laboratory abnormalities: On December 7, 2011, the applicant submitted a response to our aforementioned liver-safety information request. The submission described 23 serious liver-related cases and 8 biochemical Hy's Law (i.e., ALT >3x ULN and total bilirubin >2x ULN) cases (see Table 60). Note that three of the four clinical trial cases of biochemical Hy's law in Table 60 are not listed in Table 59. This is because cases 012/961-3006, 012/961-2501, and 305/5304-005 occurred in uncontrolled or ongoing studies. The Hy's law cases are concerning as Hy's Law is thought to predict a rate of fatal or transplant-requiring DILI at an incidence of 1/1000 the incidence of the noted Hy's Law case(s).

Table 60. Serious liver-related and biochemical Hy's Law cases described in December 7, 2011 submission*

Event/Database	Placebo	Glipizide	Pioglitazone	Alo 6.25	Alo 12.5	Alo 25	All Alo
Serious liver-related cases							
Clinical trials	1	2	2	0	7	5	12

Clinical Review
 Valerie S.W. Pratt, M.D.
 NDAs 22-271 and 22-426
 Nesina (alogliptin) and (b) (4) (alogliptin/pioglitazone FDC)

Postmarketing	N/A	N/A	N/A	2	2	7	11
Biochemical Hy's Law							
Clinical trials	1	1	2	0	1	3	4
Postmarketing	N/A	N/A	N/A	0	2	2	4

*Additional Hy's law cases were submitted to the IND and NDA after December 7, 2011 (See below)

Source: December 7, 2011 information response Tables 2, 3, 5, and 6

After receipt of this liver safety information, a consult was placed to OSE on November 10, 2011 for an assessment of the potential for severe DILI with alogliptin. My team leader, Dr. Hylton Joffe, and I also reviewed the cases, which had been reviewed, at the applicant's request, by external hepatic experts Dr. (b) (4) (blinded) and Dr. (b) (4) (unblinded). Dr. Joffe's and my review focused on the 27 cases in which Drs (b) (4) assessments of liver injury differed or described a relationship to alogliptin other than "not likely", "unlikely", or "unrelated" (see Table 61). Dr. Joffe's and my review identified 11 cases (highlighted below) and two additional recent IND submissions, for which we were particularly concerned (Table 62). A revised OSE consult which highlighted these concerning cases was placed on January 3, 2012. On January 13, 2012, the agency asked that, while alogliptin is under NDA review, the applicant submit to alogliptin NDAs 22-271, 22-426, and 203-414 all future liver events that would ordinarily come in only to the INDs.

The review by Dr. Leonard Seeff (hepatologist in OSE) was finalized on February 22, 2012 and is summarized in Table 62. It concluded, "Given the imbalance in the frequency of ALT abnormalities noted in the pre-marketing trials between those who received alogliptin and those in the control group, it seems prudent to consider whether these data taken together suggest that further study is needed regarding possible hepatotoxicity of alogliptin before general marketing of the drug is permitted in the US".

On February 22, OSE was also consulted to place the alogliptin findings in context by querying the AERS database for cases of concerning hepatotoxicity associated with sitagliptin and saxagliptin. This consult is pending. Additional assessments may also be forthcoming from Dr. Seeff, who is reviewing cases of ALT >10x ULN in completed, controlled, phase 2/3 studies as well as clinical trial cases (including uncontrolled or ongoing trials) of biochemical Hy's law. Additional OSE input will be summarized by me in a subsequent addendum or Dr. Hylton Joffe in his cross-discipline team leader (CDTL) memo.

Table 61. Cases from the December 7, 2011 submission in which Drs. (b) (4) assessments of liver injury differed or described a relationship to alogliptin other than "not likely", "unlikely", or "unrelated" (n=27)*

Subject #/Case #	Treatment	Preferred Term	Dr. (b) (4) Unblinded Assessment	Dr. (b) (4) Blinded Assessment
Serious Clinical Case (n=1)				
5304-024/305 ERD2010A00037	Alo 12.5	ALT increased	Possible/probable	Possible
Serious Postmarketing Cases (n=4)				
TCI2011A03640	Nesina 6.25	Liver disorder	Possible	Possible
TCI2011A04802	Nesina 25	Hepatic function abnormal Rash papular	Insufficient data	Insufficient data
TCI2011A01442	Nesina 6.25	Gastric antral vascular ectasia INR increase Tachycardia	Not reviewed Not a liver case	Not a liver case
TCI2011A04950	Nesina 25	Intestinal obstruction GI perforation	Not reviewed Not a liver case	Not a liver case
Nonserious Postmarketing Cases (n=13)				
TCI2010A03700	Nesina 25	Hepatic function abnormal	Possible	Unlikely
TCI2010A04583	Nesina 25	Liver function test abnormal	Insufficient	Insufficient
TCI2010A05612	Nesina 25	Hepatic function abnormal	Possible	Possible
TCI2011A00254	Nesina 12.5	Liver disorder	Unlikely	Possible
TCI2011A01464	Nesina 12.5	Liver disorder	Possible	Probable
TCI2011A01670	Nesina 25	Hepatobiliary disease Blood amylase increased	Possible	Possible
TCI2011A02538	Nesina	Liver disorder	Possible	Possible
TCI2011A04039	Nesina 25	Hepatic function abnormal Vomiting Decreased appetite	Possible	Possible
TCI2011A04850	Nesina 25	AST increased ALT increased	Insufficient	Insufficient
TCI2011A04874	Nesina 25	Hepatic function abnormal	Possible/Insufficient	Possible
TCI2011A05502	Nesina 25	Hepatic function abnormal	Insufficient	Insufficient
TCI2011A05505	Nesina 25	Hepatic function abnormal	Insufficient	Insufficient
TCI2011A00506	Nesina	Hepatic function abnormal	Insufficient	Insufficient

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Nesina (alogliptin) and (b) (4) (alogliptin/pioglitazone FDC)

Biochemical Hy's Law Postmarketing Case (n=1)				
TCI2011A04573	Nesina 25	Liver disorder	Unlikely	Possible
Clinical Cases of ALT >5xULN (n=8)				
8411-006/402	Alo 25	ALT >5xULN	Possible	Unlikely
8635-004/402	Alo 25	ALT >8xULN	Unlikely	Possible
387-3007/OPI-001	Alo 12.5	ALT >5xULN	Possible	Unlikely
395-3054/OPI-001	Alo 12.5	ALT >10xULN	Possible	Unlikely
449-7007/007	Alo 25	ALT >5xULN	Possible	Unlikely
311-9003/009	Alo 12.5	ALT >20xULN	Unlikely	Possible
452-9009/009	Alo 12.5	ALT >5xULN	Possible	Unlikely
3212-010/303	Alo 24	ALT >5xULN	Possible	Unlikely

*Highlighted cases (n=11) were particularly concerning for potential alogliptin-related DILI, based on Dr. Joffe's and my review

Table 62. Thirteen liver safety reports reviewed by OSE's Dr. Leonard Seeff*

Liver Safety Report	Summary of Case	Dr. Leonard Seeff's Assessment
Cases from the December 7, 2011 liver safety submission		
ERD2010A00037	41 year Indian male with normal baseline ALT/AST. After 4 months, ALT 130 IU/L, AST 61 IU/L, AP 83 IU/L, & bilirubin 1.17 mg/dl. Two weeks later, ALT 208 UI/L but other tests normal. US, HBsAG, and anti-HCV negative. Rabeprozole and domperidone continued but alogliptin discontinued and ALT normalized.	Possible
TCI2011A03640	64 year Japanese male, with normal baseline ALT, was switched from voglibose to alogliptin. He shortly developed nausea and vomiting. After 4 days, he stopped alogliptin. Urine darkened. Two weeks later, ALT 869 IU/L, AST 625 IU/L, AP 1169 IU/L, & bilirubin 0.5 mg/dl. He also had itching. Tests normalized over month, although renal function deteriorated and dialysis was considered.	Probable
TCI2010A05612	64 year Japanese male was started on alogliptin. After 2 months, ALT 230 IU/L, AST 108 IU/L, AP 1260 IU/L, & bilirubin 0.87 mg/dl. Alogliptin was discontinued. US showed steatosis. Hepatitis A, B, and C negative. Over weeks, labs improved. Candesartan and atorvastatin were continued.	Probable
TCI2011A01464	75 year Japanese male, with normal ALT/AST on voglibose, was changed from pioglitazone to alogliptin. Within a week, labs were mildly elevated. Possible chronic liver disease was also considered.	Possible
TCI2011A01670	67 year Japanese female, with chronic kidney disease and an unspecified quantity of regular alcohol use, started alogliptin. Two weeks later, ALT was normal. Ten days later, ALT 331 IU/L, AST 76 IU/L, AP 353 IU/L, direct bilirubin 0.3 mg/dl, & mild amylase elevation. Alogliptin was discontinued. Over weeks, labs normalized. She also took candesartan.	Possible
TCI2011A02538	54 year Japanese male, with negative hepatitis B and C, on multiple medications, and alcoholic liver disease, started alogliptin. Six weeks later, ALT 198 IU/L, AST 194 IU/L, & bilirubin 1.2 mg/dl. Two weeks later, labs improved.	Possible
TCI2011A04039	77 year Japanese male was admitted for percutaneous transluminal angioplasty and then started on alogliptin. ALT and AST were normal. Three days later he had anorexia and vomiting. On day 4, ALT 627 IU/L, AST 669. AP peak was 349 IU/L. Bilirubin was normal. Alogliptin was discontinued. Labs and symptoms improved.	Possible/probable
TCI2011A04874	55 year Japanese male on cephalosporins who started alogliptin. Approximately 15 and 10 days after stopping cephalosporins and 21 days after starting alogliptin, ALT 233 IU/L. AP >300 IU/L. Bilirubin ~1 mg/dl. Alogliptin was discontinued. Over weeks, labs improved.	Possible
TCI2011A04573	77 year Japanese female with Hashimoto's thyroiditis on voglibose and glimepiride who was started on levothyroxine and alogliptin 25 mg. Baseline ALT, AST,	Probable to highly likely

	and bilirubin were normal. Thirteen days later, ALT 57 IU/L. One month later, ALT 1178 IU/L, AST 1070 IU/L, AP 905 IU/L, & bilirubin 6.3 mg/dl. Also, increased ammonia, coagulation parameters, & fever. Alogliptin and later levothyroxine were discontinued. Treatment was started. She approached fulminant hepatitis. Coagulation worsened. Bilirubin peaked at 33.5 mg/dl. She was treated for encephalopathy and given corticosteroids. There was some improvement, but she developed pneumonia and died despite treatment with antibiotics when ALT 30 IU/L. Hepatitis A/B/C, EBB, CMV, ANA, ASMA, LKM-1 antibody, and AMA were negative.	
8635-004/402	65 year Spanish male, with chronic hepatitis, who had near normal baseline ALT/AST. On day 35, ALT 237 U/L, AST 108 U/L, AP 53 U/L, & bilirubin 0.57 mg/dl. Alogliptin was discontinued.	Insufficient data
311-9003/009	49 year male, with baseline ALT 66 mU/ml, started alogliptin 12.5 mg. On day 32, ALT 646 mU/ml, AST 585 mU/ml, AP 112 mU/ml, & bilirubin 0.39 mg/dl. Alogliptin was discontinued and the event resolved. The subject may have use alcohol.	Possible
Cases submitted to the IND after the 2011 NDA liver safety submissions		
TCI2011A06892	78 year Japanese male who drunk heavily and took glimepiride, voglibose, and alogliptin. After ~2 months, ALT 237 IU/L, AST 542 IU/L, & AP 542 IU/L. Alogliptin was discontinued. He was switched back to glimepiride. Hepatitis B and C negative. US suggested pancreatic tail cancer.	Possible
TCI2011A06837	66 year Japanese male on glimepiride and alogliptin 25 mg. Baseline ALT/AST were normal. He sometimes had three glasses of alcohol three times a week, but he decreased his intake prior to his follow up appointment. One month later, ALT 1512 IU/L, AST 2188 IU/L, AP 313 IU/L, & bilirubin 3.9 mg/dl. He was hospitalized, alogliptin discontinued, and glimepiride increased. Within 14 days, labs normalized. Hepatitis B/C and US negative. Gamma globulin normal. Rabeproazole and domperidone were continued. Drug lymphocytes stimulation tests were negative for sitagliptin and alogliptin.	Probable to highly likely

*The two cases in bold (TCI2011A04573 and TCI2011A06837) concern me due to their severity and more likely association to alogliptin.

In summary, as shown in Table 58, there is an imbalance in the number and percentage of subjects with markedly abnormal ALT values, including ALT >10x and 20x ULN, in the clinical trials. As described in the July 2009 guidance, *Drug-Induced Liver Injury: Premarketing Clinical Evaluation*, ALT is generally considered more liver-specific than AST. The finding of a higher rate of ALT elevation in drug-treated subjects than in a control group is a sensitive (but not necessarily specific) signal of the potential for drug induced liver injury (DILI). Greater aminotransferase increases (e.g., 10x-, 15xULN) in clinical trials, such as those shown in Table 58 are a more specific signal for DILI but not as specific as Hy's Law. Furthermore, I am concerned by postmarketing Hy's law cases TCI2011A04573 and TCI2011A06837 which describe moderate to severe liver

disorders and a probable or highly likely association to alogliptin. I am concerned that two cases of moderate/severe liver injury associated with alogliptin have potentially been identified after only 117,359 patient-years exposure in Japan. More cases of alogliptin-associated liver dysfunction may occur if the drug is used more widely. There are also four clinical trial cases of biochemical Hy's law (303/3128-003, 012/961-3006, 012/961-2501, and 305/5304-005) that appear to have alternative explanations. These four cases as well as cases of ALT elevation >10x ULN in the clinical trial database are undergoing review by Dr. Leonard Seeff, a hepatologist within OSE, and will be further addressed in the CDTL memorandum. However, based on even the 2 postmarketing cases of moderate/severe liver injury, unless the pending OSE consult demonstrates a similar propensity for serious liver injury with other DPP-4 inhibitors, I recommend a complete response to this application and requiring the applicant to more clearly demonstrate the liver safety of alogliptin. Specifically, I recommend the applicant analyze serious liver events in postmarketing data and the ongoing controlled, double-blind clinical studies 305, 402, and 308, which were described in their December 2011 annual report (IND 69,707 SDN 691).

Renal Data:

Outliers or Shifts from Normal to Abnormal: In original NDA 22-426, greater incidences of elevations in blood urea nitrogen, serum creatinine, and urinary albumin/creatinine ratios were observed with the combination alogliptin/pioglitazone treatment group compared to the individual alogliptin and pioglitazone treatment groups. In addition, more subjects in the combination drug treatment group experienced a shift from normal to mild or moderate renal impairment, as calculated by both the CG and MDRD formulas, when compared to the individual treatment groups.

When the number and percentage of subjects with abnormal renal function parameters were reviewed in the alogliptin and alogliptin/pioglitazone FDC safety databases in the CR, the incidence of abnormalities was approximately similar between treatment groups with the following exceptions in the FDC database (see Table 63 and Table 64).

However, a weakness of this analysis is that it does not take into account if the abnormalities resolved by the end of the trial.

- Serum creatinine >ULN with >0.3 mg/dl increase from baseline. *Comment: The four other analyses of change in creatinine were more balanced in Table 64.*
- eGFR >25% decrease from baseline (CG and MDRD formulas)
- eGFR >50% decrease from baseline (MDRD formula)

An increase in the incidence of abnormal urine albumin:creatinine ratio was not seen in the alogliptin+pioglitazone treatment group in the alogliptin/pioglitazone FDC safety database (see Table 65).

Table 63. Number and percentage of subjects with abnormal renal function parameters during treatment (Controlled phase 2 and 3 study group)

Parameter (Criterion)	Number (%) of Subjects With ≥ 1 Markedly Abnormal Result During Treatment		
	All Comparators (a) N=2910	Alogliptin 25 mg N=3453	All Alogliptin (b) N=5185
BUN ($>3 \times \text{ULN}$)	16 (0.6)	15 (0.5)	17 (0.3)
Albumin (<2.5 g/dL)	0	0	0
Serum creatinine			
$>1.5 \times \text{Baseline}$	32 (1.2)	46 (1.4)	57 (1.1)
$>1.5 \times \text{Baseline}$ and $>\text{ULN}$	20 (0.7)	22 (0.7)	27 (0.5)
$>\text{ULN}$ with >0.3 mg/dL increase from Baseline	59 (2.1)	73 (2.2)	88 (1.8)
$\geq 2 \times$ Baseline value	6 (0.2)	7 (0.2)	9 (0.2)
>2.0 mg/dL	39 (1.4)	43 (1.3)	49 (1.0)
eGFR			
$>25\%$ decrease from Baseline (C-G)	142 (5.2)	195 (5.9)	268 (5.4)
$>50\%$ decrease from Baseline (C-G)	6 (0.2)	7 (0.2)	9 (0.2)
$>25\%$ decrease from Baseline (MDRD)	227 (8.3)	328 (10.0)	463 (9.3)
$>50\%$ decrease from Baseline (MDRD)	12 (0.4)	11 (0.3)	15 (0.3)

Source: SCS Table 3.h

Table 64. NDA 22-426: Number and percentage of subjects with abnormal serum creatinine and eGFR values during treatment

Variable Criteria	Number of Subjects (%) With ≥ 1 Marked Abnormal Result		
	ALO N=407	PIO N=930	ALO+PIO N=1490
Serum creatinine			
$>1.5 \times \text{baseline}$	5 (1.2)	9 (1.0)	20 (1.3)
$>1.5 \times \text{baseline}$ and $>\text{ULN}$	0	4 (0.4)	6 (0.4)
$>\text{ULN}$ with >0.3 mg/dL increase from baseline	3 (0.7)	6 (0.6)	16 (1.1)
$\geq 2 \times$ baseline value	1 (0.2)	1 (0.1)	5 (0.3)
>2.0 mg/dL	0	1 (0.1)	2 (0.1)
eGFR			
$>25\%$ decrease from baseline (MDRD)	37 (9.1)	93 (10.0)	200 (13.4)
$>50\%$ decrease from baseline (MDRD)	1 (0.2)	2 (0.2)	7 (0.5)
$>25\%$ decrease from baseline (Cockcroft-Gault)	21 (5.2)	50 (5.4)	95 (6.4)
$>50\%$ decrease from baseline (Cockcroft-Gault)	1 (0.2)	1 (0.1)	5 (0.3)

Source: NDA 22-426 SCS Table 3.d

Table 65. NDA 22-426: Summary of abnormal urine albumin:creatinine ratio results

Criteria	Number of Subjects (%) With ≥ 1 Abnormality During Treatment		
	ALO N=171	PIO N=392	ALO+PIO N=609
Subjects with baseline value in the normal range and at least 1 post-baseline value $>ULN$	14 (8.2)	37 (9.4)	53 (8.7)
$\geq 1.25 \times \text{Baseline}$	53 (31.0)	133 (33.9)	175 (28.7)
$\geq 1.5 \times \text{Baseline}$	41 (24.0)	100 (25.5)	133 (21.8)
$\geq 2 \times \text{Baseline}$	23 (13.5)	65 (16.6)	88 (14.4)
$\geq 3 \times \text{Baseline}$	11 (6.4)	32 (8.2)	48 (7.9)

Source: NDA 22-426 Table 3.k

Shifts in renal function were analyzed in the alogliptin NDA using both the CG and MDRD methods. Both methods are comparable when patients' body weight is <120 kg, although the CG method tends to overestimate renal function when body weight is >120 kg.

Using the CG method, slightly more alogliptin 25 mg subjects shifted from moderate to severe renal impairment when compared to comparators (3.0% vs. 1.3%). Using the MDRD method, slightly more alogliptin 25 mg subjects shifted from mild to moderate renal impairment when compared to comparators (8.7% vs. 6.5%). However, more comparator subjects shifted from moderate to severe impairment using MDRD when compared to alogliptin 25 mg (2.6% vs. 1.5%). Therefore, there were no consistent findings in the shift analyses when the results from both CG and MDRD are considered together. (See Table 66 and Table 67.)

Table 66. Shift in renal function (CG) from baseline to endpoint (Controlled phase 2 and 3 study group)

Endpoint Renal Function	Number (%) of Subjects											
	All Comparators (a) N=2745				Alogliptin 25 mg N=3285				All Alogliptin (b) N=4992			
	Baseline Renal Function											
	Normal N=1469	Mild N=961	Moderate N=297	Severe N=18	Normal N=1831	Mild N=1103	Moderate N=329	Severe N=22	Normal N=2923	Mild N=1628	Moderate N=418	Severe N=23
Normal	1336 (90.9)	132 (13.7)	2 (0.7)	0	1665 (90.9)	166 (15.0)	1 (0.3)	0	2684 (91.8)	240 (14.7)	1 (0.2)	0
Mild	133 (9.1)	757 (78.8)	62 (20.9)	0	162 (8.8)	858 (77.8)	50 (15.2)	0	233 (8.0)	1284 (78.9)	71 (17.0)	0
Moderate	0	71 (7.4)	229 (77.1)	4 (22.2)	4 (0.2)	79 (7.2)	268 (81.5)	4 (18.2)	6 (0.2)	104 (6.4)	335 (80.1)	4 (17.4)
Severe	0	1 (0.1)	4 (1.3)	14 (77.8)	0	0	10 (3.0)	18 (81.8)	0	0	11 (2.6)	19 (82.6)

Source: SCS Table 3.f

Table 67. Shift in renal function (MDRD) from baseline to endpoint (Controlled phase 2 and 3 study group)

Endpoint Renal Function	Number (%) of Subjects											
	All Comparators (a) N=2746				Alogliptin 25 mg N=3285				All Alogliptin (b) N=4992			
	Baseline Renal Function											
	Normal N=486	Mild N=1742	Moderate N=494	Severe N=24	Normal N=590	Mild N=2149	Moderate N=519	Severe N=27	Normal N=955	Mild N=3295	Moderate N=714	Severe N=28
Normal	310 (63.8)	161 (9.2)	2 (0.4)	0	382 (64.7)	156 (7.3)	1 (0.2)	0	622 (65.1)	230 (7.0)	2 (0.3)	0
Mild	173 (35.6)	1467 (84.2)	135 (27.3)	0	206 (34.9)	1807 (84.1)	107 (20.6)	0	330 (34.6)	2782 (84.4)	158 (22.1)	0
Moderate	3 (0.6)	113 (6.5)	344 (69.6)	7 (29.2)	2 (0.3)	186 (8.7)	403 (77.6)	8 (29.6)	3 (0.3)	283 (8.6)	545 (76.3)	8 (28.6)
Severe	0	1 (0.1)	13 (2.6)	17 (70.8)	0	0	8 (1.5)	19 (70.4)	0	0	9 (1.3)	20 (71.4)

Source: SCS Table 3.

Marked outliers and dropouts for laboratory abnormalities: When renal function-related SAEs and discontinuations were reviewed, an increase was not observed with the use of alogliptin (see Table 68 and Table 69).

Table 68. Renal function-related SAEs (Controlled phase 2 and 3 group)

Preferred Term	Number (%) of Subjects		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232
Renal failure acute	7 (0.2)	6 (0.2)	6 (0.1)
Calculus ureteric	1 (<0.1)	3 (0.1)	3 (0.1)
Nephrolithiasis	0	1 (<0.1)	3 (0.1)
Renal colic	0	2 (0.1)	2 (<0.1)
Renal impairment	1 (<0.1)	2 (0.1)	2 (<0.1)
Calculus urinary	2 (0.1)	1 (<0.1)	1 (<0.1)
Hematuria	0	1 (<0.1)	1 (<0.1)
Hydronephrosis	0	1 (<0.1)	1 (<0.1)
Renal failure	0	1 (<0.1)	1 (<0.1)
Renal failure chronic	1 (<0.1)	1 (<0.1)	1 (<0.1)
Urinary tract obstruction	0	1 (<0.1)	1 (<0.1)
Azotemia	1 (<0.1)	0	0
Nephropathy	1 (<0.1)	0	0
Renal embolism	1 (<0.1)	0	0

Source: SCS Table 3.i

Table 69. Renal function-related AEs that led to discontinuation of study drug (Controlled phase 2 and 3 group)

Preferred Term	Number (%) of Subjects		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232
Creatinine renal clearance abnormal	1 (<0.1)	2 (0.1)	2 (<0.1)
Blood creatinine increased	1 (<0.1)	1 (<0.1)	1 (<0.1)
Blood urea increased	0	1 (<0.1)	1 (<0.1)
Creatinine renal clearance decreased	1 (<0.1)	0	0
Nephropathy	0	1 (<0.1)	2 (<0.1)
Hematuria	0	1 (<0.1)	1 (<0.1)
Renal failure acute	1 (<0.1)	1 (<0.1)	1 (<0.1)
Renal failure chronic	0	0	1 (<0.1)
Renal impairment	0	1 (<0.1)	1 (<0.1)
Calculus urinary	1 (<0.1)	0	0

Source: SCS Table 3.j

The incidence of AEs by endpoint renal function (CG and MDRD) and preferred term are shown in Sang Chung's January 18, 2012 clinical pharmacology review (Tables 8 and 9). In his review, Dr. Chung accepts the sponsor's proposed dosage adjustment for RI, in part because the safety analysis of AE incidence by baseline and endpoint renal status indicates that subjects with mild RI do not appear to be at a higher risk for AEs.

When the alogliptin/pioglitazone FDC NDA was reviewed for renal function-related SAEs and discontinuations, a small but not clinically significant increase was seen with alogliptin/pioglitazone. Furthermore, due to very low event rates, the estimates are not reliable and would be altered by +/- one event.

Table 70. NDA 22-426: Renal function-related SAEs and discontinuations

Treatment	Renal function-related SAE (n, %)	Renal function-related discontinuation (n, %)
Alogliptin (n=407)	0	0
Pioglitazone (n=930)	1 (0.1%)	1 (0.1%)
Alo+Pio (n=1490)	3 (0.2%)	2 (0.1%)

Source: NDA 22-426 SCS page 88

Summary: In summary, the sponsor's proposed alogliptin dosage adjustment for RI is acceptable. No consistent, clinically relevant changes were noted in the following CR data:

- Number and percentage of subjects with abnormal renal function parameters in the alogliptin and alogliptin/pioglitazone FDC NDAs
- Incidence of abnormal urine albumin:creatinine ratio in the FDC NDA
- Shifts in renal function (CG and MDRD formulas) in the alogliptin NDA

- Renal function-related discontinuations and SAEs in the alogliptin and alogliptin/pioglitazone FDC NDAs

Other Chemistry Data:

Outliers or Shifts from Normal to Abnormal: When the percentages of subjects with markedly abnormal test results for other chemistry parameters was reviewed in the alogliptin Summary of Clinical Safety, the percentages were small and generally similar between treatment groups (see Table 71).

Table 71. Number and percentage of subjects with markedly abnormal test results for selected other chemistry parameters (Controlled phase 2 and 3 study group)

Parameter (Criterion)	Number (%) of Subjects With ≥ 1 Markedly Abnormal Result					
	Baseline			During Treatment		
	All Comparators (a) N=2910	Alogliptin 25 mg N=3453	All Alogliptin (b) N=5185	All Comparators (a) N=2910	Alogliptin 25 mg N=3453	All Alogliptin (b) N=5185
Calcium low ($<0.8 \times \text{LLN}$)	0	0	0	2 (0.1)	2 (0.1)	2 (<0.1)
Calcium high ($>1.2 \times \text{ULN}$)	0	0	1 (<0.1)	0	0	1 (<0.1)
Potassium (<3.0 mEq/L)	0	5 (0.1)	5 (0.1)	4 (0.1)	6 (0.2)	8 (0.2)
Potassium (>5.8 mEq/L)	19 (0.7)	20 (0.6)	26 (0.5)	65 (2.4)	97 (3.0)	150 (3.0)
Protein, total ($<0.8 \times \text{LLN}$)	2 (0.1)	0	0	0	2 (0.1)	3 (0.1)
Protein, total ($>1.2 \times \text{ULN}$)	0	1 (<0.1)	1 (<0.1)	0	3 (0.1)	3 (0.1)
Sodium (<130 mEq/L)	4 (0.1)	6 (0.2)	6 (0.1)	18 (0.7)	16 (0.5)	22 (0.4)
Sodium (>150 mEq/L)	1 (<0.1)	1 (<0.1)	3 (0.1)	7 (0.3)	11 (0.3)	20 (0.4)
Uric acid (>10.5 mg/dL, men; >8.5 mg/dL, women)	19 (1.0)	25 (1.0)	49 (1.2)	47 (2.6)	68 (2.9)	116 (2.9)

Source: SCS Table 3.p

Marked outliers and dropouts for laboratory abnormalities (excluding hypo- and hyperglycemia): Regarding other clinical chemistry parameters, no alogliptin subjects experienced a related SAE in the alogliptin safety database, although two alogliptin subjects discontinued study drug due to lipase increase and one discontinued due to increased blood calcium (see Table 72). Given the small percentage of subjects discontinued and the fact that the same percentage of subjects were discontinued for lipase increase regardless of treatment group, I doubt this is clinically significant.

Table 72. Select other clinical chemistry-related AEs that lead to discontinuation of study drug (Controlled phase 2 and 3 group)

Preferred Term	Number (%) of Subjects		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232
Lipase increased	3 (0.1)	2 (0.1)	2 (<0.1)
Blood calcium increased	0	0	1 (<0.1)

Source: SCS Table 3.r

Hematology Data:

Outliers or Shifts from Normal to Abnormal: The number and percentage of subjects with markedly abnormal values for hematology parameters was small and generally similar between groups. Although shifts in platelet and white blood cell counts were observed, these events were infrequent and balanced between treatment groups (see Table 73).

Table 73. Number and percentage of subjects with markedly abnormal values for select hematology parameters (Controlled phase 2 and 3 study group)

Parameter (Criterion)	Number (%) of Subjects With ≥1 Markedly Abnormal Result					
	Baseline			During Treatment		
	All Comparators (a) N=2910	Alogliptin 25 mg N=3453	All Alogliptin (b) N=5185	All Comparators (a) N=2910	Alogliptin 25 mg N=3453	All Alogliptin (b) N=5185
Hematocrit (low; <0.8×Baseline)	N/A	N/A	N/A	46 (1.7)	53 (1.6)	73 (1.5)
Hemoglobin (low; <Baseline–3 g/dL)	N/A	N/A	N/A	37 (1.4)	40 (1.2)	54 (1.1)
Platelet count (low; <50×10 ³ /mm ³)	0	2 (0.1)	2 (<0.1)	1 (<0.1)	7 (0.2)	9 (0.2)
Platelet count (high; >600×10 ³ /mm ³)	1 (<0.1)	2 (0.1)	3 (<0.1)	5 (0.2)	5 (0.2)	10 (0.2)
Red blood cell count (low; <0.8×Baseline)	N/A	N/A	N/A	47 (1.7)	57 (1.7)	76 (1.5)
White blood cell count (low; <2×10 ³ /mm ³)	0	1 (<0.1)	2 (<0.1)	1 (<0.1)	4 (0.1)	6 (0.1)
White blood cell count (high; >20×10 ³ /mm ³)	0	0	0	2 (0.1)	2 (0.1)	5 (0.1)

Source: SCS Table 3.b

Marked outliers and dropouts for laboratory abnormalities: The incidence of hematology-related SAEs and discontinuations are show in Table 74 and Table 75. A clinically significant trend was not observed.

Table 74. Hematology-related SAES (Controlled phase 2 and 3 study group)

Preferred Term	Number (%) of Subjects		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232
Anemia	5 (0.2)	5 (0.1)	5 (0.1)
Lymphopenia	0	1 (<0.1)	1 (<0.1)
Hypercoagulation	1 (<0.1)	0	0
Iron deficiency anemia	1 (<0.1)	0	0
Hemoglobin decreased	1 (<0.1)	0	0

Source: SCS Table 3.c

Table 75. Hematology-related AEs that lead to discontinuation of study drug (Controlled phase 2 and 3 group)

Preferred Term	Number (%) of Subjects		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232
Anemia	1 (<0.1)	1 (<0.1)	1 (<0.1)
Leukopenia	1 (<0.1)	0	0

Source: SCS Table 3.d

7.4.3 Vital Signs

The vital sign entrance criteria for phase 3 alogliptin studies varied and were as follows:

- OPI-002 and OPI-004: BP <160/100 mm Hg
- OPI-001 and 301: BP ≤160/100 mm Hg
- 003, SULF-007, MET-008, TZD-009, PLC-010, and INS-011: BP ≤180/110 mm Hg
- 402: BP ≤180/110 mm Hg or lower if associated with target organ injury or symptoms

Vital signs in controlled phase 2 and 3 studies were analyzed by the mean change from baseline, incidence of abnormal results, and incidence of SAEs or discontinuations. As shown in Table 76, the mean change from baseline for blood pressure and heart rate was small and similar between the all comparator, alogliptin 25 mg, and all alogliptin groups.

Table 76. Change in vital signs from baseline (Controlled phase 2 and 3 studies)

Variable	n/N		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232
Systolic blood pressure (mm Hg)			
Baseline mean (SD)	129.1 (15.44)/2932	128.2 (15.08)/3498	128.0 (14.80)/5230
Endpoint mean (SD)	129.9 (15.37)/2780	128.8 (15.08)/3352	128.4 (14.69)/5070
Mean change from Baseline (SD)	0.7 (15.23)/2780	0.7 (14.25)/3352	0.5 (13.99)/5070
Diastolic blood pressure (mm Hg)			
Baseline mean (SD)	77.7 (8.98)/2932	77.5 (8.97)/3498	77.7 (8.88)/5230
Endpoint mean (SD)	77.8 (9.12)/2781	78.0 (9.17)/3352	77.9 (8.98)/5070
Mean change from Baseline (SD)	0.0 (9.58)/2781	0.4 (9.47)/3352	0.2 (9.25)/5070
Pulse (beats per minute)			
Baseline mean (SD)	73.4 (10.13)/2932	73.2 (9.80)/3498	73.5 (9.61)/5230
Endpoint mean (SD)	73.0 (10.15)/2781	73.5 (9.70)/3352	73.7 (9.50)/5070
Mean change from Baseline (SD)	-0.4 (9.57)/2781	0.2 (9.43)/3352	0.2 (9.19)/5070

Source: SCS Table 4.a

When the incidence of abnormal vital signs was reviewed, a greater percentage of both comparator and alogliptin-treated subjects experienced elevated systolic or diastolic blood pressure (3.4-4.4%) when compared to the percentage of subjects who experienced decreased blood pressure (0.1-0.4%). However, the difference between treatment groups was small and likely not clinically significant. Similarly, a small percentage of subjects in all treatment groups experienced abnormal heart rate (0-0.4%).

Table 77. Number and percentage of subjects with abnormal vital signs (Controlled phase 2 and 3 studies)

Variable (Criteria)	n/N (%) of Subjects With ≥1 Abnormal Measurement During Treatment		
	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232
Systolic blood pressure low (<90 mm Hg and ≥20 mm Hg decrease from Baseline)	4/2780 (0.1)	9/3352 (0.3)	13/5070 (0.3)
Systolic blood pressure high (>160 mm Hg and ≥20 mm Hg increase from Baseline)	122/2780 (4.4)	140/3352 (4.2)	197/5070 (3.9)
Diastolic blood pressure low (<50 mm Hg and ≥15 mm Hg decrease from Baseline)	10/2781 (0.4)	6/3352 (0.2)	8/5070 (0.2)
Diastolic blood pressure high (>95 mm Hg and ≥15 mm Hg increase from Baseline)	94/2781 (3.4)	126/3352 (3.8)	186/5070 (3.7)
Pulse low (<50 bpm and ≥15 bpm decrease from Baseline)	10/2781 (0.4)	7/3352 (0.2)	11/5070 (0.2)
Pulse high (>120 bpm and ≥15 bpm increase from Baseline)	1/2781 (<0.1)	0/3352	2/5070 (<0.1)

Source: SCS Table 4.b

Assuming the events occurred in separate subjects, more comparator subjects (n=8) experienced vital sign-related SAEs, when compared to all alogliptin subjects (n=2).

(See Table 78.) However, two alogliptin subjects were discontinued due to vital sign AEs (hypertension and orthostatic hypotension).

Table 78. Vital sign SAEs (Controlled phase 2 and 3 studies)

Preferred Term	All Comparators (n=2934)	Alogliptin 25 mg (n=3500)	All Alogliptin (n=5232)
Malignant hypertension	1 (<0.1)	1 (<0.1)	1 (<0.1)
Orthostatic hypotension	0	1 (<0.1)	1 (<0.1)
Hypertension	3 (0.1)	0	0
Hypertensive crisis	1 (<0.1)	0	0
Hypotension	3 (0.1)	0	0

Source: SCS Table 4.c

In summary, alogliptin does not appear to be associated with clinically meaningful changes in vital signs. Furthermore, as described in section 7.3.5 Submission Specific Primary Safety Concerns, interim analysis of CV study 402 demonstrated that alogliptin does not increase CV risk.

7.4.4 Electrocardiograms (ECGs)

Two phase 1 clinical studies were conducted to evaluate the effect of alogliptin on QTc and were reviewed during the original NDA submission. Study 004 was an evaluator-blinded, active- and placebo-controlled, multiple dose, crossover study in 48 subjects. Originally, data from three heart beats on a single ECG strip were selected and analyzed for each subject. However, in order to conform with the standard industry practice for thorough QT/QTc studies, data from two additional strips (three heart beats each) were retrospectively collected, after database unblinding and after the initial QT/QTc data were analyzed.

Due to the design flaw in study 004, the sponsor conducted a second QT/QTc study 019, which was a single blind, randomized, placebo- and positive-controlled, four-arm, parallel-group, single-center study in which two doses of alogliptin were compared with moxifloxacin and placebo. Study 019 demonstrated that alogliptin has no clinically meaningful effect on cardiac repolarization, as the upper bound of the two-sided 90% CI for the time-averaged LS mean difference from placebo in change from baseline in QTcI and QTcF using the time-averaged baseline was <10 msec for both alogliptin doses on both days.

In phase 3 studies, ECGs were recorded at each site and not read centrally. As the subjects in study 402 had ACS, study 402 was not included in the pooled analysis of ECGs which examined the mean change in ECG parameters and the incidence of abnormal ECG parameters. ECG-related SAEs and discontinuations were also reviewed.

As shown in Table 79, the mean change from baseline in heart rate and QRS for the alogliptin 25 mg group equaled that of the all comparator group, although the mean change from baseline for the alogliptin 25 mg group was greater for the PR, QT, and QTcF intervals. However, for all groups, these changes were small and are likely not clinically significant.

Table 79. Mean change from baseline in ECG parameters (Controlled phase 2 and 3 studies excluding study 402)

Variable	n/N		
	All Comparators (a) N=1855	Alogliptin 25 mg N=2430	All Alogliptin (b) N=4162
Ventricular Heart Rate (bpm)			
Baseline mean (SD)	71.5 (11.32)	71.4 (11.16)/2429	71.4 (11.23)/4160
Endpoint mean (SD)	71.8 (11.79)/1750	71.8 (11.00)/2311	71.8 (11.14)/3962
Mean change from Baseline (SD)	0.5 (9.84)/1750	0.5 (9.74)/2310	0.5 (9.52)/3961
PR Interval (msec)			
Baseline mean (SD)	161.9 (27.32)/1840	161.2 (25.60)/2414	160.6 (26.25)/4133
Endpoint mean (SD)	160.7 (26.68)/1732	161.1 (25.84)/2294	160.5 (25.98)/3932
Mean change from Baseline (SD)	-1.0 (20.38)/1732	0.1 (17.10)/2290	0.0 (17.96)/3924
QRS Interval (msec)			
Baseline mean (SD)	90.1 (17.00)	89.8 (17.44)/2429	89.2 (17.50)/4160
Endpoint mean (SD)	91.0 (17.68)/1750	90.6 (16.40)/2311	90.0 (16.67)/3962
Mean change from Baseline (SD)	0.9 (13.02)/1750	0.9 (14.79)/2310	0.8 (13.61)/3961
QT Interval (msec)			
Baseline mean (SD)	387.2 (33.16)	386.9 (32.89)/2429	386.3 (33.89)/4159
Endpoint mean (SD)	386.8 (34.92)/1750	386.5 (32.77)/2311	385.6 (33.97)/3962
Mean change from Baseline (SD)	-0.7 (29.99)/1750	-0.3 (27.58)/2310	-0.6 (28.25)/3961
QTcF Interval (msec) (c)			
Baseline mean (SD)	408.23 (26.563)	407.73 (26.711)/2429	407.16 (27.747)/4159
Endpoint mean (SD)	408.21 (28.175)/1750	408.06 (26.443)/2311	407.22 (27.777)/3962
Mean change from Baseline (SD)	-0.02 (27.101)/1750	0.61 (24.192)/2310	0.35 (25.153)/3961

Source: SCS Table 4.d

The incidence of abnormal ECG measurement was low and similar between treatment groups. (See Table 80.)

Table 80. Abnormal ECG measurements (Controlled phase 2 and 3 studies excluding study 402)

Variable (Criteria)	n/N (%) of Subjects With ≥1 Abnormal Measurement					
	Baseline			During Treatment		
	All Comparators (a)	Alogliptin 25 mg	All Alogliptin (b)	All Comparators (a)	Alogliptin 25 mg	All Alogliptin (b)
PR Interval low (<120 msec)	46/1840 (2.5)	70/2414 (2.9)	133/4133 (3.2)	70/1732 (4.0)	100/2294 (4.4)	186/3932 (4.7)
PR Interval high (>200 msec)	94/1840 (5.1)	132/2414 (5.5)	221/4133 (5.3)	109/1732 (6.3)	158/2294 (6.9)	258/3932 (6.6)
QRS Interval low (<40 msec)	2/1855 (0.1)	1/2429 (<0.1)	3/4160 (0.1)	1/1750 (0.1)	2/2311 (0.1)	5/3962 (0.1)
QRS Interval high (>120 msec)	82/1855 (4.4)	81/2429 (3.3)	161/4160 (3.9)	109/1750 (6.2)	107/2311 (4.6)	195/3962 (4.9)
QTcF Interval (>450 to 480 msec)	86/1855 (4.6)	100/2429 (4.1)	164/4159 (3.9)	122/1750 (7.0)	161/2311 (7.0)	264/3962 (6.7)
QTcF Interval (>480 to 500 msec)	7/1855 (0.4)	10/2429 (0.4)	21/4159 (0.5)	20/1750 (1.1)	15/2311 (0.6)	29/3962 (0.7)
QTcF Interval (>500 msec)	10/1855 (0.5)	7/2429 (0.3)	14/4159 (0.3)	12/1750 (0.7)	11/2311 (0.5)	15/3962 (0.4)
QTcF Interval (≥30-≤60 msec increase from Baseline)	N/A	N/A	N/A	173/1750 (9.9)	217/2311 (9.4)	368/3962 (9.3)
QTcF Interval (≥60 msec increase from Baseline)	N/A	N/A	N/A	46/1750 (2.6)	51/2311 (2.2)	85/3962 (2.1)
QTcF Interval (>500 msec and ≥60 msec increase from Baseline)	N/A	N/A	N/A	9/1750 (0.5)	4/2311 (0.2)	6/3962 (0.2)
Ventricular rate low (<50 bpm and 15 bpm decrease from Baseline)	N/A	N/A	N/A	3/1750 (0.2)	4/2310 (0.2)	6/3961 (0.2)
Ventricular rate high (>120 bpm and 15 bpm increase from Baseline)	N/A	N/A	N/A	2/1750 (0.1)	4/2310 (0.2)	5/3961 (0.1)

Source: SCS Table 4.e

When ECG-related SAEs and discontinuations were reviewed, the incidence was similarly low in all groups (<0.1). All events were single events, except for two SAEs each of arrhythmia and atrial flutter in the all comparator group.

In summary, alogliptin does not appear to result in a clinically significant change in mean ECG parameters, the incidence of abnormal ECGs, or ECG-related SAEs or discontinuations. Furthermore, as described in section 7.3.5 Submission Specific Primary Safety Concerns, interim analysis of CV study 402 demonstrated that alogliptin does not increase CV risk.

Table 81. ECG-related SAEs (Controlled phase 2 and 3 studies)

SOC/Preferred Term	All Comparators (n=2934)	Alogliptin 25 mg (n=3500)	All Alogliptin (n=5232)
Total	5 (<0.1)	3 (<0.1)	5 (<0.1)
Cardiac disorders			

Bradycardia	1 (<0.1)	0	1 (<0.1)
Atrioventricular block complete	0	1 (<0.1)	1 (<0.1)
Nodal rhythm	0	1 (<0.1)	1 (<0.1)
Supraventricular tachycardia	0	1 (<0.1)	1 (<0.1)
Arrhythmia	2 (0.1)	0	0
Atrial flutter	2 (0.1)	0	0
Investigations			
ECG change	0	0	1 (<0.1)

Source: SCS Table 4.f

Table 82. ECG-related AEs that led to discontinuation (Controlled phase 2 and 3 studies)

SOC/Preferred term	All Comparators (n=2934)	Alogliptin 25 mg (n=3500)	All Alogliptin (n=5232)
Total	0	2 (<0.1)	3 (<0.1)
Cardiac disorders			
Supraventricular tachycardia	0	1 (<0.1)	1 (<0.1)
Bundle branch block left		0	0
Investigations			
ECG T wave inversion	0	1 (<0.1)	1 (<0.1)
ECG change	0	0	1 (<0.1)

Source: SCS Table 4.g

7.4.5 Special Safety Studies/Clinical Trials

See section 7.3.5 Submission Specific Primary Safety Concerns for my review of the interim data from CV study 402.

7.4.6 Immunogenicity

No immunogenicity studies were completed. Alogliptin is a small molecule and is, therefore, not expected to be immunogenic. However, on November 17, 2011, the sponsor submitted a response to our hypersensitivity request. Please refer to section 7.3.4 Significant Adverse Events for full details.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Please refer to my previous reviews of NDA 22-271 and 22-426.

7.5.2 Time Dependency for Adverse Events

When SAEs and AEs leading to discontinuation were reviewed by time of onset, the incidence was similar between treatment groups at the individual time points (see Table 83). Therefore, alogliptin does not appear to increase the incidence of SAE or AE leading to discontinuation relative to comparators at the same time point. Please refer to my reviews of alogliptin NDA 2-271 and alogliptin/pioglitazone FDC NDA 22-426.

Table 83. SAEs and AEs (n, %) leading to discontinuation by time of onset

Event/Time of Onset	All Comparators (n=2934)	Alogliptin 25 mg (n=3500)	All Alogliptin (n=5232)
SAE			
≤1 day	4 (0.1%)	8 (0.2%)	9 (0.2%)
>1 day - <7 days	16 (0.5%)	15 (0.4%)	16 (0.3%)
≥7 days - <30 days	54 (1.9%)	48 (1.4%)	53 (1.0%)
≥30 days - <6 months	158 (5.8%)	155 (4.7%)	198 (4.0%)
≥6 months - <12 months	63 (3.7%)	56 (2.4%)	57 (1.6%)
≥12 months - <18 months	8 (1.7%)	9 (1.7%)	9 (1.7%)
Discontinuation due to AE			
≤1 day	5 (0.2%)	8 (0.2%)	13 (0.2%)
>1 day - <7 days	10 (0.3%)	5 (0.1%)	8 (0.2%)
≥7 days - <30 days	20 (0.7%)	18 (0.5%)	35 (0.7%)
≥30 days - <6 months	39 (1.4%)	45 (1.4%)	61 (1.2%)
≥6 months - <12 months	11 (0.6%)	12 (0.5%)	12 (0.3%)
≥12 months - <18 months	1 (0.2%)	1 (0.2%)	1 (0.2%)

Source : IAS Tables 8.4.6.3Ra and 8.4.7.3Ra

7.5.3 Drug-Demographic Interactions

Please refer to section 6.1.4 Analysis of Primary Endpoint(s) for a discussion of the results from study 303, which evaluated the efficacy of alogliptin as compared with glipizide on HbA1c change from Baseline at week 52 in adults 65 to 90 years of age with T2DM.

Please refer to 7.3.5 Submission Specific Primary Safety Concerns for a discussion of the exploratory subgroup MACE analysis.

Please also refer to my reviews of alogliptin NDA 22-271 and alogliptin/pioglitazone FDC NDA 22-426.

7.5.4 Drug-Disease Interactions

As discussed in section 2.5 Summary of Presubmission Regulatory Activity Related to Submission, a deficiency noted in the CR letters was the ~70% increase in mean exposure to alogliptin (as assessed by AUC) in patients with mild RI when compared to subjects with normal renal function in the renal PK study. This suggested a potential need to adjust the dose of alogliptin in subjects with mild RI. To further assess the effect of renal function on the clearance of alogliptin, the sponsor was required to compare the safety and tolerability of alogliptin in subjects with mild RI and normal renal function in controlled phase 2 and 3 trials. Please refer to the renal subsection of 7.4.2 Laboratory Findings for full details.

7.5.5 Drug-Drug Interactions

Please refer to Sang Chung's and Ritesh Jain's clinical pharmacology reviews as well as my reviews of alogliptin NDA 22-271 and alogliptin/pioglitazone FDC NDA 22-426.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please refer to the malignancy subsection of 7.3.4 Significant Adverse Events, my original NDA reviews, and David Carlson's pharmacology/toxicology reviews.

7.6.2 Human Reproduction and Pregnancy Data

Please refer to my reviews of alogliptin NDA 22-271 and alogliptin/pioglitazone FDC NDA 22-426. There were two pregnancies in phase 1 studies and four pregnancies in phase 2 and 3 trials (see Table 84). Two additional pregnancies (679-2503 and 1044-4505) occurred prior to randomization.

Table 84. Summary of pregnancies in the alogliptin clinical program

Study/ Site-Subject Age(yr)/Race	Treatment (duration)	Birth Control Method	Outcome
322OPI-002/ 679-2503 33/White	Not randomized (0 days)	Medroxyprogesterone	Normal birth to healthy male infant on (b) (6)
322OPI-004/ 1044-4505 36/White	Not randomized (0 days) (a)	Barrier method	On (b) (6) the subject underwent an elective dilation and curettage with no reported complications.
322OPI-001/ 412-3119 32/Multiracial	Alogliptin 12.5 mg (84 days)	Double-barrier method	Spontaneous abortion occurred on (b) (6) (Day 80). Subject history included spontaneous abortion (2000) and 2 C-sections (1996, 1998) and concurrent medical condition of vaginal mycosis. Subject was also taking metformin, fluconazole, clotrimazole, and alprazolam which were discontinued due to the pregnancy.
012/390-4001 (a) 32/White	Alogliptin 12.5 mg (8 days)	Barrier method	Positive pregnancy test on (b) (6) (Day 1 of Study 012). On (b) (6) Day 70, 62 days post-study drug treatment), an obstetric ultrasound showed 14-15 week gestational age fetus. Pregnancy outcome unknown.
Previous Study 010	Alogliptin 25 mg (182 days)		
012/258-7005(a) 40/White	Alogliptin 25 mg (165 days)	Barrier method	Positive pregnancy test on (b) (6) (Day 166 of Study 012). Pregnancy outcome unknown.
Previous Study 007	Alogliptin 25 mg (182 days)		
322OPI-001/ 830-3002 46/Multiracial	Alogliptin 25 mg+ Pioglitazone 45 mg (180 days)	Drospirenone with ethinylestradiol and barrier method	Spontaneous abortion occurred on (b) (6) (Day 197, 17 days post-study drug treatment). Subject history included 2 spontaneous abortions (fall in 1986, lack of glycemic control in 2000) and a 24-week preterm delivery with intrauterine fetal death due to premature rupture of membranes. Concurrent medications at time of the event were drospirenone with ethinylestradiol.

Source: SCS Table 5.j

7.6.3 Pediatrics and Assessment of Effects on Growth

On September 24, 2008, the Pediatric Review Committee (PeRC) agreed with the Division's recommendation that alogliptin studies should be deferred in T2DM subjects 10-16 years old and waived in T2DM subjects 0-9 years old.

The applicant now requests a waiver of alogliptin studies in T2DM subjects 0-9 years old. It states, "studies are impossible or highly impractical because there are too few subjects under 10 years of age diagnosed with T2DM who required pharmacologic intervention". I agree.

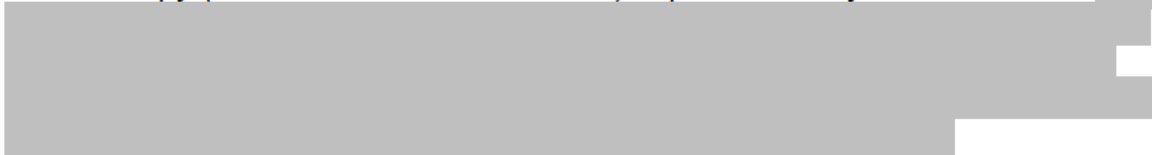

On January 20, 2012, in response to the request we sent to make this program consistent with other recent T2DM pediatric programs, the applicant revised its alogliptin pediatric plan for deferred studies in T2DM subjects 10-17 years (inclusive). It proposes the following three studies:

- SYR-322_104 (104): *A comparative, randomized, open-label, multicenter, single dose, pharmacokinetic, pharmacodynamic and safety study of alogliptin (12.5 mg and 25 mg) between children, adolescents, and adults with type 2 (non-insulin dependent) diabetes mellitus.* The purpose of this study is to confirm that the PK

and PD profiles are similar between children and adults, and that the dose selection (12.5 or 25 mg) is appropriate. Pediatric subjects will have a fasting plasma glucose level ≥ 126 mg/dl, 2-hour plasma glucose level ≥ 200 mg/dl during an oral glucose tolerance test, random plasma glucose level ≥ 200 mg/dl, or HbA1c $\geq 6.5\%$. If taken, the metformin dose must be stable for ≥ 30 days prior to Day 1. Subjects will be enrolled as follows:

- Group 1: 6 T2DM subjects aged 10 to <14 years (6 of either sex)
- Group 2: 18 T2DM subjects aged 14 to <18 years (12 of either sex)
- Group 3: 24 T2DM adults, aged 18-65 years (inclusive)
- *Comment: On December 15, 2011, the applicant submitted revised pediatric PK protocol SYR-322_104 to alogliptin IND 69,707. See my review in DARRTS. It proposed enrollment of 24 (not 36) pediatric T2DM subjects, specifically 6 subjects 10 to <14 years and 18 subjects 14 to <18 years. A comment was sent on January 13, 2012 to the applicant regarding the potential risk it is taking by reducing the sample size in this study which is required by the Pediatric Research Equity Act (PREA). On February 13, 2012, the applicant responded that the protocol allows it to continue to enroll subjects into the study. Thus, it will make every effort to assure meaningful PK data are obtained. The applicant also agreed to analyze AUC and Cmax exposure by age.*

The applicant proposes the following timelines for study 104:

- Study start date: November 11, 2009.
- Study completion date: October 2012.
- Report submission date: April 2013.
- SYR-322_307: *A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of alogliptin compared with placebo as monotherapy (with a metformin control arm) in pediatric subjects with T2DM.* (b) (4)

 - Protocol submission: December 2013
 - Study completion date: January 2019
 - Report submission date: July 2019
 - *Comment: When protocol 307 is submitted, I will consider proposing at least a 16 week primary endpoint as this is the standard primary timepoint for other pediatric T2DM programs.*
- SYR-322_309 (309): *A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of alogliptin compared with placebo when added on to metformin in pediatric subjects with type 2 diabetes.* (b) (4)


(b) (4)

- Protocol submission: December 2013
- Study completion date: January 2019
- Report submission date: July 2019

In emails on November 7-8, 2011, PeRC confirmed that alogliptin does not need to return to the committee (b) (4)

For the alogliptin/pioglitazone FDC the applicant requests a full waiver because “the product would be ineffective or unsafe...in the pediatric age group”. A pediatric protocol (b) (4) was put on clinical hold (b) (4)

On January 11, 2012, PeRC recommended a full waiver for alogliptin/pioglitazone NDA 22-426 and revised language in pediatric section 8.4 to better convey the safety risk.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Please refer to my original reviews of alogliptin NDA 22-271 and alogliptin/pioglitazone FDC NDA 22-426.

7.7 Additional Submissions / Safety Issues

The sponsor has conducted three phase 1 studies, three phase 2 clinical pharmacology studies, five phase 2/3 controlled studies, and four phase 2/3 open-label extension studies in Japan to support approval there (see Table 87). As the Japanese phase 2 and 3 studies were not included in the pooled safety database reviewed above, I will discuss deaths, SAEs, AEs leading to discontinuation, and selected adverse events of interest here.

In long-term, Japanese, phase 2 and 3 studies, 1098 subjects were exposed to alogliptin. A total of 1071 subjects completed at least 52 weeks of treatment. The following seven deaths occurred:

- OCT-001/0008-102 (voglibose [placebo in CCT-001]): Bulldozer accident on day 326
- OCT-001/0009-113 (alogliptin 12.5 mg): Starvation on day 223
- OCT-001/0040-103 (alogliptin 25 mg [placebo in CCT-001]): Past medical history included hepatic steatosis and hepatitis C virus antibody positivity. Abdominal ultrasound was negative for liver tumor on day -56. On day 112, AST and ALT were slightly elevated. On day 218, AST and ALT were elevated. On day 273, treatment was completed. On day 338, abdominal ultrasound revealed

a liver mass. An extended left lobectomy was performed on day 419. The subject died during the surgery due to blood loss.

- OCT-004/0005-401 (alogliptin 25 mg): MI on day 297
- OCT-004/0015-407 (alogliptin 25 mg [placebo in CCT-004]): Lung neoplasm malignant on day 385
- OCT-005_SU/0011-518 (alogliptin 12.5 mg): Gas gangrene on day 315
- OCT-005_SU/0022-512 (alogliptin 12.5 mg [placebo in CCT-005]): Sudden death on day 149

The causes of death in long-term Japanese phase 2 and 3 trials were single events.

When SAEs in controlled, Japanese phase 2 and 3 studies were reviewed, a dose-related trend was not observed (see Table 85). The incidence of SAEs was similar to placebo and comparator groups. Events occurred as single events within the individual trials. No cases of hepatotoxicity, hypersensitivity, or pancreatitis were identified.

Table 85. SAEs (n, %) in Japanese, controlled, phase 2 and 3 studies

Study	Placebo	Alogliptin				Comparator
		6.25	12.5	25	50	
CCT-001	1/75 (1.3)	1/79 (1.3)	1/84 (1.2)	1/80 (1.3)	2/79 (2.5)	2/83 (2.4)
CCT-003	3/75 (4.0)	-	0	1/79 (1.3)	-	-
CCT-004	-	-	1/111 (0.9)	2/113 (1.8)	-	5/115 (4.3)
CCT-005	-	-	3/105 (2.9)	1/104 (1.0)	-	0
CCT-006	-	-	0	2/96 (2.1)	-	0

Source: SCS Appendix 3 Table 2.d

When AEs leading to discontinuation were reviewed in controlled, Japanese, phase 2 and 3 trials, a dose-related trend was not observed (see Table 86). The incidence of events were similar to placebo and comparator groups. Events occurred as single events within the individual trials, although two subjects were withdrawn due to skin and subcutaneous tissue disorders in study CCT-001 (dermatitis bullous and rash).

Table 86. AEs leading to discontinuation (n, %) in Japanese, controlled, phase 2 and 3 studies

Study	n/N (%) Subjects With AEs Leading to Study Drug Discontinuation					
	Placebo	Alogliptin				Comparator (a)
		6.25 mg	12.5 mg	25 mg	50 mg	
CCT-001	2/75 (2.7)	2/79 (2.5)	2/84 (2.4)	1/80 (1.3)	2/79 (2.5)	2/83 (2.4)
CCT-003	3/75 (4.0)	NA	2/76 (2.6)	2/79 (2.5)	NA	NA
CCT-004	NA	NA	1/111 (0.9)	2/113 (1.8)	NA	4/115 (3.5)
CCT-005	NA	NA	4/105 (3.8)	1/104 (1.0)	NA	2/103 (1.9)
CCT-006	NA	NA	0	0	NA	2/96 (2.1)

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Nesina (alogliptin) and (b) (4) (alogliptin/pioglitazone FDC)

Source: SCS Appendix 3 Table 2.h

In summary, the Japanese clinical trial data do not suggest an additional safety signal.

Table 87. Japanese clinical studies

Study	Study Design	Population No. and Type	Treatment Duration	Treatment	40-week, Open-label, Extension Study
CPH-001 Single-dose	Single-dose, randomized, double-blind, placebo-controlled, parallel-group comparison	60 healthy males	Single-dose	Alogliptin 6.25, 12.5, 25, 50, 100, or 200 mg Placebo	
CPH-002 Multiple-dose	Multiple-dose, randomized, double-blind, placebo-controlled study	30 healthy males	7 day	Alogliptin 25, 50, or 100 mg Placebo	
CPH-006 Single-dose	Single-dose, open-label, randomized, 2-period, 2-way crossover study	10 healthy males	2 day (with 7 day washout)	Alogliptin 50 mg	
CPH-003 Age effect	Single-dose, open-label, PK, PD, safety study in subjects of different age	16 healthy males (21-26 or 66-72 years)	Single-dose	Alogliptin 25 mg	
CPH-004 Voglibose	Open-label, single-sequence, PK, safety study to assess the effect of voglibose	10 healthy males	Single-dose on days 1 and 11	Alogliptin 25 mg	
CPH-007 Food-effect	Open-label, randomized, crossover, PK, PD, safety, tolerability, food-effect study	48 healthy males	Single-dose crossover	Alogliptin 12.5 and 25 mg	
CCT-001 Monotherapy	Double-blind, randomized, placebo-controlled, parallel-group, efficacy, safety study	480 T2DM	12 weeks	Alogliptin 6.25, 12.5, 25, or 50 mg Placebo	OCT-001 474 T2DM
CCT-003 Add-on α -glucosidase inhibitor	Double-blind, randomized, placebo-controlled, parallel-group, efficacy, safety study with α -glucosidase inhibitor	230 T2DM who completed phase 2 dose-ranging study	24 weeks	Alogliptin 12.5 or 25 mg Placebo	OCT-003 213 T2DM
CCT-004 Add-on TZD	Double-blind, randomized, placebo-controlled, parallel-group, efficacy, safety study with TZD	339 T2DM on pioglitazone	12 weeks	Alogliptin 12.5 or 25 mg Placebo	OCT-004 331 T2DM
CCT-005 Add-on SU	Double-blind, randomized, placebo-controlled, parallel-group, efficacy, safety study with SU	312 T2DM on SU	12 weeks	Alogliptin 12.5 or 25 mg Placebo	OCT-005 287 T2DM
CCT-006 Add-on	Double-blind, randomized, placebo-controlled, parallel-group,	228 T2DM on a biguanide	12 weeks	Alogliptin 12.5 or 25 mg Placebo	OCT-005 287 T2DM

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Nesina (alogliptin) and (b) (4) (alogliptin/pioglitazone FDC)

metformin	efficacy, safety study with metformin				
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8 Postmarket Experience

Alogliptin was approved for use in Japan on April 16, 2010. Alogliptin/pioglitazone FDC was approved for use in Japan on July 1, 2011. Estimated patient exposure to alogliptin/pioglitazone FDC since launch, based on volume of shipment, through October 15, 2011 was 7,215 patient-years.

On January 20, 2012, the sponsor submitted the third Japanese alogliptin Periodic Safety Update Report (PSUR, April 16, 2011 – October 15, 2011), as requested. As of October 15, 2011, the cumulative patient-years of exposure since launch in Japan, based on volume of shipment was 117,359 patient-years. During the six-month reporting period, 171 cases of adverse drug reactions (22 serious) were received globally and met criteria for inclusion. This included 150 cases for the marketed product in Japan and 21 cases received from ongoing studies worldwide. Skin and subcutaneous tissue disorders made up nearly half of the reports (11 serious, 70 non-serious), including one case of Stevens-Johnson Syndrome and three cases of erythema multiforme. Six cases of pancreatitis were reported. (Fatal necrotizing pancreatitis case TCI2010A04635 was reported in the second PSUR and is described in section 7.4.2.) There were four reports of biochemical Hy's law, including one that came in after the reporting period. See also section 7.4.2 Laboratory Findings for a discussion of the pertinent findings from these postmarketing reports. In summary, the PSUR data supports the safety findings previously identified (i.e., hypersensitivity [particularly, skin and subcutaneous tissue disorders], liver disorders, and pancreatitis).

9 Appendices

9.1 Literature Review/References

Not applicable.

9.2 Labeling Recommendations

Please refer to my review of the original NDA submission and the following sections of this review for my proposed changes and the rationale underlying those changes.

- 1 Recommendations/Risk Benefit Assessment
- 6.1.4 Analysis of Primary Endpoint(s)
- 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations
- 6.1.5 Analysis of Secondary Endpoints(s)
- 7.3.4 Significant Adverse Events
- 7.3.5 Submission Specific Primary Safety Concerns
- 7.6.3 Pediatrics and Assessment of Effects on Growth

9.3 Advisory Committee Meeting

Not applicable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VALERIE S PRATT
02/29/2012

HYLTON V JOFFE
02/29/2012
Please see CDTL memorandum.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 22-271 & 22- Applicant: Takeda
426**

Stamp Date: July 25, 2011

**Drug Name: Alogliptin &
Alogliptin/pioglitazone FDC**

**NDA/BLA Type: Class 2
Complete Response**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				B1
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	x			Sponsor conducted requested renal evaluations.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:	x			New clinical studies include OPI-004, 301, 303, and CV study 402.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			Japanese trials and postmarketing data were included but not pooled.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?			x	Previously assessed. QT-IRT concluded no effect.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested	x			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		x		Sponsor should submit revised plan and timeline. PeRC needed.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __ YES __

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

As requested, you presented adverse events by baseline and endpoint C-G and MDRD renal function in controlled phase 2/3 studies in the Integrated Analysis of Safety (IAS) Tables 8.4.2.7Ra, 8.4.2.9Ra, 8.4.2.6Ra, and 8.4.2.8Ra. However, to facilitate the review, please reanalyze the data and submit the following:

- **N (%) for each treatment group so that, for a given preferred term (PT), all treatment groups fit on one page**
- **Results by System Organ Class (SOC) and PT, but include only those PTs reported in >2% of all alogliptin-treated patients**

In Table 15.3.3.4.2, you provided a listing of all potential CV events and corresponding adjudication outcomes (FAS). Please tally the number of investigator-reported primary CV events that were (a) adjudicated by the CEC to be events and (b) downgraded as “nonevents”.

In CV study 402’s Figure 1, you submitted a graphic display of when CV events occurred relative to the ACS diagnosis. Please also submit the requested subgroup analysis to evaluate the primary and secondary endpoints according to subjects with ACS event ≤ 2 mo or > 2 months prior to randomization.

Please submit a revised pediatric development plan for both NDAs, so we can determine your response to our February 23, 2010 recommendations. Due to the risk of bladder cancer with pioglitazone, we recommend a full waiver for pediatric studies of the alogliptin/pioglitazone FDC.

Please clarify whether or not there are other completed or ongoing phase 3 studies that were not included in the resubmission.

Reviewing Medical Officer

Date

Clinical Team Leader

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

NDA:

- 22-271 Alogliptin
- 22-426 Alogliptin/pioglitazone (alo/pio) FDC

Filing meeting: August 2011**Clinical reviewer:** Valerie S.W. Pratt, M.D.

The general structure of the sponsor's complete response (CR) was agreed to at the February 23, 2010 End of Review (EOR) meeting.

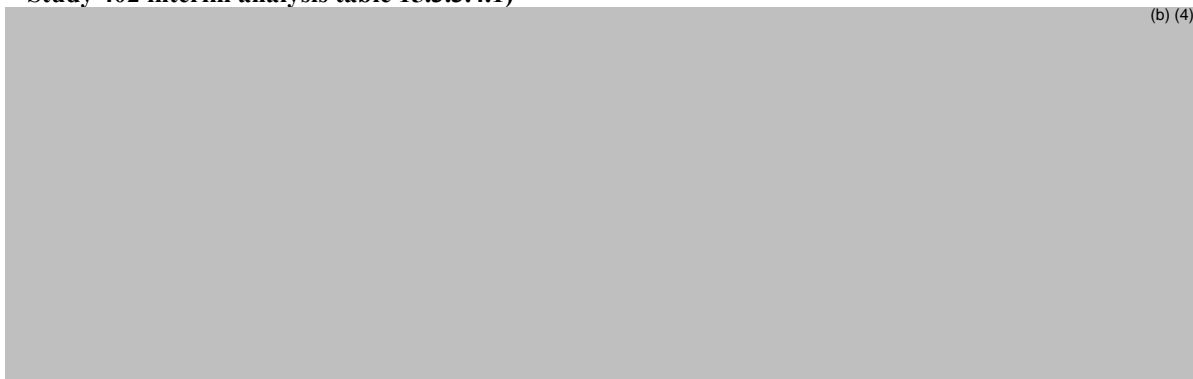
I plan to write one review for both NDA CRs. As previously discussed at the June 20, 2011 meeting, I plan to label in my review which data are interim (i.e. from cardiovascular [CV] study 402 [EXAMINE]) to aid redaction.

NDA Clinical Deficiencies and Summary of the Sponsor's CR:**Alogliptin NDA:**

- Deficiency 1: An unacceptable increase in cardiovascular (CV) risk was not ruled out as per the 2008 guidance.
 - CR: In cooperation with the agency, the sponsor designed and conducted CV study 402 a prospective, double blind study in subjects with type 2 diabetes mellitus (T2DM) and acute coronary syndrome (ACS) randomized to receive placebo or alogliptin 25 mg daily to evaluate the incidence of major adverse CV events (MACE). As agreed, the primary MACE is CV death, nonfatal MI, and nonfatal stroke. The secondary endpoint also included urgent revascularization. Results from the interim analysis were submitted. The sponsor also adjudicated MACE events in 11 other studies. The upper bound of the confidence interval (CI) is <1.8. (See Table 2.)

Table 1. NDA 22271: Summary of all potential CV events and adjudication outcomes (Source: Study 402 interim analysis table 15.3.3.4.1)

(b) (4)



Comment: In Table 15.3.3.4.2, the sponsor provided listing of all potential CV events and corresponding adjudication outcomes (FAS). The sponsor should tally the number of investigator-reported events that were adjudicated by the CEC to be events and those that were downgraded as "nonevents".

Table 2. Summary of MACE analyses (Source: Introduction to the CR Table 1)

	Hazard Ratio (Alogliptin vs Comparator)	Upper Bound of 1-Sided CI
		(b) (4)

Source: IAS Table 8.4.10.1Ra and Study 402 Table 15.3.3.1.1 and Study 402 Table 15.3.3.2.

(a) The hazard ratio was obtained from a CPH model with treatment as the single factor, stratified by geographic region and renal function at Screening. The upper bound is from a repeated 1-sided CI constructed using the group sequential method with an O'Brien-Fleming-type spending function designed to preserve an overall 1-sided false-rejection rate of 2.5%.

(b) The hazard ratio was obtained from a CPH model with treatment as the single factor, stratified by study. The upper bound is from a 1-sided 97.5% CI.

Comment: We discussed at length with the sponsor the duration between ACS diagnosis and randomization. On July 10, 2009, the sponsor chose to keep the inclusion criterion as 15-60 days following diagnosis of ACS, although the agency cautioned that if there were many early events the adequacy of the findings would be a review issue. Please see Appendix 1 for a graphic display of when events occurred relative to ACS diagnosis. The sponsor was asked to submit a subgroup analysis to evaluate the primary and secondary endpoints according to subjects with ACS event ≤ 2 mo or > 2 months prior to randomization. I could not locate this numeric analysis and will request that the sponsor provide it. Amendment 4 of CV protocol 402 changed the ACS inclusion from 15-60 days to 15-90 days.

- As discussed on April 27, 2009, a separate CV study of alo/pio FDC is not required, although ~300 patients on pioglitazone should have been included in the CV study. However, according to study 402's Table 15.1.6.2, only 27 subjects took pioglitazone concomitantly.
- Deficiency 2: A lack of controlled data beyond week 26. The CR should include controlled data for ≥ 500 patients with at least 1-year total exposure to alogliptin to supplement the ~2,000 patients with uncontrolled 1-year exposure.
 - CR: A total of 5,232 subjects have been exposed to alogliptin in controlled phase 2/3 studies. In controlled clinical trials, a total of 526 and 472 subjects received alogliptin 25 mg and all comparators for at least 1 year, respectively.
- Deficiency 3: There was a ~70% increase in mean exposure (AUC) in subjects with mild renal impairment, which may result in the need to dose adjust in these patients. The CR should include analyses of the controlled phase 2/3 program comparing safety and tolerability in subjects with normal renal function to those with mild impairment, using both the Cockcroft-Gault (C-G) and Modification of Diet in Renal Disease (MDRD) equations.
 - CR: Study 006 demonstrated that exposure to alogliptin in subjects with renal impairment increased with decreased renal function. Five of 6 subjects with mild renal impairment had AUC values within the healthy range, although one subject with borderline moderate renal impairment (CrCl 53 ml/min) had a higher AUC value which elevated the mean value. Adverse events by baseline and endpoint C-G and MDRD renal function

in controlled phase 2/3 studies are presented in Integrated Analysis of Safety (IAS) Tables, 8.4.2.7Ra & 8.4.2.9Ra (289 pages each) and 8.4.2.6Ra & 8.4.2.8Ra (291 pages each), respectively.

Comment: As requested, the applicant presented adverse events by baseline and endpoint C-G and MDRD renal function in controlled phase 2/3 studies in the Integrated Analysis of Safety (IAS) Tables 8.4.2.7Ra, 8.4.2.9Ra, 8.4.2.6Ra, and 8.4.2.8Ra. However, to facilitate the review, please reanalyze the data and submit the following:

- *N (%) for each treatment group so that, for a given preferred term (PT), all treatment groups fit on one page*
 - *Results by System Organ Class (SOC) and PT, but include only those PTs reported in >2% of all alogliptin-treated patients*
- On April 27, 2009, we agreed that, when CV study 402 is completed, approximately 200-250 subjects with moderate renal impairment and 100 subjects with severe renal insufficiency should have been exposed to alogliptin for at least one year. As discussed on February 23, 2010 and clarified on September 23, 2010, the need for a postmarketing renal safety study, especially in subjects with severe renal impairment, is a review issue. At this time, according to IAS Tables, the following number of moderate and severe renal insufficiency subjects have been exposed to alogliptin for one year, depending on the renal classification system used and definition of “one year”:
 - MDRD: 31-60 moderate and 1 severe subjects.
 - C-G: 23-40 moderate and 0 severe subjects.
 - Note that ~350-550 alogliptin-treated subjects (~10-16%) had moderate renal impairment at baseline with a mean exposure to alogliptin of ~170 days.

Table 3. NDA 22271: Baseline renal function in controlled phase 2 and 3 studies (Source: Summary of Clinical Safety Table 1 i)

Characteristic	All Comparators (a) N=2910	Alogliptin 25 mg N=3453	All Alogliptin (b) N=5185
Serum Creatinine (mg/dL) (c)			
Mean (SD)	0.98 (0.331)	0.97 (0.276)	0.96 (0.255)
Median	0.90	0.90	0.90
Min, Max	0.4, 8.1	0.5, 4.3	0.4, 4.3
Renal Function (C-G), n (%) (c)			
Normal	1520 (52.2)	1895 (54.9)	3000 (57.9)
Mild Impairment	995 (34.2)	1149 (33.3)	1685 (32.5)
Moderate Impairment	328 (11.3)	357 (10.3)	447 (8.6)
Severe Impairment	24 (0.8)	24 (0.7)	25 (0.5)
Renal Function (MDRD), n (%) (c)			
Normal	501 (17.2)	609 (17.6)	979 (18.9)
Mild Impairment	1805 (62.0)	2235 (64.7)	3397 (65.5)
Moderate Impairment	532 (18.3)	550 (15.9)	749 (14.4)
Severe Impairment	30 (1.0)	31 (0.9)	32 (0.6)

Source: IAS Table 8.3.1Ra.

Note: Actual number of evaluable subjects may vary slightly from treatment group Ns, as presented in source table.

(a) The All Comparators Grouping combines placebo and active comparator groups, which are not shown in the table.

(b) The All Alogliptin Grouping combines 25 mg with the 6.25, 12.5, 50, and 100 mg groups, which are not shown in the table.

(c) Laboratory results were not obtained from a central laboratory for Study 301, so this study is excluded from this summary.

Table 4. Alogliptin exposure (days) by baseline renal function in controlled phase 2 and 3 studies
(Source: Summary of Clinical Safety Table 5.e)

	All Comparators (a)	Alogliptin 25 mg	All Alogliptin (b)
Cockcroft-Gault			
Normal	N=1520	N=1895	N=3000
Mean (SD)	184.2 (104.07)	187.6 (96.17)	175.2 (84.18)
Median (min, max)	182.0 (1, 522)	182.0 (3, 536)	182.0 (2, 536)
Cumulative exposure (subjects-years) (c)	766.36	973.31	1438.84
Mild	N=995	N=1149	N=1685
Mean (SD)	185.2 (109.85)	192.0 (103.57)	178.9 (92.65)
Median (min, max)	181.0 (1, 529)	182.0 (1,550)	182.0 (1,550)
Cumulative exposure (subjects-years) (c)	504.45	603.99	825.41
Moderate	N=328	N=357	N=447
Mean (SD)	163.4 (115.64)	170.1 (105.64)	166.3 (97.68)
Median (min, max)	147.5 (1,533)	177.0 (1, 489)	180.0 (1, 489)
Cumulative exposure (subjects-years) (c)	146.71	166.23	203.50
Severe	N=24	N=24	N=25
Mean (SD)	94.7 (72.64)	139.8 (92.10)	141.4 (90.56)
Median (min, max)	80.0 (18, 260)	126.0 (8, 319)	135.0 (8, 319)
Cumulative exposure (subjects-years) (c)	6.22	9.18	9.68
MDRD			
Normal	N=501	N=609	N=979
Mean (SD)	188.5 (105.03)	192.5 (99.09)	179.8 (85.26)
Median (min, max)	182.0 (3, 522)	182.0 (1, 487)	182.0 (1, 487)
Cumulative exposure (subjects-years) (c)	258.58	320.97	481.83
Mild	N=1805	N=2235	N=3397
Mean (SD)	185.4 (107.21)	189.1 (99.51)	176.7 (88.07)
Median (min, max)	182.0 (1, 533)	182.0 (1, 550)	182.0 (1, 550)
Cumulative exposure (subjects-years) (c)	915.97	1157.35	1643.06
Moderate	N=532	N=550	N=749
Mean (SD)	164.7 (110.32)	173.9 (100.59)	165.5 (91.82)
Median (min, max)	160.0 (1, 470)	181.0 (1, 526)	181.0 (1, 526)
Cumulative exposure (subjects-years) (c)	239.91	261.82	339.47
Severe	N=30	N=31	N=32
Mean (SD)	114.1 (87.50)	148.1 (110.72)	149.2 (109.08)
Median (min, max)	98.0 (17, 303)	130.0 (8, 489)	144.5 (8, 489)
Cumulative exposure (subjects-years) (c)	9.37	12.57	13.07

Source: IAS Tables 8.1.1.2Ra, 8.1.1.3Ra, 8.1.2.2Ra, and 8.1.2.3Ra.

(a) The All Comparators Grouping combines placebo and active comparator groups, which are not shown in the table.

(b) The All Alogliptin Grouping combines 25 mg with the 6.25, 12.5, 50, and 100 mg groups, which are not shown in the table.

(c) Duration of exposure in days is calculated as date of last dose - date of first dose + 1. Last dose date is estimated for subjects ongoing in Study 402 using the earlier of the interim data cut date and the last study drug dispensing date plus the number of days in the dosing interval.

Alogliptin/pioglitazone NDA:

- Deficiencies 1-3: See above.
- Deficiency 4: There were greater incidences of elevated BUN, creatinine, and urinary/creatinine ratios with alo/pio when compared to alogliptin and pioglitazone used separately. Also, more subjects on combination therapy shifted from normal to mild or moderate renal impairment. Manufacture dosage strengths that include 6.25 mg for severe renal impairment.
 - According to the sponsor, for the albumin:creatinine ratio, mean baseline values were higher than the normal range for all treatment groups, due to a few outliers. Furthermore, baseline values were only available for ~64%

- of subjects. Median changes from baseline were small and similar among groups. Shifts from normal to high levels were also similar among groups.
- On February 23, 2010, we agreed with the sponsor that they need not manufacture alo/pio FDC tablets with 6.25 mg alogliptin, because <2% of patients using the FDC are expected to use this dose. Product labeling can address dosing of patients with severe renal impairment through the co-administration of alogliptin and pioglitazone. Note, there is a precedent with sitagliptin/simvastatin FDC NDA 202-343 of not requiring the manufacturing of FDC tablets (with sitagliptin 25 mg) for subjects with severe and end stage renal impairment.

New Clinical Information:

- Five phase 3 placebo- or active-controlled, double-blind studies:
 - OPI-001: Efficacy and safety study of alo + pio in 1,554 subjects on metformin. New to the alogliptin NDA, previously reviewed under the alo/pio NDA.
 - OPI-002: Efficacy and safety study of alo + pio in 655 subjects. New to the alogliptin NDA, previously reviewed under the alo/pio NDA.
 - OPI-004: Efficacy and safety study of alo 25 mg + pio 30 mg vs. pio 45 mg in 803 subjects on metformin.
 - 301: Efficacy (change in postprandial triglycerides) and safety study of alo 25 mg, alo 25 mg + pio 30 mg, or placebo in 71 subjects on diet/exercise or metformin, a sulfonylurea (SU), nateglinide, or repaglinide. *Comment: I do not see proposed labeling based upon this study, although it is included in both NDAs' safety pool.*
 - 303: Efficacy and safety study of alo 25 mg vs. glipizide 5-10 mg in 441 elderly subjects (ages 65-87 years) on diet/exercise or monotherapy.
- Two phase 1 studies: 103 (bioavailability) and 101 (PK of QD vs. BID dosing)
- Interim results from CV study 402
- Japanese studies:
 - CPH studies: 003, 004, and 007
 - CCT studies: 001, 003, 004, 005, and 006
 - OCT studies: 001, 003, 004, 005_MET, and 005_SU
- Japanese postmarketing data: Alogliptin was approved in Japan on April 16, 2010. As of April 15, 2011, approximately 36,500 patients have been exposed (30,423 patient-years exposure). The alo/pio FDC was approved in Japan on July 1, 2011.

Safety:

For the safety analysis in alogliptin NDA 22-271, studies were pooled as shown in Table 5.

Table 5. NDA 22271: Pooled study groups (Source: Summary of Clinical Safety Table 1.a)

Study Group	Studies in Original NDA	Studies in Resubmission
Controlled Phase 2 and 3	003, 007, 008, 009, 010, 011	003, 007, 008, 009, 010, 011, 303, 301, 402 (a), 322OPI-004, 322OPI-001, 322OPI-002 Updated to add 6 studies.
All Phase 2 and 3	003, 007, 008, 009, 010, 011, 012 (b)	003, 007, 008, 009, 010, 011, 012 (c) Not updated or presented; SAE reports are provided for Study 012.
US Phase 1	001, 002, 004, 005, 014, 015, 016, 017, 018, 019, 020, 021, 022, 024, 025, 026, 027, 029 (d)	001, 002, 004, 005, 014, 015, 016, 017, 018, 019, 020, 021, 022, 024, 025, 026, 027, 029 (d) Not updated; 2 new studies (101 and 103) are summarized separately.
Japanese Phase 1	CPH-001, CPH-002, CPH-006	CPH-001, CPH-002, CPH-006 Not updated; 3 new studies (CPH- 003, 004, and 007) are summarized separately with 9 new phase 2/3 Japanese studies.

(a) Interim data (as of 29 April 2011) and SAE reports (as of 31 May 2011) from Study 402.

(b) Interim data (as of 31 January 2008) from Study 012.

(c) SAE reports (as of 31 May 2011) from Study 012.

(d) Renal- (006) and hepatic- (023) impairment studies summarized separately.

The following studies were pooled for alo/pio NDA 22-426's safety analysis: OPI-002, OPI-001, OPI-004, and 301.

The safety data appears generally consistent with the findings from the original submission and that of other DPP4 inhibitors. Rash and pruritis were reported more frequently in the alogliptin 25 mg group when compared to placebo (rash: 1.3% vs. 0.9%; pruritis: 1.2% vs. 0.4%).

Table 6. NDA 22271: Common AEs (≥3%) reported in controlled phase 2/3 studies in the original NDA and the CR (Source: Introduction to the CR Table 5)

Preferred Term	Number (%) of Subjects					
	Original NDA			NDA Resubmission		
	Placebo N=534	Alogliptin 25 mg N=910	All Alogliptin (b) N=1961	All Comparators (a) N=2934	Alogliptin 25 mg N=3500	All Alogliptin (b) N=5232
Any AE	347 (65.0)	586 (64.4)	1260 (64.3)	1651 (56.3)	2052 (58.6)	3146 (60.1)
Back pain	13 (2.4)	27 (3.0)	54 (2.8)	65 (2.2)	92 (2.6)	143 (2.7)
Diarrhea	18 (3.4)	30 (3.3)	58 (3.0)	105 (3.6)	94 (2.7)	138 (2.6)
Edema peripheral	14 (2.6)	32 (3.5)	59 (3.0)	64 (2.2)	88 (2.5)	129 (2.5)
Headache	21 (3.9)	40 (4.4)	86 (4.4)	103 (3.5)	136 (3.9)	214 (4.1)
Hypertension	16 (3.0)	32 (3.5)	61 (3.1)	85 (2.9)	101 (2.9)	159 (3.0)
Nasopharyngitis	27 (5.1)	49 (5.4)	97 (4.9)	98 (3.3)	137 (3.9)	213 (4.1)
Upper respiratory tract infection	28 (5.2)	32 (3.5)	71 (3.6)	70 (2.4)	122 (3.5)	180 (3.4)
Urinary tract infection	25 (4.7)	37 (4.1)	93 (4.7)	108 (3.7)	130 (3.7)	212 (4.1)

Source: IAS Table 8.4.2.1Rc and IAS Table 8.4.2.1Ra.

(a) The All Comparators Grouping combines placebo and active comparator dose groups, which are not shown in the table.

(b) The All Alogliptin Grouping includes the alogliptin 6.25, 12.5, 50, and 100 mg dose groups, which are not shown in the table.

Adverse events of special interest, as discussed on February 23, 2010, include infections, angioedema, malignancy, pancreatitis, skin reactions, hepatotoxicity, and renal safety.

Pediatric Studies:

The sponsor completed and submitted a 4-week oral toxicity study in juvenile Sprague-Dawley (SD) rats and an 8-week SD rat male reproductive toxicity study.

On July 28, 2011, we received email confirmation from the sponsor that the original pediatric filings are still applicable. Our last PREA-related discussion was held with the sponsor at the February 23, 2010 End of Review (EOR) meeting. At that time, the sponsor proposed the following:

- SYR-322_104: A comparative, randomized, open-label, multicenter, single dose, PK, PD, and safety study of alogliptin (12.5 and 25 mg) between children, adolescents, and adults with T2DM.
- SYR-322_307: An international, multicenter, randomized, double-blind, placebo-controlled, metformin-referenced study to evaluate the efficacy and safety of alogliptin compared with placebo in subjects aged 10- 17 years with T2DM.
 - First subject to be randomized: 2/28/11
 - Last subject to be randomized: 2/28/13
 - Last subject out: 2/27/14
 - Design: (b) (4)

(b) (4)

(b) (4)

Comments:

- *The sponsor should submit a revised pediatric development plan for both NDAs, so we can see how they responded to our February 23, 2010 recommendations.*
- *Alogliptin NDA 22-271 was discussed at PeRC on September 28, 2008. The decision was to waive studies in 0-9 years and defer studies in 10-16 years.* (b) (4)

(b) (4)

Given the change in age group and study duration, we will contact PeRC and ask whether these changes can be addressed with PeRC via email or whether PeRC wants us to return for a face-to-face meeting for alogliptin NDA 22-271 (perhaps these changes can be addressed when we go to PeRC for the alogliptin/pioglitazone NDA – see below).

- *Alogliptin/pioglitazone NDA 22-426 did not go to PeRC previously and needs to go during this review cycle. As part of the clinical development of pioglitazone, a PK study was conducted in T2DM subjects 12 to <17 years and found to be similar to adults.* (b) (4)

(b) (4)

However, a partial clinical hold exists for pediatric studies of pioglitazone. As previously stated, the sponsor should submit a revised pediatric development plan with timelines before we take NDA 22-426 to PeRC.

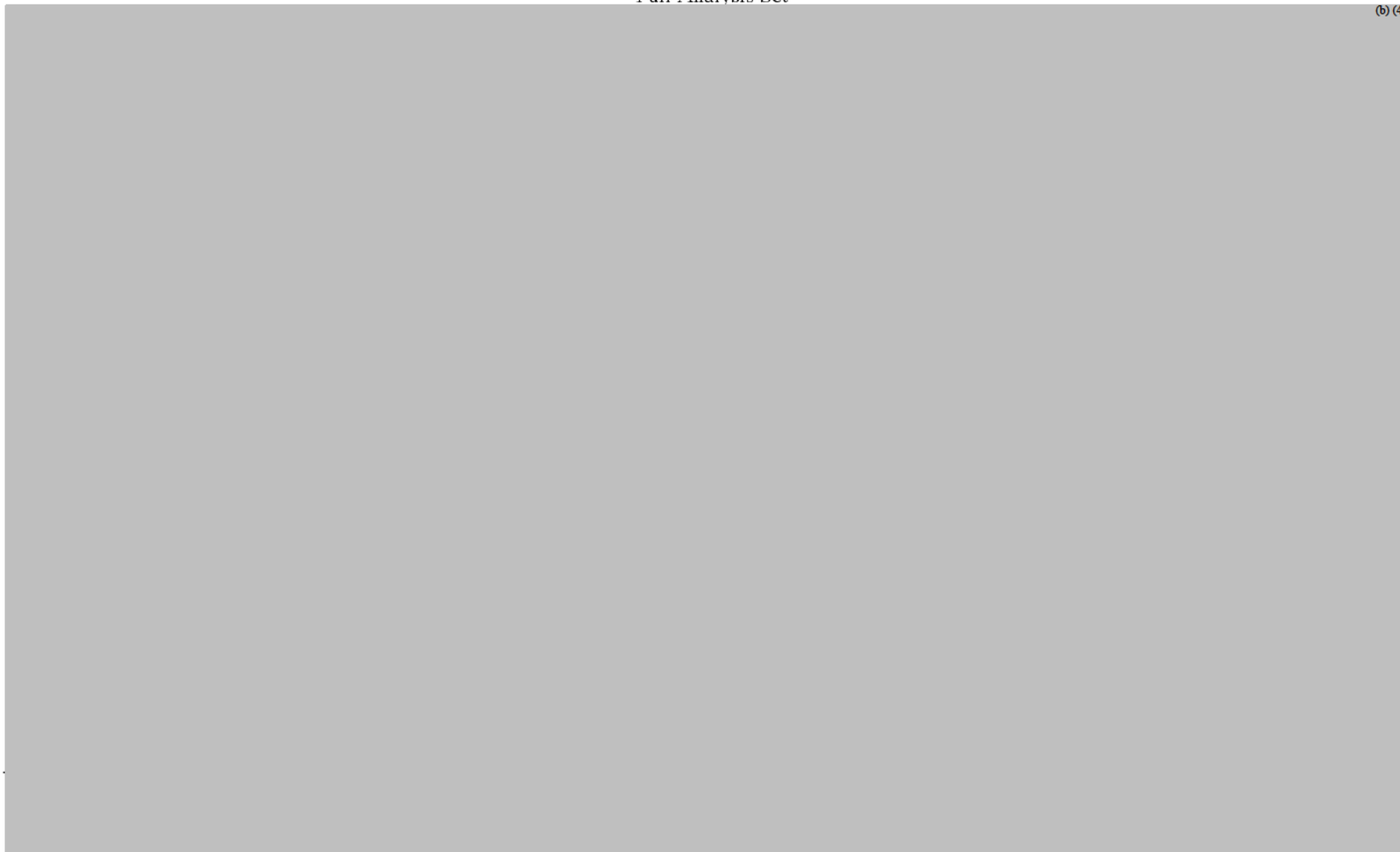
As discussed on February 23, 2010, the sponsor is interested in pursuing a Written Request after approval.

Appendix 1. NDA 22-271: Event chart for time from index ACS event to first primary MACE composite event (Full analysis set). Source:

TGRD
SYR-322_402 Ad Hoc Analysis

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Figure 1
Event Chart for Time from Index ACS Event to First Primary MACE Composite Event
Full Analysis Set



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VALERIE S PRATT
08/09/2011

HYLTON V JOFFE
08/09/2011

**Medical Officer Safety Review
Division of Metabolism and Endocrinology Products (DMEP)**

IND 69,707 Alogliptin SDN 633 (May 5, 2011)

- Contents: Cardiovascular (CV) protocol 402 amendment 8

NDA 22-271 Alogliptin SDN 47 and 22-426 Alogliptin/pioglitazone fixed dose combination (FDC) SDN 28 (May 25, 2011)

- Contents: Type C meeting request

Sponsor: Takeda

Indication: Type 2 diabetes mellitus (T2DM)

Medical Reviewer: Valerie Pratt, M.D.

Medical Team Leader: Hylton Joffe, M.D.

Background: A complete response letter was sent to the sponsor of alogliptin NDA 22-271 on June 26, 2009. The following three clinical deficiencies were noted:

- A numerical imbalance in serious CV events, not favoring alogliptin.
- Inclusion of only uncontrolled data beyond week 26
- Approximately 70% increase in area under the time-concentration curve (AUC) in subjects with mild renal impairment, which suggests there may be a need to adjust the dosage in these subjects

While the alogliptin NDA was under review, FDA published the 2008 Guidance to Industry, *Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. This guidance asks sponsors to rule out an unacceptable increase in cardiovascular risk to support approval of new treatments for type 2 diabetes. Two other NDAs for type 2 diabetes (saxagliptin and liraglutide) were also under review when this guidance was issued. FDA determined that all three NDAs would need to show adequate evidence of cardiovascular safety to support approval. Because the sponsor for alogliptin was unable to do so, the alogliptin NDA was not approved and the sponsor was required to provide evidence of CV safety that satisfies the 1.8 upper bound criterion in the above-mentioned Guidance.

On July 29, 2009 (SDN 423), the sponsor submitted amendment 1 to CV protocol SYR-322_402 (402), *A multicenter, randomized, double-blind, placebo-controlled study to evaluate CV outcomes following treatment with alogliptin in addition to standard of care in subjects with type 2 diabetes and acute coronary syndrome*, which included agreements reached during previous teleconferences (May – July 2009) and communications (July 15, 2009). The protocol was reviewed by DMEP and the Division

of Cardio-Renal Products (DCRP). Comments were conveyed on January 4, 2010. An additional teleconference was held with the sponsor on January 14, 2010. On April 2, 2010, the sponsor submitted CV protocol 402 Amendments 4 and 5, which incorporated agreements reached during the aforementioned teleconference.

On July 13, 2010, the sponsor submitted Amendment 6 which clarified where documents for safety reporting would be sent and introduced (b) (4) as an additional vendor responsible for defined trial activities.

On September 3, 2010, Amendment 7 updated the protocol in regards to additional safety monitoring and withdrawal criteria.

The sponsor now submits amendment 8 to CV protocol 402 as well as a type C meeting request to discuss aspects of the upcoming NDA resubmissions in July 2011.

IND 69,707 SDN 633: CV Protocol 402, Amendment 8

Summary of Protocol 402: Study 401 is a multicenter, randomized, double-blind, placebo-controlled, 2-arm study, comparing the CV safety of alogliptin to placebo, in addition to standard care in T2DM subjects with acute coronary syndrome (ACS). The primary major adverse cardiac event (MACE) endpoint includes CV death, nonfatal myocardial infarction (MI), and nonfatal stroke. A sufficient number of subjects will be screened so that approximately 5400 subjects will be randomly assigned to study drug treatment (alogliptin or placebo).

The overall duration of the study is dependent on the number of MACE. However, the maximum length of follow-up is ~4.75 years. The length of study participation for each subject will vary but is estimated to be a median of 2 years.

Subjects will participate in a Screening Period lasting up to 2 weeks. Subjects must have a diagnosis of T2DM who either are receiving monotherapy or combination antidiabetic therapy (with the exception of a dipeptidyl peptidase-4 [DPP-4] inhibitor or glucagon-like peptide-1 [GLP-1] analogue). Subjects must have an HbA1c level between 6.5% - 11.0% (inclusive) at Screening (or, between 7.0% - 9.0% [inclusive, see also proposed change below] if the subject's antidiabetic regimen includes insulin). In addition, subjects must have a diagnosis of ACS within 15 to 90 days prior to randomization. Randomization will be stratified based on country and screening renal function (normal/mild impairment versus moderate/severe impairment).

Subjects with normal renal function or mild impairment (eGFR ≥ 60 ml/min using the Modification of Diet in Renal Disease [MDRD] formula) will receive alogliptin 25 mg daily or placebo. Subjects with moderate renal impairment (eGFR between ≥ 30 and < 60 ml/min) will receive alogliptin 12.5 mg daily or placebo. Subjects with severe renal impairment (eGFR < 30 ml/min) will receive alogliptin 6.25 mg daily or placebo. Medication doses will be adjusted during the study as needed according to renal function.

A Steering Committee will oversee the conduct of the study. A Data Monitoring Committee will oversee the safety data for the study. An independent CV Endpoints Committee (CEC) will adjudicate potential MACE events.

Proposed Changes, Rationales, and Response (in bold):

Change #1. Increase of HbA1c upper limit to 11.0% for subjects on insulin (rather than 9%).

Rationale: This modification was determined to be appropriate as all subjects will be allowed to have adjustments made to their antidiabetic treatments throughout the study therefore adequate glycemic control can be achieved.

Change #2. Increase number of participating sites from 1000 to 1300.

Rationale: The number of sites participating in the study has been increased due to expansion into additional countries to assist in subject recruitment for the study.

Change #3. Requirement for morning study visits has been removed.

Rationale: To allow flexibility in subject visit scheduling. Subjects are not required to return in the morning, only after an 8 hour fast.

Change #4. Revisions to statistical sections.

- “Countries will be pooled into geographic regions for statistical analysis purposes. Region assignment of individual countries will be summarized in the statistical analysis plan.”
- Revised Text: “If the upper bound of a 1-sided repeated CI for the hazard ratio is demonstrated to be less than 1.3 for the primary MACE composite, a 1-sided *repeated* CI will be generated for the hazard ratio (alogliptin to placebo) of the secondary MACE composite using the *same critical value*, the FAS and a Cox model as described above. (b) (4)

Note: Secondary endpoints include CV death, nonfatal MI, nonfatal stroke, and urgent revascularization due to unstable angina.

Rationale: Clarification and update of statistical analyses. To ensure that the overall false-rejection rate for the study is 2.5%.

Internal Comment: See also Dr. Eugenio Andraca-Carrero’s (Division of Biometrics 7) review. The proposed change was found to be acceptable by statistics.

Change #5. Update to contact information in various sections.

Rationale: Information updated to include contact information as appropriate for sites utilizing (b) (4) and Japan Clinical Operations.

Change #6. Addition of Principal/Coordinating Investigator.

Rationale: Information updated to include contact information for Principal Investigator/Coordinating Investigator.

Change #7. Addition of Exploratory Endpoint of total incidence of revascularizations.

Rationale: Addition of Exploratory Endpoint which has clinical impact on Quality-of-Life as well as cost for treating subjects with T2DM and acute coronary syndrome.

Change #8.

(b) (4)

Rationale: Added additional manufacturing location.

Internal Comment: This change was found to be acceptable by Dr. Su Tran (CMC).

Change #9. Clarification of process for rechallenging study medication due to IP discontinuation, liver safety withdrawal criteria and renal safety withdrawal criteria.

- Revised Discontinuation Text: “A subject’s study medication may be temporarily suspended or permanently ceased at any time at the discretion of the investigator. Subjects are free to stop taking study medication at any time without prejudice to further treatment. Subjects who stop taking medication will continue in the study and will follow the schedule of study procedures as defined in the protocol until the required number of MACE composite events have occurred. If a subject refuses to return to the clinic for study visits, information can be collected via telephone contact reports at the time of the regularly scheduled study visits; however, this is not preferred nor recommended.

Subjects who temporarily suspend or permanently discontinue study medication may be re-started on study medication at anytime during the course of the study at the discretion of the investigator and with the approval from the Medical Monitor.”

- Revised Liver Text: In each of these instances, the patient should be followed to a satisfactory conclusion (ie, until the adverse event resolves, the laboratory value returns to baseline, or the condition becomes stable). *If a reasonable alternative etiology can be established for the event, study medication may be re-started at the discretion of the investigator, after consulting with the Medical Monitor.* If either of the above circumstances occurs at any time during the study, the abnormality should be documented as an AE, and a LFTA Form completed. If a subject meets liver safety criteria and must discontinue study drug, the subject will continue to be followed per the protocol schedule until the study is completed.”
- Revised Renal Text: “The subject should be followed to a satisfactory conclusion of this event (ie, until the AE resolves, the laboratory value returns to baseline, or the condition becomes stable). *If a reasonable alternative etiology can be established for the event, study medication may be re-started at the discretion of the investigator, after consulting with the Medical Monitor.* If a subject meets

renal safety criteria and study drug is discontinued, the subject will continue to be followed per the protocol schedule until the study is completed. If the subject refuses to return for study visits, then telephone visits may be conducted; however, this is not preferred nor recommended. The reason for discontinuation of study drug should be listed as an AE.”

Rationale: Clarification given for study drug reinitiation.

Change #10. Addition of the word optional for completing genitourinary examination

Rationale: To allow flexibility for the completion of genitourinary exams during complete physical exams.

Change #11. Removal of requirement of reporting partner pregnancies for male subject.

Rationale: Cumulative evidence that alogliptin does not result in spermatotoxicity

Note: Reproductive toxicity studies demonstrated a slightly increased percentage of sperm abnormalities in males (NOAEL \approx 67x MRHD). The male findings were consistent with sporadic male reproductive toxicity seen in other non-clinical toxicity studies at high alogliptin doses. Nevertheless, rat sperm abnormalities did not affect fertility.

Internal Comment: This change is acceptable, as discussed with Dr. David Carlson (nonclinical).

Change #12. Clarification of when to call into the interactive voice response (IVR) system when study drug is permanently discontinued.

Rationale: To instruct sites to enter each scheduled study visit (clinic or telephone) into IVR system.

Change #13. Revision to wording regarding when to report a CPK elevation as an AE.

- Revised Text: In the event that an elevation in a subject’s CPK level $>2x$ ULN is observed, the investigator should determine whether or not symptoms consistent with cardiac etiology coincided with this elevation. If cardiac symptoms were reported at the time of the CPK elevation, additional testing with ECG, CPK fractions, and troponins should be considered. *Only elevations in CPK $>2X$ ULN, which are considered to be clinically significant, should be reported as an AE.*”

Rationale: To clarify that CPK >2 X ULN, which are considered clinically significant are to be reported as an AE.

Change #14. Changes to Appendix E Hospitalization with Unstable Angina Requirement.

- Revised Text: “A new finding of ST-segment depression of at least 0.05 mV, or transient (<20 minutes) ST-segment elevation of at least 0.1 mV, or T-wave inversion of at least 0.3 mV in at least 2 *contiguous* leads *AND*”

Rationale: To correct typographical errors and clarify that the required ECG changes must be observed in at least 2 contiguous leads.

Reviewer’s comments: Change #4 was found to be acceptable by Dr. Janice Derr (statistics) and Dr. Eugenio Andraca-Carrero (Division of Biometrics 7). Changes #8 and #11 were found to be acceptable by Dr. Su Tran (CMC) and Dr. David Carlson

(nonclinical), respectively. Change #13 is acceptable because we will focus our analyses on the objective CPK data. I find the remaining proposed revisions to be acceptable.

NDA 22-271 SDN 47 and NDA 22-426 SDN 28: Type C Meeting Request

Questions, Rationales, and Responses (in bold):

Question #1. As has been discussed previously with the Division, Takeda has established appropriate firewalls to ensure that the ongoing conduct of EXAMINE is being performed by individuals who have not been made aware of the results from the interim analysis. Based on the outcome of the Agency's review, EXAMINE could be ongoing at the time of the Agency's approval of alogliptin.

Has the Agency considered how the integrity of the double blind study will be maintained after approval in light of the Freedom of Information Act (FOI) (e.g. redaction of the *EXAMINE interim analysis results in reviews posted on the Drugs@FDA website*)?

Internal Comment: Reviewers should label, in their NDA reviews, which results are interim and should be redacted.

Response #1: Yes. Interim results from ongoing cardiovascular outcomes trials for anti-diabetic medications will be redacted from FDA's clinical and statistical reviews prior to posting of these reviews on the FDA website. In addition, these interim results will not be included in the approved package insert.

Question #2. During the Post-Action Feedback meeting with the Agency on January 12, 2010 and the End-of-Review meeting held on February 23, 2010, Takeda stressed its high level of commitment to submitting complete and high quality re-submissions for the alogliptin and alogliptin/pioglitazone FDC. In addition, Takeda emphasized the need for timely communications, transparency and review efficiencies within the Agency following the re-submissions. To that end, Takeda would like the Agency to re-confirm the following:

a) The user fee goal date for a re-submission is 6 months from receipt of the amendment to the NDA. If the alogliptin and alogliptin/pioglitazone FDC re-submissions are provided to the Agency at the same time, they will be on the same review clock and have the same user fee goal date.

Response #2a. Yes.

b) Labeling discussions will begin at least 4 weeks prior to the scheduled action dates should the data from the application support approval.

Response #2b: Yes.

c) The proposed tradenames for alogliptin and alogliptin/pioglitazone FDC (Nesina and (b) (4) respectively) will be reviewed within 90 days of the NDA re-submissions.

Response #2c. Yes. Please refer to the Guidance for Industry entitled *Contents of a Complete Submission for the Evaluation of Proprietary Names* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf>).

d) In general, the re-submission review timelines will be communicated to the Sponsor so that Takeda can promptly provide responses to the Agency's requests, ensuring efficiency of the overall review process.

Response #2d. We will establish internal timelines to ensure timely review of your re-submissions within the 6-month review clock. Early in the review process, we will inform you of when we expect to communicate proposed labeling and, if necessary, any requests for postmarketing commitments or postmarketing requirements. If we have information requests during our review we will send these to you as soon as they are identified.

e) Does the Agency anticipate conducting clinical site inspection(s) based on the additional studies included in the re-submission? If so, what is the timing with respect to the review clock for the conduct and completion of the site inspection(s)?

Response #2e. A determination of whether or not clinical site inspections need to be conducted will be made at the time of NDA re-submission. Because of the short timeline, in order for us to efficiently prepare for inspections, we request that the information in the attached documents be submitted at the time of the submission of the application.

Internal Comment: For the attachments, please see the final preliminary meeting comments that were entered into DARRTS on June 17, 2011.


f) Although no new Chemistry, Manufacturing and Controls (CMC) information will be included in the re-submissions, does the Agency anticipate conducting Prior Approval Inspections (PAIs) of the manufacturing facilities?

Response #2f. Yes, we may decide to conduct a PAI. Form FDA 356h of the resubmissions should include all the facilities involved in the manufacture and testing of the commercial drug substance and drug product and a statement that they are immediately ready for GMP-inspection.

g) Can the Agency confirm that if the issues cited in the Complete Response Letter have been adequately addressed and no further issues are identified during the review, an Advisory Committee meeting would not be necessary?

Response #2g. An advisory committee (AC) meeting will likely not be needed if we determine that you definitively address the deficiencies in the Complete Response letter and we do not identify any unexpected efficacy or safety findings during our review. A final determination of whether or not an AC meeting will be required will be made after NDA re-submission.

Question #3. Takeda would like to propose language to be included in the prescribing information (e.g. under Adverse Reactions) with the available cardiovascular safety data on alogliptin. (b) (4)



While Takeda recognizes that the Agency cannot comment on specific labeling language at this time, will the Agency consider Takeda's proposal to provide physicians cardiovascular safety information based on a meta-analyses that includes integration of the EXAMINE interim data?

Response #3. No. FDA is not permitting cardiovascular outcomes data that meet the 1.8 cutpoint in approved labeling, regardless of whether these data are derived from completed or ongoing trials. Approval of a new treatment for type 2 diabetes implies that the 1.8 cutpoint has been met because our Guidance states that this cutpoint must be met to support approval. Please also see our response to Question 1.

Please also respond to the following questions:

1. Question 3 states "In order to preserve the integrity of the ongoing EXAMINE trial, only data from the integrated meta-analysis that includes EXAMINE would be proposed for label inclusion." However, at our April 27, 2009 meeting, we agreed that the cardiovascular (CV) study should stand alone for assessing CV safety. Please clarify to which meta-analysis you are referring.

2. What is the status of the EXAMINE study with respect to the pre-specified group sequential procedure corresponding to the 1.8 hazard ratio non-inferiority margin? The procedure specifies interim analyses at 80, 100, and 125 adjudicated primary MACE events and a final analysis at 150 events. We would like to know the total number of adjudicated primary events in the MACE composite in EXAMINE that were analyzed and used as the basis of the decision to re-submit the NDA. We would also like to confirm (yes or no) that the test statistic for this analysis satisfied the group sequential boundary. However, until the time the NDA is re-submitted, we would like to remain blinded to the number of events in each treatment arm and to the value of the test statistic.

3. What is the anticipated number of patients with at least one year of exposure to study drug in the EXAMINE trial at the time of NDA resubmission? What is the anticipated mean exposure for the trial?

4. Clarify what else you are planning to include in the NDA resubmission besides the interim results from EXAMINE.

Question #4. As per Takeda's agreement with the Agency, Takeda is planning on continuing the EXAMINE trial until the protocol planned final analysis. However, the Data Monitoring Committee (DMC) has recently requested guidance on how to proceed with reviewing the cardiovascular safety data from the ongoing EXAMINE trial should the MACE hazard (b) (4)

(b) (4) Takeda would like to discuss guidance that can be given to the DMC to ensure that the study is not stopped until the study has (b) (4) Following the NDA re-submissions, Takeda plans to submit a meeting request to discuss this topic further.

Does the Agency agree with Takeda's proposal?

Response #4. Based upon information submitted in your briefing jacket, it is unclear (b) (4) would be incorporated into your protocol. Based on the pre-specified statistical plan for assessing the 1.3 margin, it appears that you will not (b) (4). More detailed information on your proposed changes to the study design and stopping rules is needed in order to evaluate your proposal. With that being said, the following are some points to consider.

(b) (4) Please, therefore, submit your meeting request to discuss this topic prior to NDA resubmission and our review of the data.

(b) (4) Adequate statistical and operational justification should be provided for any proposed changes, including details on the alpha-spending function and power. If previously submitted simulations are no longer representative of the modified trial, a new set of simulations may be required. All proposed changes should also be discussed and approved by the DMC to ensure they are in the best interest of the patients. If at some point the DMC recommends

prematurely stopping EXAMINE, we recommend that you notify FDA before stopping the trial.

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/s/

VALERIE S PRATT
06/21/2011

HYLTON V JOFFE
06/21/2011

Summary Basis for Regulatory Action

Date	June 20, 2009
From	Mary H. Parks, M.D.
Subject	Division Director Summary Review
NDA/BLA #	22-271
Supplement #	
Applicant Name	Takeda Pharmaceuticals
Date of Submission	December 27, 2007
PDUFA Goal Date	October 27, 2008
Proprietary Name / Established (USAN) Name	Nesina® (alogliptin)
Dosage Forms / Strength	6.25-mg, 12.5-mg, and 25-mg tablets
Proposed Indication(s)	Glycemic control in adults with type 2 diabetes mellitus
Action:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Valerie Pratt, M.D.
Statistical Review	Janice Derr, Ph.D. J. Todd Sahlroot, Ph.D.
Pharmacology Toxicology Review	David Carlson, Ph.D. Todd Bourcier, Ph.D.
CMC Review/OBP Review	Suong Tran, Ph.D. Chien-Hua Niu, Ph.D.
Microbiology Review	NA
Clinical Pharmacology Review	Sang Chung, Ph.D.
DDMAC	No reviews completed at this time (deferred)
DSI	Susan Leibenhaut, M.D.
CDTL Review	Hylton Joffe, M.D., M.M.Sc.
OSE/DMEPA	Jinhee Jahng, Pharm.D. Kellie Taylor, Pharm.D.
OSE/DPV	NA
OSE/DRISK	No reviews completed at this time (deferred)

Division Director Memo

1. Introduction

Alogliptin is a dipeptidyl peptidase-4 enzyme inhibitor (DPP4-inhibitor) developed for the management of hyperglycemia in patients with type 2 diabetes mellitus (T2DM). This is a relatively new class of anti-diabetic therapy whose mechanism of action targets the impaired release and availability of the incretin hormone, glucagon-like peptide-1 (GLP-1) in patients with type 2 diabetes. GLP-1 and another incretin hormone, glucose-dependent insulintropic polypeptide (GIP), are released from the gastrointestinal tract in response to meals to further stimulate insulin release. Because GLP-1 is rapidly degraded by the serine protease, dipeptidyl peptidase 4, an inhibitor of this enzyme will prolong the half-life of this incretin hormone allowing for a more sustained effect on glucose control.

Unlike other anti-diabetic therapies, which control hyperglycemia through stimulation of insulin release from the pancreas (e.g. sulfonylureas or glinides), incretin-based therapies control hyperglycemia through a glucose-dependent manner thereby mitigating the risk of hypoglycemia. GLP-1 receptor agonists are another class of incretin-based therapies. These agents are manufactured to avoid susceptibility to enzyme degradation while maintaining sufficient cross-reactivity with the GLP-1 receptor to impart similar effects on glucose control as the native hormone.

Currently, Januvia (sitagliptin) is the only marketed DPP4-inhibitor in the United States. One other DPP4-inhibitor (Galvus or vildagliptin) was not approved due to hepatic and skin lesion safety concerns. The Division is simultaneously reviewing alogliptin and another DPP4-inhibitor, saxagliptin, and a GLP-1 receptor agonist, liraglutide.

2. Background

Over the past two to three years, concerns regarding the cardiovascular safety profile of certain anti-diabetics have resulted in much debate within the scientific and regulatory community on the adequacy of the development programs for anti-diabetic therapies to ensure that these drugs do not contribute to excess cardiovascular mortality and morbidity in a patient population that is already at 2- to 4-fold risk of dying from heart disease.

On July 1 and 2, 2008, the FDA convened a public advisory committee meeting to discuss the role of CV assessment in the pre- and postmarket settings. The pivotal question raised to the panel members was:

It should be assumed that an anti-diabetic therapy with a concerning CV safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk. (vote yes/no requested).

The outcome was 14 “yes” and 2 “no” votes.

Following this advisory committee meeting, the FDA issued a Final Guidance to Industry in December 2008 titled, *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. With its release, the FDA also publicly announced that the recommendations in this guidance will be applied to all ongoing diabetes development programs and marketing applications pending before the agency. At the time of its issuance, the FDA had three NDAs under review: alogliptin (Nesina), saxagliptin (Onglyza), and liraglutide (Victoza). Saxagliptin and liraglutide were each presented at a public advisory committee meeting on April 1 and 2, 2009, respectively, and will be discussed in separate memos. Alogliptin was not presented before an advisory committee panel because it was deemed deficient for approval.

The deficiency precluding approval of this NDA was insufficient data to ensure an adequate CV risk assessment based on the recommendations outlined in the December 2008 guidance. In order to gain approval applicants must compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8. Because none of these 3 NDAs conducted its Phase 2/3 trials with knowledge of these new recommendations, the review division applied a uniform approach to assessing risk for these NDAs. This approach is clearly described by Drs. Joffe and Pratt in their clinical reviews. For alogliptin, all different analyses performed by Dr. Janice Derr from the Office of Biometrics were associated with an upper bound of the 95% CI exceeding the 1.8 goal post.

In addition to this primary deficiency, review of this NDA identified other safety concerns discussed in this memo which will need to be better characterized in ongoing and future trials.

3. CMC/ /Device

Please see ONDQA reviews from Drs. Fraser, Niu, and Tran. Dr. Joffe has listed the key findings from the CMC review in his cross-discipline team leader memo. The final recommendation from ONDQA summarized in Dr. Tran’s review dated 3/20/09 is approval. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

Please see reviews of Drs. Carlson and Bourcier. Final recommendation – approval.

Overall, the nonclinical program has not detected serious safety concerns at exposures corresponding to the maximal recommended human dose (MRHD) of 25 mg qd. Drug-related deaths were only observed in multi-dose studies in mice and rats, but at 50- and 400-fold the MRHD, respectively. Target organs of toxicities included testes, kidney, liver, bladder, and lung; however, these findings were observed only at $\geq 280\times$ MRHD.

Alogliptin is not teratogenic at doses exceeding 200x the expected human exposure and pregnancy category B is recommended. Recently, nonclinical studies showed embryofetal toxicity with another DPP4-inhibitor, saxagliptin, when used in combination with metformin. This was an unexpected finding as saxagliptin alone was not associated with any teratogenicity at many-fold exposures above clinical doses and metformin is not known to be teratogenic. The applicant for saxagliptin has been informed that it will need to conduct a 2nd study in which three treatment groups are evaluated (DPP4-inhibitor alone, metformin alone, and the combination of the two products). As a result of the saxagliptin findings, Takeda has also been notified that it will need to conduct a similar rat embryofetal study. The applicant has agreed to conduct such a study. The action letter will need to state that these results will need to be submitted to the agency before or at the time of the resubmission for alogliptin.

Some other DPP4-inhibitors in development have been associated with peripheral skin lesions, cutaneous sores, peripheral edema, and severe swelling associated with CK and LFT elevations. As a result, all manufacturers are required to conduct a 13-week monkey study to evaluate the potential for causing the peripheral lesions which may be due to non-selectivity of the compound for other dipeptidyl peptidases. Alogliptin is highly selective for DPP4 with a similar profile to Januvia (sitagliptin). The 13-week monkey study did not reveal any evidence of peripheral lesions, clinically, macroscopically, or histologically. The NOAEL in this 13-week monkey study provided a 31-fold safety margin over the expected human exposure.

A focus on thyroid cancers in the carcinogenicity studies was prompted by recent concerns of c-cell tumors in animals dosed with the long-acting GLP-1 analogues. In rats, there was an increased incidence of thyroid c-cell adenomas and carcinomas in males, but this was at 288x MRHD. There were no thyroid tumor findings in mice.

As discussed under Section 5, the kidney is a major route of excretion and moderate, severe and ESRD increase alogliptin levels sufficiently to warrant dose adjustments in these patients. As noted in Dr. Carlson's review, the kidney is a target organ of toxicity and drug concentrations are elevated in the kidney and renal medulla at approximately 7-fold compared to plasma levels. However, the only notable finding was chronic progressive nephropathy observed in female rats at 279x MRHD, providing a very reassuring safety margin with respect to this special population.

In the 9-month dog study, animals had clinical signs of reddened/flushing ears and face, along with body and facial swelling. However, the animals were able to continue dosing throughout the duration of the study and these symptoms did not appear dose-limiting. This finding may suggest a hypersensitivity-like reaction which was not observed pre-clinically/pre-marketing with the only marketed DPP4-inhibitor, Januvia, but was detected postmarketing. Since its approval, the label for Januvia has been updated to include reports of hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome under the Warnings and Precautions section of the package insert. There was a higher incidence of hypersensitivity-like reactions with alogliptin versus control in the Phase 2/3 trials (see Section 8 below).

As noted by Drs. Joffe, Carlson, and Bourcier, there was no evidence of CV toxicity from the non-clinical studies. Although these studies are performed in healthy, non-diabetic animals, other anti-diabetic compounds with known clinical cardiac toxicity (e.g, PPAR-gamma agonists) have had similar findings noted in non-disease animal models.

5. Clinical Pharmacology/Biopharmaceutics

(Please see OCP review dated 8/28/08 in DFS.) Final recommendation – approval.

Notable findings from the OCP review that I will briefly highlight in my memo include:

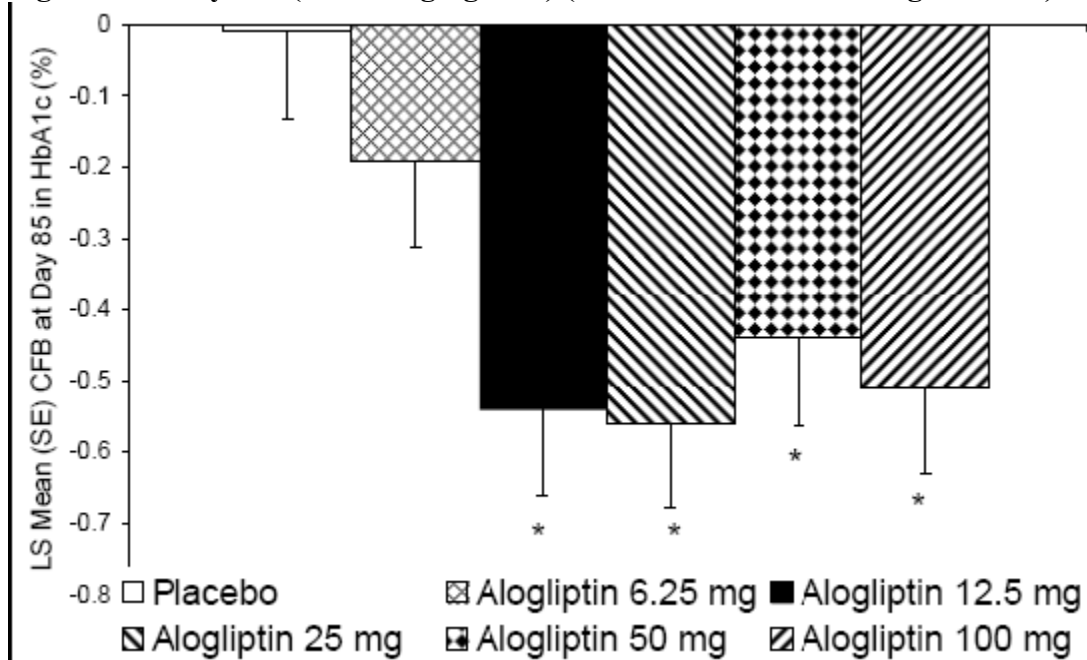
- Exposure-response relationship
- ADME of alogliptin and its metabolites
- Intrinsic factors affecting PK
- Extrinsic factors affecting PK

Exposure-Response Relationship

Much of these data are derived from the Phase 1 studies assessing the degree of DPP4-inhibitory activity and the Phase 2 dose-ranging study (Study 003).

This class of drugs has targeted development of doses that can demonstrate a minimum 80% inhibition of DPP4 activity over a 24 hour time period. Alogliptin 25 mg was the minimum dose to achieve this cut-point in single-dose and 14-day, multi-dose Phase 1 studies; however, the Phase 2 dose-ranging study continued to evaluate a broader range of doses which better informed dose-selection for the Phase 3 program. Study 003 was a 12-week, randomized, double-blind, placebo-controlled trial in 265 patients with T2DM. Between 43-45 patients were enrolled into each of the following treatment groups: placebo, 6.25, 12.5, 25, 50, and 100 mg alogliptin. The primary efficacy measure was Change from Baseline in HbA1c at Day 85. Mean Baseline HbA1c levels ranged from 7.9 to 8.2. The following figure summarizes the HbA1c reduction observed across all treatment groups.

Figure 1. Study 003 (dose-ranging trial) (obtained from Dr. Chung's review)



Based on this Phase 2 study, alogliptin 12.5 mg was the lowest effective dose despite having < 80% DPP4-inhibitory activity. From Figure 1, there was minimal difference between the 12.5 mg and 25 mg dose and there was clearly no further glycemic benefit with doses exceeding 25 mg. Based on these findings, Takeda evaluated only the 12.5 mg and 25 mg doses in its Phase 3 program.

ADME of Alogliptin and its Metabolites

Alogliptin is metabolized to M1 and M2, which are considered minor metabolites comprising < 1% and 4% of total alogliptin exposure, respectively. M1 has comparable DPP4 inhibitory activity as the parent drug while M2 has no inhibitory activity. These metabolites have also been observed in animal toxicology studies and have therefore been characterized in the nonclinical program.

Approximately 68% of an oral dose of alogliptin is excreted in the urine hence the drug is primarily eliminated via the kidneys. Effect of renal clearance and function on drug PK is discussed below.

In vitro evaluation of alogliptin in human CYP isoenzymes did not show inhibitory potential on CYP1A2, 2C8, 2C9, and 2C19. Potential for inhibitory activity on CYP2D6 and 3A4/5 were further evaluated clinically and there were no clinically relevant increases in the 2D6 substrate, dextromethorphan, or 3A4 substrates, midazolam and atorvastatin. Similarly, there was a signal for potential induction of CYP3A4/5 in human hepatocytes but clinical evaluation did not show any clinically relevant changes in exposure of CYP3A4 substrates (midazolam and atorvastatin) to support a conclusion that alogliptin is not a major inducer of CYP3A4/5.

Intrinsic Factors Affecting Pharmacokinetics

Except for renal impairment, gender, age, and race resulted in only modest changes in drug exposures. On average AUCs and C_{max} increased by approximately 20% in elderly vs young (no change in C_{max} by age), women vs. men, and Whites vs. Blacks. There are no recommendations for dose adjustments based on these intrinsic factors.

There were no differences in exposure between patients with moderate hepatic impairment and patients with normal hepatic function. Patients with mild- and severe- hepatic impairment were not evaluated.

The overall recommendation from the Office of Clinical Pharmacology (OCP) is that alogliptin can be approved at the doses proposed by Takeda for marketing. However, OCP has a different dosing recommendation than proposed by Takeda for specific renal impairment. The following table summarizes the proposals for dosing by Takeda and OCP and the effect of renal function of alogliptin pharmacokinetics (AUC and C_{max}).

Table 1. Proposing Dosing Regimen by Applicant and Office of Clinical Pharmacology

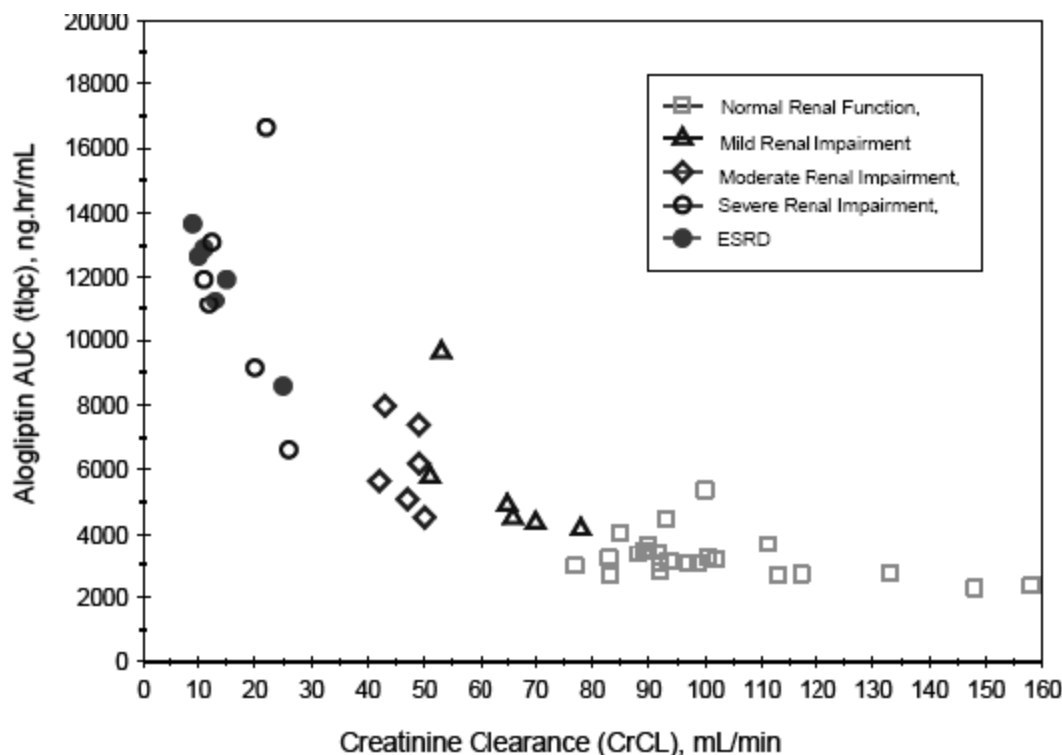
	Takeda	OCP	AUC/C _{max} increase relative to patients with normal renal function
Normal renal function	25 mg daily	25 mg daily	---
Mild renal impairment	25 mg daily	12.5 mg daily	69%/13%
Moderate renal impairment	12.5 mg daily	12.5 mg daily	108%/42%
Severe renal impairment	6.25 mg daily	6.25 mg daily	219%/27%
ESRD	6.25 mg daily	6.25 mg daily	281%/32%

The only difference in dosing recommendation is to the population of patients with mild renal impairment (highlighted yellow in Table 1). Because these patients exhibit a 69% increase in drug exposure (AUC), OCP recommends that these patients receive a 12.5 mg daily dose of alogliptin instead of 25 mg daily dosing recommended by Takeda. This recommendation is based on the observation that there is similar mean HbA_{1c} reduction between the 12.5 mg and 25 mg doses from the Phase 2 study (0.54% vs 0.57% reduction, respectively). While not stated, it is assumed that this recommendation is also based on an expected increase in alogliptin exposure in the mildly renal-impaired patient, which may not be the full 25 mg dose but will approximate this amount. In other words, the expected exposure in patients with mild renal impairment dosed with 12.5 mg alogliptin will likely provide adequate efficacy while maintaining drug levels within the dose range for which the majority of clinical safety data have been derived.

Dr. Pratt is recommending in her clinical review that patients with mild renal impairment may be treated with the 25 mg dose since the nonclinical safety data provide a safety margin of $\geq 32\times$ MHRD. I would further note that her argument is bolstered by the observation that the increased *mean* exposure of 69% in the mild renal impaired population is influenced by the

single outlier (see triangle icon below) out of a total of 6 patients. The remaining 5 patients with mild renal impairment had AUCs within the range observed for patients with normal renal function (see triangle and square icons in figure below).

Figure 2. Exposure Differences by Renal Function Status (obtained from Dr. Chung's review)



However, I recognize that the data presented above are derived from a small number of study participants, and that more information will be gained on the appropriate dosing recommendation in patients with mild renal impairment from a cardiovascular safety trial proposed by the applicant. This study in patients with acute coronary syndrome will randomize patients to alogliptin 25 mg daily vs placebo and will also enroll patients with mild renal impairment. As this application will receive a Complete Response action pending the conduct of this CV safety trial, a final decision on dosing for patients with mild renal impairment is deferred until additional data are submitted from the CV safety trial.

Extrinsic Factors Affecting PK

Table 7 from the OCP review summarizes the findings from the DDI studies conducted. These studies were conducted to evaluate the effect of certain metabolic modulators on alogliptin exposure, the effect of alogliptin on other drug exposures of clinical interest and selected DDIs. In the majority of evaluations, the GMR (90% CI) was close to 1.0 with the 90% CI falling within the range for BE criteria. The following *notable* “out of range” results were observed and were not considered clinically relevant.

- Gemfibrozil and cyclosporine increased the AUC of M1 metabolite by 91% and 47%, respectively. However, since M1 comprises < 1% of total alogliptin exposure, this change was not deemed to be clinically significant.
- Alogliptin increased exposures of dextromethorphan and fexofenadine by approximately 26% and 32%. The potential for 2D6 inhibitory activity was predicted from in vitro testing; however, this degree of exposure increase was not considered clinically relevant.
- There was an increase in metformin and atorvastatin exposures in the DDI studies but these increases were modest (~28% increased AUC exposure based on the upper bound of the 90% CI) that is unlikely to be of any safety concern. This interaction will not attenuate efficacy of these two drugs.

Alogliptin exposure is not affected by food.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Please see Drs. Derr's and Sahlroot's Statistical Reviews and Drs. Pratt's and Joffe's Medical Reviews for a detailed discussion of study designs, conduct, and results.

Like other anti-diabetic therapies, the efficacy variable targeted for approval was a reduction in HbA1c, as a measure of glycemic control. In support of an indication to treat hyperglycemia in adults with T2DM, Takeda submitted the results from five Phase 3 studies summarized in Table 2. All 5 studies were multicenter, randomized, double-blind, placebo-controlled studies with a treatment duration of 26 weeks that was preceded by a 4-week, placebo-controlled stabilization period. Except for Study 011 (add-on to insulin), the Baseline HbA1c inclusion criteria were identical for all the Phase 3 studies. Treatment assignment was also stratified by HbA1c < or ≥ 8% (9% for Study 011). The primary efficacy endpoint was change from Baseline in HbA1c at Week 26. Fasting plasma glucose was a secondary efficacy endpoint.

Table 2. Summary of Phase 3 Trials

Study No.	Treatment Groups	N per treatment group (randomized)	N per treatment group (completed)	Mean Baseline HbA1c
010	Alo 12.5 mg	133	105	7.9
	Alo 25 mg	131	107	7.9
	Placebo	65	40	8.0
				59.9% cohort < 8.0%
007	Alo 12.5 mg + SU	203	153	8.1
	Alo 25 mg + SU	198	148	8.1
	Placebo + SU	99	62	7.9
				44.2% cohort < 8.0%

008	Alo 12.5 mg + met	213	176	7.9
	Alo 25 mg + met	210	165	7.9
	Placebo + met	104	72	8.0
57.1% cohort < 8.0%				
009	Alo 12.5 mg + pio	197	153	8.1
	Alo 25 mg + pio	199	160	8.0
	Placebo + pio	97	71	8.1
51.1% cohort < 8.0%				
011	Alo 12.5 mg + insulin	131	83	9.3
	Alo 25 mg + insulin	129	77	9.3
	Placebo + insulin	130	55	9.3
41.5% cohort < 9.0%				

A point emphasized by Dr. Janice Derr in her statistical review was the high discontinuation rate in these trials, particularly due to glycemic rescue, which may impact the efficacy findings. For all Phase 3 trials, FPG was employed as the measure for determining need for glycemic rescue prior to Wk 12 and HbA1c was employed after Wk 12. The rescue criteria are summarized below:

Weeks 0-12

- following one week of treatment but prior to Wk 4 visit: single FPG ≥ 275 mg/dL for Studies 010, 007, 008, and 009 or single FPG ≥ 300 mg/dL for Study 011
- from Wk 4 but prior to Wk 8 visit: single FPG ≥ 250 mg/dL for Studies 010, 007, 008, and 009 or single FPG ≥ 275 mg/dL for Study 011
- following Wk 8 but prior to Wk 12 visit: single FPG ≥ 225 mg/dL for Studies 010, 007, 008, and 009 or single FPG ≥ 250 mg/dL for Study 011

Weeks 12-26

- From Wk 12 to 26: HbA1c $\geq 8.5\%$ and $< 0.5\%$ reduction in HbA1c as compared with Baseline for Studies 010, 007, 008, and 009 and for Study 011 a HbA1c $\geq 8.7\%$ and $< 0.5\%$ reduction from Baseline

From Table 2, it is evident that a significant percentage of patients randomized (21-44%) did not complete the trial with need for glycemic control being the reason for discontinuation in 12 to 27% of patients. From Table 4 and Figure 2 of Dr. Derr's review, the percentage of discontinuation due to glycemic rescue was most notable after Week 12, when HbA1c was the measure for determining treatment failure. More patients in the placebo treatment group required glycemic rescue than the alogliptin treatment group. Patients in the higher HbA1c stratum had a greater discontinuation rate due to glycemic rescue.

Efficacy analyses were conducted on two populations:

- Full Analysis Set (FAS) included all randomized patients with a baseline efficacy assessment and at least one post-baseline efficacy measurement. Patients who

discontinued before Wk 26 had their last HbA1c measurement carried forward to the study endpoint.

- Per Protocol (PS) included all FAS subjects who had no major protocol violations

Overall, alogliptin 12.5 and 25 mg dosed daily provided statistically significant reductions in HbA1c from Baseline at Week 26, relative to placebo. The range of this net effect was 0.4 to 0.6 % across the 5 Phase 3 trials. There was no statistically significant difference between the two doses, which was not the objective of these trials. However, with exception for Study 008 (add-on to metformin), the mean HbA1c reduction was numerically greater with the 25 mg than the 12.5 mg dose in all the other trials, supporting the availability of both doses as some individuals may derive greater glycemic control with 25 mg.

Table 3. Primary Efficacy Results (FAS population – adapted from Table 7 in Dr. Janice Derr’s review)

Study No.	Treatment Groups	N	Difference in adjusted mean change (95% CI)
010	Alo 25 mg	128	-0.57 (-0.80, -0.35)
	Alo 12.5 mg	131	-0.54 (-0.76, -0.31)
	Placebo	63	
007	Alo 25 mg + SU	197	-0.53 (-0.73, -0.33)
	Alo 12.5 mg + SU	201	-0.39 (-0.59, -0.19)
	Placebo + SU	97	
008	Alo 12.5 mg + met	203	-0.48 (-0.67, -0.30)
	Alo 25 mg + met	210	-0.50 (-0.68, -0.32)
	Placebo + met	103	
009	Alo 25 mg + pio	195	-0.61 (0.80, -0.41)
	Alo 12.5 mg + pio	196	-0.47 (-0.67, -0.28)
	Placebo + pio	95	
011	Alo 25 mg + insulin	126	-0.59 (-0.80, -0.37)
	Alo 12.5 mg + insulin	130	-0.51 (-0.72, -0.30)
	Placebo + insulin	126	

Dr. Derr performed several sensitivity analyses to determine whether the high discontinuation rate had a marked impact on efficacy conclusions. In her Tables 8 through 12, she presented efficacy data for each of the Phase 3 studies by the FAS, PP, completers, and rescued/discontinued populations. The FAS population provides efficacy results, for the most part, in the randomized population. While discontinuations resulted in some patients not contributing efficacy data at Week 26, the efficacy data evaluated in this population reflect on-assigned-treatment data. The PP population is comparable to the FAS population, excluding protocol violators. The completers analysis focused on only those patients who responded with respect to glycemic control, not necessitating any rescue therapy. Although this analysis provides data in patients who can remain in the trial for the entire treatment duration, it is a highly selected population primarily limited to patients with less severe disease at baseline with mean HbA1c < 8.0% in the non-insulin trials. The rescued/discontinued group limited

efficacy analysis to those who were not able to complete the trial. As expected, Baseline HbA1c in this subgroup is higher than the other subgroups.

The sensitivity analyses in the PP and completers population demonstrated significant reductions in HbA1c across all the trials. The point estimate of effect was variable and in the rescue/discontinued group, the effect was not significant in some studies although a mean reduction was still observed. Overall, I concur that the primary efficacy analysis on the FAS population and the sensitivity analyses support a conclusion that both alogliptin 12.5 and 25 mg treatment significantly reduces HbA1c. A true estimate of glycemic control is limited due to the high discontinuation rate; however, the data from these studies and other DPPIV-inhibitors would suggest modest efficacy for alogliptin. I would also point out that the secondary efficacy analyses discussed in the statistical and medical reviews lend additional support to a conclusion of glycemic efficacy.

Alogliptin has a neutral effect on weight gain.

HbA1c reduction is more pronounced in the higher HbA1c stratum (≥ 8 or 9%). This has been observed with other anti-diabetic therapies. However, in Figures 14-18 of her review, Dr. Derr shows clear illustrations of the higher discontinuation rate in these strata which limit our conclusion of the true effect of drug in this subgroup. I concur with her that any future labeling negotiations with the firm should not allow presentation of efficacy data by subgroup of Baseline HbA1c if these are the only data available for such discussion.

8. Safety

Please see Dr. Joffe's CDTL memo and Dr. Pratt's primary medical review for a thorough discussion of the safety findings in this NDA. My memo will focus primarily on the CV safety findings in the FDA-requested MACE analysis and the basis for this application receiving a complete response action with a requirement to conduct a large CV safety study prior to approval. Other safety findings of interest that are touched on in my memo include hypersensitivity reactions and pancreatitis.

Cardiovascular Safety

Drs. Joffe and Pratt have thoroughly described the CV events captured by the applicant and the events in which there was discordance in coding. My memo will not discuss this, as much of these data include the uncontrolled portions of the studies not evaluated in the MACE analysis. I concur with them that the lack of pre-specified adjudication contributes to the uncertainty in the true number of CV events. Regardless, the overall number of events is low and further deliberation on these few potentially miscoded reports in a post-hoc fashion does not change the overall conclusion for this application.

The assessment of CV risk in this NDA was limited because of the study population evaluated which had a low risk for any CV event, a randomization scheme of 2:2:1 for alogliptin 12.5 mg, 25 mg, and placebo in the majority of the Phase 3 trials, the absence of any pre-specified CV events adjudication, and the absence of long-term controlled data. All controlled data were limited to only 6-months duration. Of these limitations, I believe the low-risk population

and the absence of long-term controlled data were the predominant limitations in this program which ultimately impacted the ability to rule out an upper-bound of 1.8 for CV risk assessment.

The safety database was bolstered late in the review cycle by the submission of data from 2 other studies in which alogliptin was co-administered with pioglitazone. These two studies have also been submitted separately under the NDA for the fixed-dose combination of alogliptin and pioglitazone. Although these two studies (referred to as 001 and 002) included additional exposure to alogliptin in 1,528 patients, the controlled portion was still limited to 6-months duration.

As discussed extensively by Drs. Joffe and Pratt, the Division was concurrently reviewing 3 NDAs for T2DM which were subject to the recent requirements to demonstrate an acceptable CV safety profile based on the December 2008 Guidance to Industry. None of these programs was designed to assess CV risk in a prospective fashion so to ensure a consistent approach to reviewing these applications that were “caught in the midst” of change in the regulatory requirements for anti-diabetic therapies, all three applicants were requested to present CV events for a MACE analysis of only the controlled clinical trials using a uniform approach. In response to FDA’s request, Takeda provided in January 2009 the number of events meeting the broad definition of SMQ MACE and the more specific Custom MACE. These data are derived from the dose-finding Phase 2 study, 5 pivotal Phase 3 studies, and the two combination trials (001 and 002). The following table summarizes the preferred terms selected to define SMQ or Custom MACE.

Table 4. SMQ vs Custom MACE preferred terms

	“Broad MACE SMQ”	“FDA Custom MACE”
Myocardial Infarction Terms		
Acute coronary syndrome	x	
Acute myocardial infarction	x	X
Blood creatine phosphokinase abnormal	x	
Blood creatine phosphokinase increased	x	
Blood creatine phosphokinase MB abnormal	x	
Blood creatine phosphokinase MB increased	x	
Cardiac arrest		
Cardiac enzymes increased	x	
Circulatory collapse		
Coronary artery embolism	x	
Coronary artery occlusion	x	
Coronary artery reocclusion	x	
Coronary artery thrombosis	x	X
Coronary bypass thrombosis	x	
Electrocardiogram Q wave abnormal	x	
Electrocardiogram ST segment abnormal	x	
Electrocardiogram ST segment elevation	x	
Electrocardiogram ST-T segment elevation	x	
Infarction	x	
Myocardial infarction	x	X
Myocardial reperfusion injury	x	
Papillary muscle infarction	x	X
Postinfarction angina	x	

	“Broad MACE SMQ”	“FDA Custom MACE”
Postprocedural myocardial infarction	x	X
Scan myocardial perfusion abnormal	x	
Silent myocardial infarction	x	X
Troponin I increased	x	
Troponin increased	x	
Troponin T increased	x	
Vascular graft occlusion	x	
Stroke Terms		
Agnosia	x	
Amaurosis fugax	x	
Angiogram cerebral abnormal	x	
Aphasia	x	
Balint’s syndrome	x	
Basal ganglia hemorrhage	x	
Basilar artery occlusion	x	
Basilar artery stenosis	x	
Basilar artery thrombosis	x	X
Brain stem hemorrhage	x	
Brain stem infarction	x	X
Brain stem ischemia	x	
Brain stem stroke	x	X
Brain stem thrombosis	x	X
Capsular warning syndrome	x	
Carotid aneurysm rupture	x	
Carotid arterial embolus	x	X
Carotid arteriosclerosis	x	
Carotid artery aneurysm	x	
Carotid artery bypass	x	
Carotid artery disease	x	
Carotid artery dissection	x	
Carotid artery insufficiency	x	
Carotid artery occlusion	x	
Carotid artery stenosis	x	
Carotid artery stent insertion	x	
Carotid artery thrombosis	x	X
Carotid endarterectomy	x	
Central pain syndrome	x	
Cerebellar artery occlusion	x	
Cerebellar artery thrombosis	x	
Cerebellar embolism	x	
Cerebellar hematoma	x	
Cerebellar hemorrhage	x	
Cerebellar infarction	x	X
Cerebellar ischemia	x	
Cerebral aneurysm ruptured syphilitic	x	
Cerebral arteriosclerosis	x	
Cerebral arteriovenous malformation hemorrhagic	x	
Cerebral artery embolism	x	X
Cerebral artery occlusion	x	
Cerebral artery stenosis	x	

	“Broad MACE SMQ”	“FDA Custom MACE”
Cerebral artery thrombosis	x	X
Cerebral hematoma	x	
Cerebral hemorrhage	x	
Cerebral hemorrhage fetal	x	
Cerebral hemorrhage neonatal	x	
Cerebral infarction	x	X
Cerebral infarction fetal	x	
Cerebral ischemia	x	
Cerebral thrombosis	x	X
Cerebral vasoconstriction	x	
Cerebral venous thrombosis	x	
Cerebrovascular accident	x	X
Cerebrovascular accident prophylaxis	x	
Cerebrovascular disorder	x	
Cerebrovascular insufficiency	x	
Cerebrovascular spasm	x	
Cerebrovascular stenosis	x	
Charcot-Bouchard microaneurysms	x	
Cranial nerve palsies multiple		
Diplegia	x	
Dysarthria	x	
Embolic cerebral infarction	x	X
Embolic stroke	x	X
Facial palsy		
Hematomyelia	x	
Hemiparesis	x	
Hemiplegia	x	
Hemorrhage intracranial	x	
Hemorrhagic cerebral infarction	x	X
Hemorrhagic stroke	x	X
Hemorrhagic transformation stroke	x	X
Intracerebral aneurysm operation	x	
Intracerebral hematoma evacuation	x	
Intracranial aneurysm	x	
Intracranial hematoma	x	
Intraventricular hemorrhage	x	
Intraventricular hemorrhage neonatal	x	
Ischemic cerebral infarction	x	X
Ischemic stroke	x	X
Lacunar infarction	x	X
Lateral medullary syndrome	x	X
Meningorrhagia	x	
Millard-Gubler syndrome	x	
Monoparesis	x	
Monoplegia	x	
Moyamoya disease	x	X
Paralysis	x	
Paralysis flaccid	x	
Paraparesis	x	
Paraplegia	x	
Paresis	x	
Postprocedural stroke	x	X

	“Broad MACE SMQ”	“FDA Custom MACE”
Precerebral artery occlusion	x	
Putamen hemorrhage	x	
Quadriparesis	x	
Quadriplegia	x	
Red blood cells cerebrospinal fluid positive	x	
Reversible ischemic neurologic deficit	x	
Ruptured cerebral aneurysm	x	
Spastic paralysis	x	
Spastic paraplegia	x	
Spinal artery embolism	x	
Spinal cord hemorrhage	x	
Spinal epidural hemorrhage	x	
Spinal hematoma	x	
Stroke in evolution	x	X
Subarachnoid hemorrhage	x	
Subarachnoid hemorrhage neonatal	x	
Subdural hemorrhage	x	
Subdural hemorrhage neonatal	x	
Thalamic infarction	x	X
Thalamus hemorrhage	x	
Thrombotic cerebral infarction	x	X
Thrombotic stroke	x	X
Transient ischemic attack	x	
Vascular encephalopathy	x	
Vertebral artery occlusion	x	
Vertebral artery stenosis	x	
Vertebral artery thrombosis	x	
Vertebrobasilar insufficiency	x	
Visual midline shift syndrome	x	
Wallenberg syndrome	x	X

Despite an extensive list of PTs under the SMQ MACE category, there were only 32 events within this category and 18 Custom MACE events.

Given the few number of events and the unequal distribution of exposure to drug and control, Dr. Derr applied several statistical methodologies to assess risks based on the SMQ and Custom MACE events in a meta-analysis derived from 8 studies. Her analyses are included in Dr. Pratt’s review on pages 118-120. I have copied below from Dr. Pratt’s review, the forest plots produced by Dr. Derr in which the CV risks based on the SMQ MACE and Custom MACE events were performed using an analytical approach in which groups with zero events were assigned a 0.5 continuity correction.

Figure. 3 SMQ MACE, Odds Ratios and 95% CIs from stratified asymptotic method (M-H) with continuity correction (Forest plot and statistical analysis performed by Dr. Janice Derr)

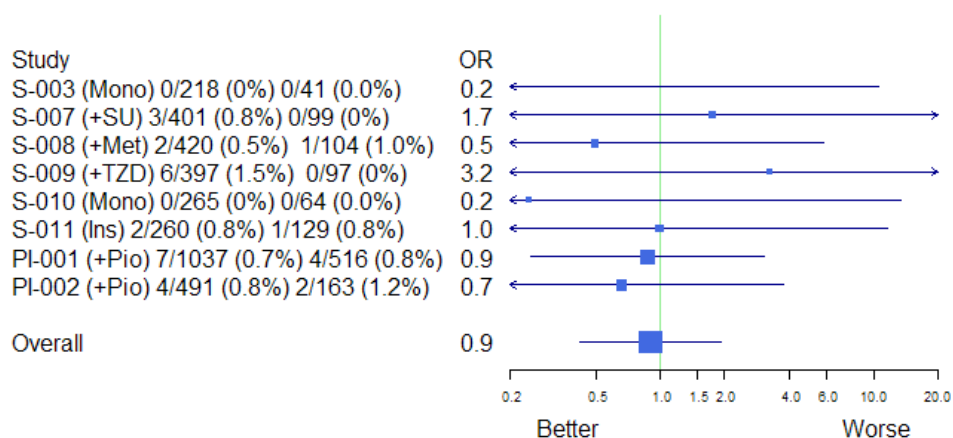
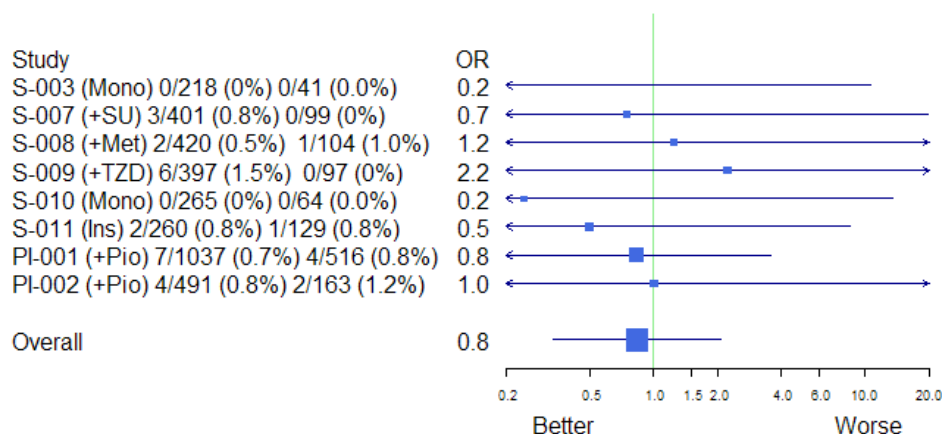


Figure 4. Custom MACE, Odds Ratios and 95% CI from stratified asymptotic method (M-H) with continuity correction (Forest plot and statistical analysis performed by Dr. Janice Derr)



The point estimate in both these analyses approximates one; however, the upper bound of the 95% CI exceeds 1.8. When groups with zero events are excluded, the point estimate exceeds 1.0 and the upper bound of the 95% CI exceeds 4.0. Of note, the Custom MACE analysis yielded point estimates of 1.4 and 1.3 with accompanying CIs which included 1.0 (See Table 12 from Dr. Joffe's review). While this is concerning, I do not see compelling evidence to conclude that CV risk exists with alogliptin. There are clearly too few CV events and in those analyses which suggest a signal based on an incidence ratio > 1.0, I am reminded that the CI is wide, the few events are adjudicated retrospectively, and unlike the CV safety concerns raised with the PPAR-agonists and certain sulfonylurea drugs, no cardiac toxicity was observed in the non-clinical program despite many-fold exposures studied relative to the MRHD.

Nonetheless, the December 2008 Guidance to Industry applies to this novel anti-diabetic agent and additional CV risk assessment will be required to reassure us that this agent, whose glycemic efficacy is modest, will not carry a potential for an 80% excess risk of CV disease prior to approval.

The applicant has been informed that a dedicated CV safety trial must be undertaken prior to approval. To this end, the applicant is proposing to conduct Study SYR-322-402 titled, “A multicenter, randomized, double-blind, placebo-controlled study to evaluate cardiovascular outcomes following treatment with alogliptin in addition to standard of care in subjects with T2DM and ACS” with approximately 3800 patients enrolled (1:1 to alogliptin vs placebo). Alogliptin doses of 6.25 mg, 12.5 mg and 25 mg will be employed depending on the Baseline renal status.

This study protocol is still under negotiations with the agency but several critical elements have been agreed to, including the study population of ACS patients and the primary endpoint, which will be the time from randomization to the first occurrence of any event in the primary MACE composite of CV death, nonfatal MI, or nonfatal stroke. Evaluating CV risk in this high-risk patient population will clearly capture a large number of events as the placebo event rate for this composite endpoint is estimated to be ~6% per year.

One objection regarding this CV safety trial is that the applicant may be able to meet the 1.8 cut point necessary for approval after approximately (b) (4) due to the predicted high early event rate. Based on Drs. Derr’s and Sahlroot’s calculations, this would represent a median exposure of 6 months with a very low likelihood of any exposures out to one year. Although there were 1,443 patients exposed to alogliptin for at least one year and 422 were exposed for at least 18 months (meeting the exposure requirements outlined in the February 2008 Draft Guidance for Diabetes Drug Development) in this current NDA, all the exposure beyond 6.5 months was uncontrolled, which severely limited conclusions on not just CV safety but other notable adverse events. Indeed, emerging drug class safety concerns such as pancreatitis and hypersensitivity reactions may require longer term controlled data to evaluate risk.

Although the Diabetes Guidance does not specify one-year *controlled* exposures, two other NDAs currently under review have one-year controlled data in > 800 patients randomized to investigational drug. Takeda has two ongoing, one-year controlled clinical studies which combined, will provide an additional 400 patients exposed to alogliptin. Of note, one of these studies is comparing alogliptin to a sulfonylurea in elderly patients, a population that may be susceptible to drug-related adverse events. In addition to requiring a sufficient duration of exposure in the CV safety trial, the complete response letter should specify that these two other studies need to be submitted with the CV safety trial results to ensure adequate long-term controlled data for safety evaluation beyond CV concerns.

Hypersensitivity Reactions

Data from the controlled Phase 2/3 program reveal a higher incidence of hypersensitivity-type reactions. Dr. Joffe describes two cases of angioedema coded as a serious AE. One patient was started on alogliptin 25 mg 3 days before reporting difficulty breathing and swallowing

with edema of the uvula, face, and neck. The patient was on concomitant angiotensin receptor blocker (valsartan) initiated 10 days before the event. Both drugs were interrupted with resolution of symptoms. However, difficulty swallowing and speaking recurred on Day 174. Valsartan was discontinued while alogliptin was interrupted. Reinitiation of therapy with alogliptin but not the ARB was uneventful.

Angioedema is a known side effect with angiotensin converting enzyme inhibitors (ACE-inhibitors) and more rarely with angiotensin receptor blockers. Of interest are published studies reporting a role of decreased dipeptidyl peptidase IV activity or DPP4 deficiency resulting in an increased susceptibility to ACE-inhibitor-induced angioedema.^{1,2,3} There are no published literature for a similar interaction with ARBs. As these two classes of drugs are used extensively in the diabetic population for hypertension and diabetic kidney disease, hypersensitivity reactions, particularly angioedema, should be a safety finding of interest in the postmarketing setting for the DPP4-inhibitors.

A history of ACE-I or ARB-associated angioedema was an exclusion criterion in the alogliptin clinical trials; however, these drugs were commonly co-prescribed in up to 48% of the study population. I note that on page 102 of Dr. Pratt's review, 2 of the 3 angioedema events resulting in discontinuation were associated with concomitant use of an ACE-inhibitor or ARB (ramipril and losartan, respectively). The CR letter should request that additional studies include a plan for prospective evaluation of these types of events with an analysis by use of ACE-inhibitors/ARBs.

Pancreatitis

In February 2009, Merck submitted a CBE for Januvia to include acute pancreatitis as an event reported in the postmarketing setting. The Office of Surveillance and Epidemiology has also been consulted on evaluating the reporting rates of pancreatitis between Januvia and Byetta, a GLP-1 receptor agonist. Both of these drugs have also had post-marketing reports of hemorrhagic necrotizing pancreatitis although there have been more reports observed with Byetta than Januvia. Dr. Joffe has summarized the 4 cases of pancreatitis reported in this NDA. All were in alogliptin-treated patients, which might reflect the 4:1 randomization scheme employed in the majority of the Phase 3 trials. There were no reports of hemorrhagic/necrotizing pancreatitis. The CR letter should note this emerging concern for this class of drugs and that ongoing studies need to include a plan for prospective evaluation of these types of events.

¹ Brown JB et al. Dipeptidyl peptidase IV in angiotensive-converting enzyme inhibitor associated angioedema. *Hypertension*. 2008 Jan; 51(1):141-147.

² Byrd JB et al. Dipeptidyl peptidase IV deficiency increases susceptibility to angiotensive converting enzyme inhibitor-induced peritracheal edema. *J Allergy Clin Immunol*. 2007Aug; 120(2): 403-408.

³ Lefebvre J et al. Dipeptidyl peptidase activity in patients with ACE-inhibitor-associated angioedema. *Hypertension*. 2002 Feb; 39(2):460-4.

9. Advisory Committee Meeting

An advisory committee meeting was deemed unnecessary, as this application will not gain approval this review cycle.

10. Pediatrics

Please see Dr. Joffe's CDTL memo where is has thoroughly summarized the pediatric plan which has already been discussed with the Pediatric Research Committee (PeRC).

11. Other Relevant Regulatory Issues

Please see Dr. Joffe's CDTL memo for detail regarding tradename review, financial disclosure information, and DSI audits.

12. Labeling

Deferred since this application will not be approved this review cycle.

13. Recommendations/Risk Benefit Assessment

- Regulatory Action

Complete Response

- Risk Benefit Assessment

Alogliptin 12.5 and 25 mg was associated with statistically significant reductions in HbA1c, a measure of glycemic control which has been well-correlated with microvascular risk reductions in both the type 1 and type 2 diabetes population. However, the degree of glycemic control (0.4 to 0.6% HbA1c reduction) is modest compared to other available therapies. This modest efficacy limits any argument for dismissing concerning safety signals observed in the clinical trial database.

The safety signals observed in this NDA included a numeric imbalance in CV adverse events and an increased incidence of hypersensitivity reactions. Interpretability of the CV adverse events was severely restricted by the absence of long-term controlled data beyond 6 months and the low-risk population studied. The recent issuance of the Final Guidance to Industry titled *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* requires that sponsors of new therapies for type 2 diabetes show that these treatments do not result in an unacceptable increase in cardiovascular risk. While the Guidance did not mandate the trial design, patient population or methodological approach for statistical comparison between treatment groups, the basic requirement for initial approval

required a demonstration that the upper bound of the 95% CI for the estimated risk ratio comparing relevant CV adverse events in investigational drug to comparator not exceed 1.8.

Recognizing that this development program preceded the issuance of this guidance, different statistical methodologies were employed to assess risk based on criteria for selecting MACE endpoints that were consistently applied to other concurrently reviewed NDAs for T2DM. In all analyses, the upper bound of the 95% CI exceeded 1.8.

While I acknowledge the applicant's grievances and that the signal of CV risk more likely reflects too few events in a low-risk population that was enrolled at a time when there was FDA concurrence for such study designs, I believe that the modest benefit this drug has to offer requires more extensive evaluation, not only to meet the recent CV risk assessment guidelines but to assess emerging risks in the class of incretin mimetics, to ensure a favorable risk-benefit profile.

- Recommendation for Postmarketing Risk Management Activities

Not applicable at this time.

- Recommendation for other Postmarketing Activities/Phase IV commitments

Not applicable at this time.

- Comments to be Conveyed to the Applicant

Please see Complete Response action letter.

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/s/

Mary Parks
6/26/2009 10:26:21 AM
MEDICAL OFFICER

Summary Basis for Regulatory Action

Date	June 26, 2009
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	NDA 22-271
Applicant Name	Takeda Pharmaceuticals
Proprietary / Established (USAN) Names	Nesina alogliptin
Dosage Forms / Strength	Tablets 6.25 mg, 12.5 mg, 25 mg
Proposed Indication(s)	Glycemic control in adults with type-2 diabetes mellitus
Action:	<i>Complete Response</i>

Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding alogliptin and the reader should refer to the reviews in the action package for a more detailed discussion. Alogliptin is an inhibitor of the serine protease enzyme - dipeptidyl peptidase IV (DPP-4). It is thought that the mechanism of action for this class of drugs is that they enhance the impaired release and availability of the incretin hormone, glucagon-like peptide-1 (GLP-1). GLP-1, along with glucose-dependent insulintropic polypeptide (GIP), are short-lived intestinal peptides released in response to food ingestion that have an inhibitory effect on glucagon (which would result on inhibiting hepatic glucose synthesis) and an enhancing effect on insulin secretion when serum glucose is elevated. DPP-4 inhibitors therefore enhance the effect of the incretins by inhibiting their metabolism by the enzyme DPP-4. Of note is that incretins have minimal, if any, effect on insulin secretion when glucose is normal or low and therefore would likely have less hypoglycemia as compared to some of the other agents used to treat diabetes.

The Agency has recently approved two agents that manifest their activity in the incretin pathway. The first is sitagliptin, a DPP-4 inhibitor like alogliptin that is also administered orally, and exenatide, a 34-amino acid GLP-1 analogue that has agonistic activity at the GLP-1 receptor, given by injection.

Over the last two to three years, concerns over the cardiovascular safety of certain diabetic drugs have led to debate regarding the adequacy of development programs to assure that these agents don't increase the cardiovascular risk in diabetic populations, which already have a 2x to 4x increase risk compared to matched non-diabetic populations. These issues were discussed at an Advisory Committee meeting in July of 2008, where the panel recommended that glycemic control agents for type 2 diabetes coming before the agency for approval should have pre-approval cardiovascular assessment screening, with further post-approval testing to determine that an adverse effect is not noted. After much internal deliberation, we issued a

final guidance incorporating recommendations from the advisory committee. This guidance allows for a two-step, ‘step-wise’ assessment of potential cardiovascular risk during drug development. The first ‘step-one’ is to make a determination that the investigational agent has an upper bound of a two-sided 95 percent confidence interval for the estimated risk ratio of less than/equal to 1.8 compared to a control group (with a point estimate near unity) would allow marketing while a longer and larger outcome study is conducted. The concept was that any further pre-approval testing would be too burdensome to drug develop, but this level of assurance would be feasible and would provide some assurances while further testing was underway. Further testing would be accomplished by a larger outcome study that must demonstrate that the investigational agent has an upper bound of a two-sided 95 percent confidence interval for the estimated risk ratio of less than/equal to 1.3 compared to a control group in order for continued marketing to occur.

These principles incorporate recommendations from the advisory committee. The details of this approach are outlined in the guidance¹, but of relevance is that at the time of issuance of the guidance, three NDA’s were in review. We concluded that recommendations should apply to all ongoing programs including those with applications pending with the agency at the time of guidance issuance. Although not totally in alignment with the guidance, two of the three seemed to, in spirit, fulfill ‘step-one’ which would allow for marketing while awaiting the results of a definitive study. These two applications were presented at an Advisory Committee meeting (April 1 and 2, 2009), where the majority of the panel members agreed with our conclusion. The results and discussions of the panel members from these meetings also indicated to us that the application for alogliptin would not fulfill ‘step-one’ marketing criteria. As such, this will be a major deficiency for this application. Please see Drs. Parks, Joffe and Pratt’s reviews for further details.

As another point for consideration, there has been some concern with the DPP-4 inhibitors in regard to their potential adverse event profile based on their promiscuity toward other DPP enzymes, in particular DPP-8/9. During phase 3 development of a different DPP-4 agent, it was noted that monkeys developed dose and duration dependent cutaneous lesions that ranged from some flaking and blistering to frank ulceration and necrosis requiring euthanasia of the animals. Therefore, 13-week monkey studies (the most sensitive species) have been required of all DPP-4 agents in development. Alogliptin is highly selective for DPP4 (like sitagliptin) and pre-clinical or clinical concerns for this issue were not noted.

Efficacy

This has been thoroughly discussed in Drs. Derr, Pratt, Joffe and Parks reviews and I agree with their conclusions. The following table from Dr. Joffe’s review (Page 10), demonstrates the efficacy results for the randomized trials.

Table 2. Primary efficacy results for the phase 2 and 3 clinical trials (FAS population with LOCF)					
Study	N	Baseline mean ± SE	Change from baseline	Difference in adjusted mean change	p-value

¹ Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, December 2008, Clinical/Medical.

			Adj. mean \pm SE	95% CI	
Study 003 (dose-ranging) – 12-week trial					
Alo 6.25 mg	42	8.0 \pm 0.2	-0.2 \pm 0.1	Not reported	
Alo 12.5 mg	42	7.9 \pm 0.2	-0.5 \pm 0.1	Not reported	
Alo 25 mg	45	8.0 \pm 0.2	-0.6 \pm 0.1	Not reported	
Alo 50 mg	43	8.1 \pm 0.2	-0.4 \pm 0.1	Not reported	
Alo 100 mg	44	8.0 \pm 0.2	-0.5 \pm 0.1	Not reported	
Placebo	41	8.2 \pm 0.2	0.0 \pm 0.1	Not reported	
Study 010 (monotherapy) – 26-week trial					
Alo 25 mg	128	7.9 \pm 0.1	-0.6 \pm 0.1	-0.6 (-0.8, -0.4)	<0.001
Alo 12.5 mg	131	7.9 \pm 0.1	-0.6 \pm 0.1	-0.5 (-0.8, -0.3)	<0.001
Placebo	63	8.0 \pm 0.1	0.0 \pm 0.1		
Study 007 (add-on to sulfonylurea) – 26-week trial					
Alo 25 mg	197	8.1 \pm 0.1	-0.5 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
Alo 12.5 mg	201	8.1 \pm 0.1	-0.4 \pm 0.1	-0.4 (-0.6, -0.2)	<0.001
Placebo	97	8.2 \pm 0.1	0.0 \pm 0.1		
Study 008 (add-on to metformin) – 26-week trial					
Alo 25 mg	203	7.9 \pm 0.1	-0.6 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
Alo 12.5 mg	210	7.9 \pm 0.1	-0.6 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
Placebo	103	8.0 \pm 0.1	-0.1 \pm 0.1		
Study 009 (add-on to pioglitazone) – 26-week trial					
Alo 25 mg	195	8.0 \pm 0.1	-0.8 \pm 0.1	-0.6 (-0.8, -0.4)	<0.001
Alo 12.5 mg	195	8.1 \pm 0.1	-0.7 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
Placebo	95	8.0 \pm 0.1	-0.2 \pm 0.1		
Study 011 (add-on to insulin) – 26-week trial					
Alo 25 mg	126	9.3 \pm 0.1	-0.7 \pm 0.1	-0.6 (-0.8, -0.4)	<0.001
Alo 12.5 mg	130	9.3 \pm 0.1	-0.6 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
Placebo	126	9.3 \pm 0.1	-0.1 \pm 0.1		
FAS=full analyses set; LOCF=last-observation-carried-forward; SE=standard error; CI=confidence interval					

I agree with the conclusions of the reviewers that the results above, while modest, do demonstrate that alogliptin has a clinically important hypoglycemic effect. I also agree that, the 25 mg dose, while not statistically different from the 12.5 mg dose, does have a greater point estimate of HbA1c change and that some patients would probably benefit from this dose that may not from the 12.5 mg dose. Therefore, if the safety findings are similar, I would support availability of both doses.

It is interesting to note that 80% DPP4-inhibitory activity is the target used by sponsors in developing dose, but that is achieved by alogliptin starting at the 25 mg dose. Since there does not seem to be much difference between the 12.5 vs the 25 mg dose in regards to efficacy, one could wonder if the 80% inhibitory target is indeed correct.

Safety

The available safety data and conclusions are outlined in Drs. Pratt, Joffe and Parks reviews and I agree with there conclusions. I will only comment on a couple of the issues.

Regarding the cardiovascular evaluation performed by the sponsor, I agree with Dr. Joffe that there are too few events to draw any firm conclusions. In addition, this application, as opposed to the other two diabetic medications we are currently reviewing, does not meet the current recommendations for 'step-one' approval of diabetic medications, despite looking at the available data in many different ways as is outlined in the reviews. As such, this is a major limitation of this application and will require more cardiovascular safety information prior to any form of marketing.

Dr. Parks notes that there are cases of angioedema noted in the safety database (2 of 3 events associated with concomitant use of ACE-inhibitor or ARB), cases in the dog studies of reddened/flushing ears and face, along with body and facial swelling, as well as post-marketing reports of hypersensitivity with Januvia. Dr. Parks also notes that there are published studies reporting a role of decreased DPP4 activity of deficiency resulting in increased susceptibility to ACE-inhibitor-induced angioedema and that these medications are used extensively in the diabetic population. I agree with her that this is a finding of interest and that further trials should include a plan for prospective evaluation of these types of events and the population studied should assure use of ACE-inhibitors and ARBs so we can get a better idea of potential problems.

Dr. Parks also notes that there have been post-marketing reports of pancreatitis for Januvia and Byetta that have resulted in recommendations for changes in the warning section of their labeling. There were a few cases of pancreatitis in the safety database for alogliptin, but too few to determine if there is any causative effect. I agree with her that future trials should include prospective evaluation, and this in itself may help to determine the utility of amylase/lipase screening and evaluation in this population as the incidence of pancreatitis in diabetic populations has been a question and asymptomatic diabetic patients have been noted to have abnormal serum amylase and lipase levels.

Conclusions and Recommendations

Alogliptin has demonstrated efficacy for the 12.5 mg and 25 mg doses in reduction of HbA1c levels. This application does not have adequate cardiovascular evaluation data, and this will be a major deficiency. There are other concerns as noted above, but none that would rise to the level of not allowing marketing. The sponsor will need to provide an adequate safety database to fulfill the 'step-one' requirement in order to market alogliptin and address other concerns as outlined by the reviewers.

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/s/

Curtis Rosebraugh
6/26/2009 10:22:38 AM
MEDICAL OFFICER

Cross-Discipline Team Leader Review

Date	May 27, 2009
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Cross-Discipline Team Leader Review
NDA #	22-271
Applicant	Takeda Pharmaceuticals
Date of Submission	December 27, 2007
PDUFA Goal Date	October 27, 2008
Proprietary Name / Established (USAN) names	Nesina (alogliptin)
Dosage forms / Strength	6.25 mg, 12.5 mg, and 25 mg tablets
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommended:	<i>Complete Response</i>

Cross Discipline Team Leader Review

1. Introduction

Incretin hormones, such as glucagon-like peptide (GLP)-1 and glucose-dependent insulintropic polypeptide (GIP), are released from the gastrointestinal tract during meals and stimulate insulin release from the pancreatic beta-cell in a glucose-dependent manner.

GLP-1 and GIP have short half-lives (<2 minutes) due to rapid degradation by the dipeptidyl peptidase (DPP)-4 enzyme. Incretin-based pharmacologic therapies for type 2 diabetes are directed toward administering a pharmacologic dose of synthetic GLP-1 that is resistant to DPP-4 degradation (GLP-1 analogues, such as exenatide) or slowing native incretin degradation (DPP-4 inhibitors).

Alogliptin (proposed tradename Nesina) is an oral DPP-4 inhibitor that has been developed by Takeda as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. This memorandum discusses the alogliptin new drug application (NDA) with a focus on key findings from the various review disciplines and the phase 2/3 development program.

2. Background

DPP-4 inhibitors tend to have modest efficacy but these medications appear to be generally well-tolerated with neutral effects on body weight and a low risk for hypoglycemia. Currently, Januvia (sitagliptin phosphate) is the only FDA-approved DPP-4 inhibitor. Saxagliptin is another DPP-4 inhibitor that is under FDA review.

Labeled safety concerns with Januvia include postmarketing reports of hypersensitivity reactions, including Stevens-Johnson Syndrome, and minor increases in serum creatinine in patients with moderate or severe renal impairment. Postmarketing reports of pancreatitis in association with Byetta and Januvia are under FDA review. Other toxicities associated with at least one DPP-4 inhibitor include necrotic skin lesions in monkeys, sometimes near clinical exposures (e.g. vildagliptin, dutogliptin) and possible hepatotoxicity (vildagliptin).

In July 2008, the Division convened a public, 2-day advisory committee meeting to discuss cardiovascular assessment for drugs and biologics developed for the treatment of type 2 diabetes. After considering the recommendations of the advisory committee panel and other data, the Division published a December 2008 Guidance for Industry entitled *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. This guidance document requests that sponsors of new pharmacologic therapies for type 2 diabetes show that these treatments do not result in an unacceptable increase in cardiovascular risk. Although the alogliptin NDA was submitted to FDA prior to the July 2008 advisory committee meeting and prior to the December 2008 guidance, FDA has publicly communicated that all new unapproved therapies for type 2 diabetes (even pending NDAs, like alogliptin) should provide adequate evidence of cardiovascular safety in accordance with the

guidance. Therefore, cardiovascular safety was a major focus of the clinical and statistical reviews for alogliptin.

3. CMC

Alogliptin benzoate is a synthetic, small molecule. Alogliptin tablets are available in dosage strengths of 6.25 mg, 12.5 mg, and 25 mg. (b) (4)

(b) (4) The three tablets otherwise have identical types and amounts of excipients. All chemistry/manufacturing/controls (CMC) issues have been resolved. All Drug Master Files are acceptable or the pertinent information has been adequately provided. The CMC reviewers have determined that the drug product is acceptable and recommend approval of the application (please see reviews by Drs. Chien-Hua Niu, Suong Tran, and Blair Fraser for further details).

Based on stability testing, the CMC reviewers recommend an initial expiration dating period of 3 years for the 12.5 mg and 25 mg strengths and 30 months for the 6.25 mg strength.

(b) (4)
(b) (4)
(b) (4) Therefore, Dr. Tran requests that the action letter inform the sponsor that the (b) (4) strength was not reviewed as part of the NDA.

CMC has determined that the application qualifies for a categorical exclusion from an environmental assessment report because the expected introduction concentration of the active moiety at the point of entry into the aquatic environment is less than 1 part per billion.

The Office of Compliance issued an acceptable recommendation on the manufacturing and testing facilities of the drug product (please see Dr. Tran's memorandum).

4. Nonclinical Pharmacology/Toxicology

The non-clinical pharmacology/toxicology reviewers recommend approval pending agreement on labeling (please see reviews by Drs. David Carlson and Todd Bourcier).

Dr. Carlson has determined that alogliptin has a benign toxicological profile in rats, mice, dogs, and monkeys. Dr. Bourcier notes that very large exposures (≥ 200 -fold excess relative to clinical exposures) were required to identify target organs in animals, which included kidney, lung, liver, and male reproductive organs. Of note, alogliptin was not associated with skin lesions in monkeys at doses tested up to 31-times expected human exposure (DPP-4 selectivity is similar to that seen with Januvia, which also does not cause skin lesions in monkeys).

Dogs developed reddening and flushing of the ears and face, along with body (e.g., foot, neck) and facial edema that was tolerated throughout dosing and was not dose-limiting. These

symptoms did not occur in every animal and did not occur at the same doses across the 4-week, 3-month, and 9-month dog toxicity studies (margins for the no-observed-adverse-effect-level ranged from 6 to 99-fold relative to the 25 mg clinical dose). Dr. Carlson predicts that similar reactions could occur in humans and has attributed these observations to a hypersensitivity or pseudoallergy-type response (the sponsor did not conduct mechanistic studies for these symptoms but similar reactions with another DPP-4 inhibitor were associated with increased histamine release). Both Dr. Carlson and Dr. Bourcier conclude that alogliptin may have a greater frequency and severity of hypersensitivity reactions post-approval compared with Januvia, because premarketing findings were seen in animals with alogliptin but not with Januvia.

Alogliptin binds to melanin but is not phototoxic.

Alogliptin is only teratogenic at doses that cause maternal toxicity, which provide a 100- to 200-fold safety margin compared to clinical exposures. Therefore, Dr. Carlson is recommending Pregnancy Category B. Exposure in human milk is expected because alogliptin is detected in rat milk.

Alogliptin causes thyroid C-cell adenomas and carcinomas in male rats only (≥ 288 -fold above the maximum recommended human dose of 25 mg). In mice, there was a 5% incidence of benign hepatocellular adenomas at 74-times the maximum recommended human dose, which is considered within the historical range of some studies. Dr. Bourcier concluded that these findings pose negligible clinical risk.

Of note, there was no evidence of cardiovascular toxicity based on the non-clinical data, but this conclusion is limited because only healthy animals were tested.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewers recommend approval pending agreement on labeling (please see Dr. Sang Chung's review for details).

Renal excretion is the major elimination pathway; approximately two-thirds of an oral dose is excreted in the urine as alogliptin.

Alogliptin is metabolized to an active M1 metabolite ($<1\%$ of alogliptin exposure) by CYP2D6. An inactive M2 metabolite is also formed ($<4\%$ of alogliptin exposure). Dr. Carlson notes that these metabolites occur in all tested animal species.

Alogliptin is dose proportional over the 25-400 mg range. With a single 25 mg dose, the mean time to reach C_{max} (T_{max}) occurs at 1-2 hours and the mean elimination half-life is 26 hours. Protein binding is 28-38%. Least-squares mean alogliptin exposures (area under the time-concentration curve or AUC) are increased 28% in the elderly, 19% in women, and 28% in Caucasians (compared to Blacks).

Table 1 summarizes the percent increases in mean alogliptin exposures occurring in patients with various degrees of renal impairment.

Table 1. Percent increases in mean alogliptin exposures in patients with renal impairment		
Degree of renal impairment	AUC	C_{max}
Mild	69%	13%
Moderate	108%	42%
Severe	219%	27%
End-stage renal disease	281%	32%
AUC = area under the time-concentration curve		

Based on the results of the renal pharmacokinetic study, the sponsor is proposing no dosage adjustment (i.e., (b) (4) 25 mg) for patients with mild renal impairment, 12.5 mg only for patients with moderate renal impairment, and 6.25 mg only for patients with severe renal impairment or end-stage renal disease. However, the clinical pharmacology reviewers are (b) (4) recommending dosage adjustment to 12.5 mg for patients with mild renal impairment because mean AUC was increased by approximately 70% in this patient population and the 12.5 mg and 25 mg doses had similar efficacy across the phase 3 clinical trials.

There was no effect of moderate hepatic impairment on alogliptin exposures. The sponsor did not assess the effects of mild or severe hepatic impairment on alogliptin pharmacokinetics.

The sponsor conducted numerous drug interaction studies (e.g., with metabolic modulators, P450 probe substrates, ethinyl estradiol, norethindrone, glyburide, metformin, pioglitazone, warfarin, atorvastatin, and digoxin). The clinical pharmacology reviewers have concluded that none of the tested drug interactions are clinically significant.

There is no significant effect of food on alogliptin exposures.

In the Thorough QT Study, the sponsor administered supratherapeutic doses (50 mg and 400 mg) of alogliptin and assessed the QTc interval after a single dose and at steady state after 7 days of repeat dosing (a previous sponsor had conducted a Thorough QT Study, but FDA did not review the QTc results from this prior study because Takeda had concerns about the study design and chose to conduct a second Thorough QT Study, the results of which are summarized below). The study incorporated a positive control (moxifloxacin). The mean steady state C_{max} with the 50 mg dose was 2-fold higher than the C_{max} of the 25 mg clinical dose. The mean steady state C_{max} with 400 mg was 19-fold higher than the C_{max} of the 25 mg clinical dose. Thirty minutes after dosing on Day 7, the 400 mg dose resulted in lengthening of QTcI to 7 msec with an upper one-sided 95% confidence bound of 13 msec, which is greater than the threshold value of 10 msec discussed in the International Conference on Harmonisation (ICH) E14 Guidance. The maximum mean effect of 400 mg on QTcF occurred at T_{max} (1 hour after dosing) and was 8 msec with a one-sided 95% upper bound of 11 msec. In contrast, repeat dosing with 50 mg did not result in lengthening of the QTc interval to greater than 10 msec at any timepoint. Because patients with renal impairment are expected to have the highest exposure to alogliptin, and because such increases are far below the exposures seen with the 400 mg dose, the Interdisciplinary Review Team (IRT) for

Thorough QT Studies concluded that there is no clinically meaningful effect of alogliptin on QTc.

The sponsor has shown that the commercial alogliptin formulation is bioequivalent to the alogliptin formulation used in phase 3 studies. The Division of Scientific Investigation (DSI) reviewed the pivotal bioequivalence study and noted inaccuracies in adverse event reporting (2 of 28 patients had adverse events on the source document that were not reported on the case report form – one patient had conjunctivitis and another had cellulitis of the upper lip) and transcription errors involving urine collection times and urine volumes for 4 of 46 reviewed documents (see Dr. Samuel Chan's review for further details). All remaining data were deemed acceptable and the above findings do not impact on the assessment of bioequivalence.

Dr. Chung notes that 25 mg was the minimum dose that achieved more than 80% inhibition of DPP-4 over 24 hours, which is a typical target used by sponsors developing DPP-4 inhibitors.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

This section will focus on the efficacy results from the controlled, phase 2/3 clinical trials, which consisted of one 12-week phase 2 dose-ranging study and five 26-week phase 3 clinical trials. Please see Dr. Valerie Pratt's clinical review for further details.

The sponsor conducted two additional phase 3 trials that evaluated alogliptin in combination with pioglitazone to support an NDA for the alogliptin/pioglitazone fixed-dose combination tablet (OPI-001 and OPI-002). The sponsor decided to submit these 2 trials to the alogliptin NDA within 3 months of the action goal date to provide additional cardiovascular data to support approvability after the clinical reviewer raised concerns about a potential imbalance in serious cardiovascular events in the alogliptin NDA. This submission was not classified as a major amendment but select cardiovascular and other safety data have been reviewed (see Section 8). The efficacy data and remaining safety data from these two trials will be reviewed under the NDA for the alogliptin/pioglitazone fixed-dose combination tablet, which is currently in-house.

The alogliptin NDA also contains results from an open-label, long-term, uncontrolled extension trial (OLE-012) that enrolled patients who completed the 7 controlled phase 3 trials mentioned above. This extension trial will not be discussed in detail because the uncontrolled design limits efficacy and safety conclusions.

The controlled phase 2/3 clinical trials included in the original NDA were all randomized, multinational, double-blind, and placebo-controlled. The phase 3 trials had a 4-week placebo-controlled run-in period prior to randomization. Approximately 44% of randomized patients in the phase 3 program were enrolled in the United States.

The phase 2 study evaluated alogliptin doses of 6.25 mg, 12.5 mg, 25 mg, 50 mg, and 100 mg vs. placebo in patients with inadequate glycemic control on diet and exercise alone. The 5 controlled phase 3 trials evaluated alogliptin doses of 12.5 mg and 25 mg vs. placebo in the following settings:

PLC-010: Monotherapy in patients with inadequate glycemic control on diet and exercise

- <7 days of antidiabetic therapy within the 3 months prior to screening

MET-008: Add-on to metformin

- Metformin monotherapy for ≥ 3 months prior to screening
- Stable metformin dose $\geq 1,500$ mg (or maximally-tolerated dose) for ≥ 8 weeks prior to randomization

TZD-009: Add-on to pioglitazone

- Rosiglitazone or pioglitazone alone or in combination with metformin or a sulfonylurea for ≥ 3 months prior to screening
- Patients were switched to pioglitazone and were to be taking ≥ 30 mg daily at the start of the run-in period

SULF-007: Add-on to sulfonylurea

- Sulfonylurea monotherapy for ≥ 3 months prior to screening
- Stable sulfonylurea dose equivalent to ≥ 10 mg of glyburide (≥ 5 mg if higher doses not tolerated) for ≥ 8 weeks prior to randomization

INS-011: Add-on to insulin

- Insulin alone or in combination with metformin for ≥ 3 months prior to screening
- Stable insulin dose of 15-100 units/day for ≥ 8 weeks prior to randomization
- Metformin dose (if applicable) stable for ≥ 8 weeks prior to randomization

The two trials conducted to support the alogliptin/pioglitazone fixed-dose combination tablet (OPI-001 and OPI-002) were also 26-week, double-blind, controlled trials. Study OPI-001 randomized patients with inadequate glycemic control on metformin to 1 of 12 treatment groups: pioglitazone monotherapy (15 mg, 30 mg, or 45 mg), alogliptin monotherapy (12.5 mg or 25 mg), alogliptin plus pioglitazone (12.5 mg + 15 mg, 12.5 mg + 30 mg, 12.5 mg + 45 mg, 25 mg + 15 mg, 25 mg + 30 mg, 25 mg + 45 mg), or placebo. Study OPI-002 randomized patients with inadequate glycemic control on diet and exercise to 1 of 4 treatment groups: alogliptin 25 mg alone, pioglitazone 30 mg alone, alogliptin 25 mg + pioglitazone 30 mg, and alogliptin 12.5 mg + pioglitazone 30 mg.

Background anti-diabetic medication was to remain stable throughout the treatment periods. For all 3 treatment arms in the add-on to insulin trial, the baseline and Week 26 median daily insulin doses were identical (56 units in placebo group, 56 units in the alogliptin 12.5 mg group, and 50 units in the alogliptin 25 mg group).

The primary efficacy endpoint in these trials was change from baseline in HbA1c. Other efficacy endpoints included change from baseline in fasting plasma glucose (FPG), HbA1c responder analyses, and incidence of glycemic rescue. These are typical endpoints for trials designed to support approvability of anti-diabetic medications.

These clinical trials had similar inclusion and exclusion criteria. Entry criteria included age between 18-80 years and type 2 diabetes with baseline HbA1c 7-10% (8-10% in the add-on to insulin trial; 7.5-10% in OPI-001; 7.5-11% in OPI-002). Exclusion criteria included serum creatinine >2.0 mg/dL (≥ 1.5 mg/dL for men and ≥ 1.4 mg/dL for women in the add-on to metformin trials) and history of coronary intervention or myocardial infarction within 6 months prior to screening or New York Heart Association Class III or IV heart failure.

The five phase 3 trials in the original NDA used the following glycemic rescue criteria:

- Single FPG ≥ 275 mg/dL during Weeks 1-3
- Single FPG ≥ 250 mg/dL during Weeks 4-7 (≥ 275 mg/dL in the insulin study)
- Single FPG ≥ 225 mg/dL during Weeks 8-11 (≥ 250 mg/dL in the insulin study)
- HbA1c $\geq 8.5\%$ and $\leq 0.5\%$ reduction from baseline from Week 12 onwards (HbA1c $\geq 8.7\%$ in the insulin study).

All data beyond Week 26 in the alogliptin clinical development program are uncontrolled. Patients who completed the 26-week phase 3 trials and those who required glycemic rescue were eligible for enrollment in the voluntary, uncontrolled extension trial. Completers of the feed-in trials were randomized 1:1 to open-label alogliptin 12.5 mg daily or 25 mg daily for up to 2 years. Patients who required glycemic rescue during a feed-in trial received 25 mg of open-label alogliptin in the extension trial. Patients who failed to achieve adequate glycemic control during the extension trial (as determined by the investigator) were given additional anti-diabetic therapy or their existing medications could be adjusted. The NDA submission contained data from the open-label trial through the cut-off date of August 29, 2007. The 120-day safety update contains data from this open-label trial through the cut-off date of January 31, 2008.

Randomization was stratified by Week -1 HbA1c <8% vs. $\geq 8\%$ (<9% vs. $\geq 9\%$ for 011) and geographic region. For the add-on to pioglitazone trial, randomization was also stratified by baseline anti-diabetic treatment (pioglitazone alone vs. pioglitazone+metformin vs. pioglitazone+sulfonylurea). For the add-on to insulin trial, randomization was also stratified by baseline anti-diabetic treatment (insulin alone vs. insulin+metformin). In the add-on to insulin trial, patients were randomized 1:1:1 to alogliptin 12.5 mg, alogliptin 25 mg, and placebo. In the other four phase 3 trials, patients were randomized 2:2:1 to alogliptin 12.5 mg, alogliptin 25 mg, and placebo. The sponsor used a gate-keeper strategy to control type 1 error for HbA1c, testing alogliptin 12.5 mg against placebo contingent on a statistically significant result for the comparison of alogliptin 25 mg vs. placebo.

As discussed by Dr. Janice Derr, the biostatistics reviewer, the primary statistical population termed “Full Analysis Set (FAS)” consisted of all randomized patients with a baseline and at least one post-baseline assessment of the parameter of interest. The last-observation-carried-forward method was used for patients with missing data and for patients who initiated

glycemic rescue therapy. The primary efficacy analysis was conducted using analysis of covariance (ANCOVA). The primary model included study treatment and geographic region as class variables and diabetes duration and baseline HbA1c as continuous covariates.

The per-protocol population included all patients in the FAS population who had no major protocol violations.

Demographics: Dr. Pratt discusses the patient demographics in detail. Briefly, the mean age across the five phase 3 trials was approximately 55 years. Most patients (75%-83%) were <65 years old. Men comprised 58% of patients randomized into the add-on to pioglitazone trial but only 41% of patients randomized into the add-on to insulin trial. Gender was more equally balanced in the remaining phase 3 trials. Most patients were Caucasian (65%-77%), approximately 8-12% were Asian, and 4-13% were Black. As expected, mean duration of diagnosed diabetes was shortest in the monotherapy trial (3 years), longest for the add-on insulin trial (13 years), and intermediate for the other add-on trials (6-8 years). Mean body mass index ranged from 30.1-32.5 kg/m². Mean baseline HbA1c was approximately 8.0% in all trials except in the add-on to insulin trial (9.3%)

Efficacy Results:

HbA1c: Table 2, adapted from Dr. Derr's statistical review, summarizes the primary efficacy results using the FAS population. In the 12-week phase 2 trial, alogliptin doses from 12.5 mg to 100 mg daily resulted in similar and statistically significant HbA1c reductions from baseline (approximately 0.5% reduction relative to placebo). The 6.25 mg dose had slightly less than one-half the efficacy of the other doses. These data suggest that daily doses ≥ 12.5 mg are at the top of the dose-response curve for HbA1c.

In the 5 phase 3 trials, alogliptin resulted in similar placebo-corrected mean reductions in HbA1c from baseline to Week 26 (0.4-0.5% with 12.5 mg and 0.5-0.6% with 25 mg), all statistically significant ($p < 0.001$). As Dr. Derr notes, the net effect of the 12.5 mg and 25 mg doses are not separable statistically, although this was not an objective of the trials.

A sensitivity analysis using the per-protocol population yielded similar results (0.4-0.5% mean reduction in HbA1c relative to placebo for the 12.5 mg dose and 0.5-0.6% mean reduction in HbA1c relative to placebo for the 25 mg dose). A sensitivity analysis using only patients who completed the 26-week treatment period yielded supportive results, although the magnitude of effect of alogliptin in the completer analysis was generally less than that seen above (0.2-0.4% mean reduction in HbA1c relative to placebo for the 12.5 mg dose and 0.4-0.6% mean reduction in HbA1c relative to placebo for the 25 mg dose). Dr. Derr concluded that the completer analyses are biased due to the differential dropout rates in the alogliptin and placebo treatment arms and the overall high dropout rates across the phase 3 program (see below).

Across the phase 3 trials, the maximal effect of alogliptin on HbA1c typically occurred at Week 12 with a relatively constant placebo-corrected effect from Weeks 12-26. However, Dr. Derr notes that the change in glycemic rescue criteria at Week 12 (from FPG to HbA1c) resulted in a substantial proportion of glycemic rescues and discontinuations from Week 12-

16. These rescued and discontinued patients had HbA1c values from Week 12 carried forward for the HbA1c analyses, which contributes to this apparent stabilization.

Table 2. Primary efficacy results for the phase 2 and 3 clinical trials (FAS population with LOCF)					
Study	N	Baseline mean \pm SE	Change from baseline Adj. mean \pm SE	Difference in adjusted mean change 95% CI	p-value
Study 003 (dose-ranging) – 12-week trial					
Alo 6.25 mg	42	8.0 \pm 0.2	-0.2 \pm 0.1	Not reported	
Alo 12.5 mg	42	7.9 \pm 0.2	-0.5 \pm 0.1	Not reported	
Alo 25 mg	45	8.0 \pm 0.2	-0.6 \pm 0.1	Not reported	
Alo 50 mg	43	8.1 \pm 0.2	-0.4 \pm 0.1	Not reported	
Alo 100 mg	44	8.0 \pm 0.2	-0.5 \pm 0.1	Not reported	
Placebo	41	8.2 \pm 0.2	0.0 \pm 0.1	Not reported	
Study 010 (monotherapy) – 26-week trial					
Alo 25 mg	128	7.9 \pm 0.1	-0.6 \pm 0.1	-0.6 (-0.8, -0.4)	<0.001
Alo 12.5 mg	131	7.9 \pm 0.1	-0.6 \pm 0.1	-0.5 (-0.8, -0.3)	<0.001
Placebo	63	8.0 \pm 0.1	0.0 \pm 0.1		
Study 007 (add-on to sulfonylurea) – 26-week trial					
Alo 25 mg	197	8.1 \pm 0.1	-0.5 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
Alo 12.5 mg	201	8.1 \pm 0.1	-0.4 \pm 0.1	-0.4 (-0.6, -0.2)	<0.001
Placebo	97	8.2 \pm 0.1	0.0 \pm 0.1		
Study 008 (add-on to metformin) – 26-week trial					
Alo 25 mg	203	7.9 \pm 0.1	-0.6 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
Alo 12.5 mg	210	7.9 \pm 0.1	-0.6 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
Placebo	103	8.0 \pm 0.1	-0.1 \pm 0.1		
Study 009 (add-on to pioglitazone) – 26-week trial					
Alo 25 mg	195	8.0 \pm 0.1	-0.8 \pm 0.1	-0.6 (-0.8, -0.4)	<0.001
Alo 12.5 mg	195	8.1 \pm 0.1	-0.7 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
Placebo	95	8.0 \pm 0.1	-0.2 \pm 0.1		
Study 011 (add-on to insulin) – 26-week trial					
Alo 25 mg	126	9.3 \pm 0.1	-0.7 \pm 0.1	-0.6 (-0.8, -0.4)	<0.001
Alo 12.5 mg	130	9.3 \pm 0.1	-0.6 \pm 0.1	-0.5 (-0.7, -0.3)	<0.001
Placebo	126	9.3 \pm 0.1	-0.1 \pm 0.1		
FAS=full analyses set; LOCF=last-observation-carried-forward; SE=standard error; CI=confidence interval					

Fasting plasma glucose: In 3 trials (monotherapy, add-on to sulfonylurea, and add-on to insulin), the alogliptin 25 mg dose resulted in numerically greater mean placebo-corrected reductions in FPG compared to the 12.5 mg dose (Table 3). However, in the add-on to metformin and add-on to pioglitazone trials, the 25 mg and 12.5 mg doses resulted in virtually identical placebo-corrected reductions in FPG. Results were not statistically significant for either dose in the add-on to sulfonylurea trial and for the 12.5 mg dose in the add-on to insulin trial.

Table 3. Fasting plasma glucose results for the 3 clinical trials (FAS population with LOCF)					
Study	N	Baseline mean \pm SE	Change from baseline Adj. mean \pm SE	Difference in adjusted mean change 95% CI	p-value
Study 010 (monotherapy)					
Alo 25 mg	131	172 \pm 4	-16 \pm 4	-28 (-40, -15)	<0.001
Alo 12.5 mg	133	174 \pm 4	-10 \pm 4	-22 (-34, -9)	<0.001
Placebo	64	173 \pm 7	11 \pm 5		
Study 007 (add-on to sulfonylurea)					
Alo 25 mg	198	174 \pm 4	-8 \pm 3	-11 (-22, 1)	0.07
Alo 12.5 mg	201	172 \pm 4	-5 \pm 3	-7 (-18, 5)	0.24
Placebo	99	177 \pm 5	2 \pm 5		
Study 008 (add-on to metformin)					
Alo 25 mg	204	172 \pm 3	-17 \pm 3	-17 (-26, -9)	<0.001
Alo 12.5 mg	211	168 \pm 3	-19 \pm 3	-19 (-27, -10)	<0.001
Placebo	104	180 \pm 5	0 \pm 4		
Study 009 (add-on to pioglitazone)					
Alo 25 mg	197	170 \pm 3	-20 \pm 3	-14 (-23, -5)	0.003
Alo 12.5 mg	196	173 \pm 3	-20 \pm 3	-14 (-23, -5)	0.003
Placebo	97	171 \pm 5	-6 \pm 4		
Study 011 (add-on to insulin)					
Alo 25 mg	128	186 \pm 6	-12 \pm 6	-18 (-33, -2)	0.03
Alo 12.5 mg	131	190 \pm 5	2 \pm 6	-4 (-19, 12)	0.66
Placebo	127	196 \pm 7	6 \pm 6		
FAS=full analyses set; LOCF=last-observation-carried-forward; SE=standard error; CI=confidence interval					

HbA1c responder analyses and glycemic rescue: Table 4 summarizes the proportion of patients achieving HbA1c $\leq 7\%$ and the proportion of patients requiring glycemic rescue in the phase 3 trials. A greater proportion of patients in the alogliptin groups achieved the HbA1c target than did patients in the placebo group, although results were either borderline significant or not statistically significant for the 12.5 mg group in the add-on to sulfonylurea trial and for both dose groups in the add-on to insulin trial. A numerically greater proportion of patients in the 25 mg group achieved the HbA1c target compared to the 12.5 mg group in both the add-on to sulfonylurea and add-on to pioglitazone trials. However, in the monotherapy, add-on to metformin, and add-on to insulin trials, the 25 mg group did not confer an advantage over the 12.5 mg group with respect to the proportion of patients achieving the HbA1c target.

In each trial, the proportion of patients requiring glycemic rescue was virtually identical for the 12.5 mg and 25 mg groups (Table 4). The proportion of patients requiring glycemic rescue was significantly lower in the alogliptin groups compared to the placebo groups, except in the add-on to pioglitazone trial, which had a low placebo event rate. As discussed by Dr. Derr, a large proportion of patients required glycemic rescue were prematurely discontinued from the phase 3 trials (45% in the add-on to insulin trial and 21-27% in the remaining trials). These discontinuation rates are higher than those observed in typical diabetes trials and are largely attributable to the change in glycemic rescue criteria from FPG to HbA1c at Week 12. Dr. Derr

raises concerns that having such high glycemic rescue/dropout rates impedes the ability to estimate the true treatment difference without bias, particularly in the add-on to insulin trial, where these rates were highest. However, Dr. Derr does not go as far as to say that the efficacy findings cannot be included in labeling.

Table 4. Proportion of patients achieving glycemic targets or requiring glycemic rescue				
	Proportion of patients achieving HbA1c $\leq 7\%$		Proportion of patients requiring glycemic rescue	
Study	n/N (%)	p-value*	n/N (%)	p-value*
Study 010 (monotherapy)				
Alo 25 mg	58/131 (44%)	0.008	10/131 (8%)	<0.001
Alo 12.5 mg	63/133 (47%)	0.001	13/133 (10%)	0.001
Placebo	15/64 (23%)	-	19/64 (30%)	-
Study 007 (add-on to sulfonylurea)				
Alo 25 mg	69/198 (35%)	0.002	31/198 (16%)	0.03
Alo 12.5 mg	60/203 (30%)	0.057	30/201 (15%)	0.02
Placebo	18/99 (18%)	-	28/99 (28%)	-
Study 008 (add-on to metformin)				
Alo 25 mg	92/207 (44%)	<0.001	17/207 (8%)	0.003
Alo 12.5 mg	110/213 (52%)	<0.001	19/211 (9%)	0.004
Placebo	19/104 (18%)	-	25/104 (24%)	-
Study 009 (add-on to pioglitazone)				
Alo 25 mg	98/199 (49%)	0.004	18/199 (9%)	0.43
Alo 12.5 mg	87/197 (44%)	0.02	19/196 (10%)	0.10
Placebo	33/97 (34%)	-	12/97 (12%)	-
Study 011 (add-on to insulin)				
Alo 25 mg	10/129 (8%)	0.23	25/128 (20%)	<0.001
Alo 12.5 mg	11/131 (8%)	0.05	27/131 (21%)	<0.001
Placebo	1/129 (1%)	-	52/129 (40%)	-
*comparison to placebo				

Subgroup analyses for HbA1c: Dr. Derr notes that patients with higher baseline HbA1c generally had greater mean reductions in HbA1c compared to patients with lower baseline HbA1c values. This finding occurred in the placebo and alogliptin treatment arms and has been noted in clinical studies of other diabetes medications.

Dr. Derr conducted other subgroup analyses of HbA1c and has concluded that the mean response was relatively similar in the younger and older age groups (< 65 and ≥ 65 years) and in men and women. Dr. Derr determined that there were too few non-Caucasians to adequately evaluate potential race-related differences in HbA1c reduction. In the two studies with reasonable representation in the Hispanic/Latino ethnicity category, Dr. Derr obtained similar results for the Hispanic/Latino subgroup and for the non-Hispanic/Latino subgroup. There were no consistent differences in HbA1c response between categories of baseline body mass index across the 5 trials.

8. Safety

The safety dataset consists of all randomized patients who received ≥ 1 dose of study drug. Adverse events in the integrated safety database were coded with MedDRA version 10.0 regardless of the MedDRA version used in the individual clinical study reports. A hands-on review comparing MedDRA preferred terms affected by the switch to version 10.0 did not raise any concerns about miscoding. Table 5 summarizes patient exposures in the alogliptin development program at the time of NDA submission and in the 120-day safety update. Although 1-year exposures to alogliptin were low at the time of NDA filing, the 1-year exposures at the time of the 120-day safety update are consistent with the recommended NDA filing exposures described in the February 2008 draft guidance for industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*. Of note, the alogliptin NDA was submitted to FDA prior to publication of this draft guidance. In addition, the 1-year patient exposures in the original NDA and 120-day safety update exceeded the agreed upon patient exposures at the Pre-NDA meeting (>300 at 1-year at NDA filing and $>1,100$ at the 120-day safety update).

Although the number of patients with 1-year exposure to alogliptin appears adequate, the long-term data are limited because all data beyond Week 26 are uncontrolled, substantially affecting interpretability. In contrast, other recently submitted NDAs (e.g., Januvia, liraglutide, saxagliptin) have had controlled long-term data up to or beyond 1-year.

Table 5. Patient exposures to alogliptin			
Exposure	Alogliptin 12.5 mg	Alogliptin 25 mg	All alogliptin
At NDA filing			
≥ 6 months	841	1109	1749
≥ 1 year	144	228	654
At 120-day safety update			
≥ 6 months	1073	1417	2024
≥ 1 year	384	616	1318
120-day safety update plus OPI-001 and OPI-002 data			
≥ 6 months	1625	2125	3255
≥ 1 year	409	649	1443
≥ 18 months	95	134	422
OPI-001 and OPI-002 are the 6-month controlled phase 3 trials conducted to support the alogliptin/pioglitazone fixed-dose combination tablet (NDA 22-426)			

In the above table, the “all alogliptin” exposures represent cumulative exposure to any dose of alogliptin. The “all alogliptin” exposures are not the sum of the exposures in the alogliptin 12.5 mg and alogliptin 25 mg columns because some patients received different doses of alogliptin in a controlled study than in the open-label extension study. For example, a patient who received 6 months of exposure to alogliptin 12.5 mg in a controlled study and 8 months of exposure to alogliptin 25 mg in the open-label extension study will appear in only the “ ≥ 6 months” row for each dose but will appear in both the “ ≥ 6 months” and “ ≥ 1 year” rows for “all alogliptin” because the combined exposure to all doses is 14 months.

Depending on the formula used (Cockcroft-Gault or MDRD), approximately 700-1,800 patients with baseline mild renal impairment, 50-110 patients with baseline moderate renal impairment, and <5 patients with baseline severe renal impairment were exposed to alogliptin for at least 6 months up to the cutoff date for the 120-day safety update submission, including data from OPI-001 and OPI-002. Corresponding exposures for patients exposed to alogliptin for at least 1 year were 330-890 for patients with baseline mild renal impairment and 30-70 for patients with baseline moderate renal impairment. The sponsor is planning to either conduct dedicated renal studies in patients with moderate and severe renal impairment or will evaluate these patient populations within the planned cardiovascular safety trial. Of note, the sponsor did not perform subgroup analyses comparing safety and tolerability in patients with normal renal function to those with mild renal impairment, as defined using Cockcroft-Gault or the MDRD formula. This may impact on whether the 12.5 mg dose only (as recommended by clinical pharmacology) or the 12.5 mg and 25 mg doses (as recommended by the sponsor and Dr. Pratt) should be recommended in patients with mild renal impairment.

Because there was 2:2:1 randomization to alogliptin 12.5 mg, alogliptin 25 mg, and placebo in 4 of the 5 phase 3 clinical trials included in the original NDA, the controlled phase 2 and 3 program (the 12-week phase 2 dose finding study and the 5 clinical trials described above) consisted of 1,961 alogliptin-treated patients and 534 placebo-treated patients (i.e., approximately 4-times as many alogliptin-treated patients compared to placebo-treated patients). When OPI-001 and OPI-002 are included, there are 3,490 alogliptin-treated patients and 1,214 non-alogliptin-treated patients in controlled phase 3 trials, corresponding to a randomization ratio of 3:1. This imbalance in randomization and the differential dropout rates between the alogliptin and placebo-treated patients introduce challenges in data interpretation, particularly when event rates are low.

Patient disposition: Table 6 summarizes patient disposition in the pooled phase 2/3 program for the placebo, alogliptin 12.5 mg and alogliptin 25 mg groups. A greater proportion of the 12.5 mg and 25 mg alogliptin-treated patients (76%) completed the trials compared to placebo-treated patients (60%), mainly driven by lower rates of hyperglycemic rescue in the alogliptin groups (12% vs. 29% with placebo). The placebo and alogliptin groups had a comparable proportion of patients who prematurely discontinued from the trials for other reasons (11-12%), although discontinuations due to adverse events were numerically higher in the alogliptin groups (2.7% with 12.5 mg; 2.6% with 25 mg) compared to placebo (2.1%). Discontinuations due to adverse events are discussed in greater detail below.

Table 6. Patient disposition– controlled phase 2/3 program

Disposition	Placebo N=534 n (%)	Alogliptin treatment groups	
		12.5 mg N=922 n (%)	25 mg N=910 n (%)
Completed	318 (60)	702 (76)	689 (76)
Hyperglycemic rescue	157 (29)	114 (12)	109 (12)
Discontinued for other reasons	59 (11)	104 (11)	111 (12)
Adverse event	11 (2.1)	25 (2.7)	24 (2.6)
Major protocol deviation	8 (1.5)	13 (1.4)	12 (1.3)
Lost to follow-up	7 (1.3)	14 (1.5)	13 (1.4)
Voluntary withdrawal/investigator discretion	32 (6.0)	50 (5.4)	61 (6.7)
Other	1 (0.2)	2 (0.2)	1 (0.1)

Deaths: This section includes data from the original NDA and from OPI-001 and OPI-002 (the 2 trials conducted to support the alogliptin/pioglitazone fixed-dose combination tablet). As discussed by Dr. Pratt, there were 7 reported deaths in these trials and 4 additional deaths reported in the 120-day safety update. Of these 11 deaths, 5 occurred during the controlled portions of the clinical trials – 4 in alogliptin-treated patients (3 taking 12.5 mg and 1 taking 25 mg) and 1 in a pioglitazone-treated patient. The 4:1 ratio of deaths in the controlled portions of the clinical trials is consistent with the randomization scheme. These 5 deaths were cardiovascular-related (1 case of hypertensive heart disease, 1 case of myocardial infarction, and 2 cases of sudden death in the alogliptin group and 1 case of sudden death in a pioglitazone-treated patient). The 6 deaths during the open-label extension trial included 1 case of cardiac arrest, 2 cases of sudden death, 1 case of pneumococcal sepsis, 1 case of myocardial infarction, and 1 case of trauma probably due to a mechanical fall. The lack of a control group in the open-label extension trial limits interpretability of these 6 deaths. As would be expected for a patient population with type 2 diabetes, most of the 11 deaths were cardiovascular-related. In summary, there is no concerning signal for death with alogliptin, although event rates were low.

Serious adverse events: In the phase 2/3 clinical trials, treatment-emergent serious adverse events were defined as serious adverse events occurring or worsening after the first dose of study medication and within 14 days after the last dose of study medication. Because serious adverse events were relatively infrequent, data from the controlled phase 2/3 program have been pooled to increase the likelihood of detecting important differences between treatment groups. Dr. Pratt has reviewed all relevant patient narratives. Please see her review for further details. Table 7 summarizes the serious adverse events occurring in >1 patient in any treatment group in the controlled phase 2/3 program. Most of the individual preferred terms occurred infrequently, typically reported in 0-5 patients in any given treatment group. None of the preferred terms appeared to have a relationship to alogliptin dose. Only the two System-Organ-Classes discussed below appear to have an imbalance not favoring alogliptin:

Table 7. Serious adverse events occurring in more than 1 patient in any treatment group in the controlled phase 2/3 program

System Organ Class Preferred term	Placebo N=534	Alogliptin				
		All doses N=1961	6.25 mg N=42	12.5 mg N=922	25 mg N=910	50/100 mg N=87
Patients with at least 1 SAE	20 (3.7)	80 (4.1)	1 (2.4)	36 (3.9)	42 (4.6)	1 (1.1)
Cardiac disorders	2 (0.4)	23 (1.2)	0	11 (1.2)	11 (1.2)	1 (1.1)
Angina pectoris	0	7 (0.4)	0	1 (0.1)	5 (0.5)	1 (1.1)
Angina unstable	2 (0.4)	1 (0.1)	0	0	1 (0.1)	0
Atrial fibrillation	0	2 (0.1)	0	2 (0.2)	0	0
Cardiac failure congestive	0	4 (0.2)	0	1 (0.1)	3 (0.3)	0
Coronary artery disease	0	2 (0.1)	0	2 (0.2)	0	0
Myocardial infarction	0	4 (0.2)	0	2 (0.2)	2 (0.2)	0
General disorders/admin site	0	8 (0.4)	1 (2.4)	4 (0.4)	3 (0.3)	0
Noncardiac chest pain	0	6 (0.3)	1 (2.4)	2 (0.2)	3 (0.3)	0
Sudden death	0	2 (0.1)	0	2 (0.2)	0	0
Hepatobiliary disorders	1 (0.2)	3 (0.2)	0	2 (0.2)	1 (0.1)	0
Cholecystitis	0	2 (0.1)	0	2 (0.2)	0	0
Infections and infestations	5 (0.9)	16 (0.8)	0	5 (0.5)	11 (1.2)	0
Cellulitis	2 (0.4)	2 (0.1)	0	0	2 (0.2)	0
Pyelonephritis	0	2 (0.1)	0	0	2 (0.2)	0
Musculoskeletal/connective tissue	1 (0.2)	5 (0.3)	0	3 (0.3)	2 (0.2)	0
Arthralgia	0	3 (0.2)	0	2 (0.2)	1 (0.1)	0

Cardiac Disorders: The table above, adapted from the sponsor's submission reports 23 alogliptin-treated patients vs. 2 placebo-treated patients with a serious adverse event in the Cardiac Disorders System-Organ-Class. To further bolster events, Dr. Pratt also evaluated serious cardiovascular events occurring in OPI-001 and OPI-002, the two phase 3 clinical trials conducted to support the alogliptin/pioglitazone fixed-dose combination NDA. In these two trials, a total of seven serious cardiovascular events were reported (5 in alogliptin-treated patients and 2 in non-alogliptin treated patients). Therefore, when these two trials are included, there are 28 total events among the alogliptin-treated patients and 4 total events among the non-alogliptin-treated patients. Dr. Derr calculated the incidence ratio for alogliptin relative to comparator for these overall cardiovascular serious adverse events and notes that the corresponding confidence interval is wide with an upper bound exceeding 1.8 (2.3 with the stratified asymptotic method and 2.2 with the exact method).

Dr. Pratt has reviewed the narratives for all 32 events, and questions the coded preferred term for some of the patients. Perhaps the best example is alogliptin-treated patient 422/9009 who has preferred terms of "Angina pectoris" and "Coronary artery disease". However, the narrative mentions that the patient was hospitalized with elevated creatinine phosphokinase (CPK) and elevated CPK-MB fraction in the setting of chest pain, which is consistent with an acute myocardial infarction.

The events in Table 8 are based on Dr. Pratt's hands-on review of the 32 narratives (a range is provided in those cases where diagnoses may be in doubt). When the phase 2/3 program is combined with OPI-001 and OPI-002, there are a total of 3,489 alogliptin-treated patients and 1,213 comparator-treated patients (randomization scheme approximately 3:1). Therefore, there is an imbalance not favoring alogliptin for overall serious cardiovascular events (28:4) and for some categories of serious cardiovascular adverse events (e.g., 5-7:1 for myocardial infarction; 7-12:0-1 for angina). However, the most appropriate conclusion is that event rates are too low to definitively determine whether alogliptin has an adverse effect on serious cardiovascular events, because a few more events in the comparator groups or a few less events in the alogliptin group would yield ratios consistent with the randomization scheme. Nonetheless, these findings, together with the inability of the current data to meet the recommendations of the new diabetes cardiovascular guidance (see below) support a "Complete Response" action on this NDA.

Table 8. Serious cardiovascular events in the alogliptin phase 2/3 program (includes OPI-001 and OPI-002)				
Event	Per sponsor preferred terms		Per Dr. Pratt's hands-on review	
	Alogliptin	Comparator	Alogliptin	Comparator
Myocardial infarction	5	1	5-7	1
Angina	7*	0	8-12	1
Unstable angina	3	2	2-3	2
Angina/unstable angina	10	2	10-15	3
Heart failure	4	0	4	0
Atrial fibrillation/flutter	2	0	4-5	0
Bradycardia	1	0	1	0
Palpitations	1	0	-	-
Coronary artery disease	3*	1	-	-
Arteriosclerosis	1	0	-	-
Myocardial ischemia	1	0	-	-
Coronary artery stenosis	1	0	-	-
*One patient had 2 preferred terms ("Angina pectoris" and "Coronary artery disease")				

General Disorders and Administration Site Conditions: There were 8 alogliptin-treated patients and no placebo-treated patients with a reported serious adverse event in the General Disorders and Administration Site Conditions System-Organ-Class. Six of these events were reported as non-cardiac chest pain and 2 events were reported as sudden death. I reviewed the narratives for the 6 events of non-cardiac chest pain and concur that none of these patients appeared to have a cardiac cause for their symptoms.

Withdrawals due to adverse events: Because withdrawals due to adverse events were also relatively infrequent, data from the controlled phase 2/3 program have been pooled to increase the likelihood of detecting important differences between treatment groups (Table 9). The proportion of patients withdrawing due to an adverse event was 2.3% with alogliptin 12.5 mg, 2.4% with alogliptin 25 mg, and 2.1% with placebo (Table 6 shows all adverse events leading to patient discontinuation, whereas the data in Table 9 are only treatment-emergent adverse

events leading to patient discontinuation). Findings were generally consistent with the randomization scheme.

Table 9. Withdrawals due to adverse events occurring in more than 1 patient in any treatment group in the controlled phase 2/3 program

System Organ Class Preferred term	Placebo N=534	Alogliptin				
		All doses N=1961	6.25 mg N=42	12.5 mg N=922	25 mg N=910	50/100 mg N=87
≥1 event leading to withdrawal	11 (2.1)	48 (2.4)	0	21 (2.3)	22 (2.4)	5 (5.7)
Cardiac disorders	1 (0.2)	5 (0.3)	0	2 (0.2)	3 (0.3)	0
Cardiac failure congestive	0	2 (0.1)	0	0	2 (0.2)	0
General disorders/admin site	0	5 (0.3)	0	3 (0.3)	2 (0.2)	0
Sudden death	0	2 (0.1)	0	2 (0.2)	0	0
Investigations	0	7 (0.4)	0	4 (0.4)	3 (0.3)	0
Liver function test abnormal	0	3 (0.2)	0	2 (0.2)	1 (0.1)	0
Nervous system disorders	2 (0.4)	8 (0.4)	0	3 (0.3)	2 (0.2)	3 (3.4)
Headache	1 (0.2)	4 (0.2)	0	1 (0.1)	1 (0.1)	2 (2.3)
Potentially important events leading to withdrawal and occurring in ≤1 patient in any treatment group						
Alanine aminotransferase increased	0	1 (0.1)	0	0	1 (0.1)	0
Serum sickness	0	1 (0.1)	0	0	1 (0.1)	0
Pancreatitis acute	0	0	0	0	1 (0.1)	0
Skin/subcutaneous tissue disorders	1 (0.2)	7 (0.4)	0	2 (0.2)	3 (0.3)	2 (2.3)
Dermatitis	0	1 (0.1)	0	1 (0.1)	0	0
Dermatitis contact	0	1 (0.1)	0	1 (0.1)	0	0
Drug eruption	0	1 (0.1)	0	0	1 (0.1)	0
Rash	0	1 (0.1)	0	0	0	1 (0.1)
Rash maculopapular	0	1 (0.1)	0	0	0	1 (0.1)
Subcorneal pustular dermatosis	0	1 (0.1)	0	0	1 (0.1)	0
Urticaria	0	1 (0.1)	0	0	1 (0.1)	0

Potentially important adverse events associated with study medication discontinuation are summarized below:

Alanine aminotransferase increased: One patient treated with alogliptin 25 mg had a baseline alanine aminotransferase (ALT) of 62 U/L (upper limit of the reference range is 25 U/L). At Week 8, the ALT was 114 U/L and total bilirubin was 1.3 mg/dL (baseline total bilirubin was 1.0 mg/dL and the upper limit of the reference range is 1.1 mg/dL). Viral hepatitis serologies were negative. Abdominal ultrasound showed mild hepatomegaly with fatty liver. Study medication was discontinued on Day 84. ALT on Day 153 was reported to be normal.

Liver function test abnormal: One alogliptin 12.5 mg-treated patient was discontinued because of elevated ALT. The ALT was 63 U/L at Week 2; however, the baseline ALT was 73 U/L. Another alogliptin 12.5 mg-treated patient had a mildly elevated ALT at baseline (39 U/L) that peaked at 112 U/L around Week 8. Total bilirubin was normal. CT scan showed fatty liver. One alogliptin 25 mg-treated patient was discontinued due to ALT of 357 U/L at Week 1. However, his baseline ALT was 430 U/L.

Liver test abnormalities are discussed in further detail in the laboratory section below.

Serum sickness: One alogliptin 25 mg-treated patient developed a diffuse rash, periorbital edema, arthralgias, nausea, diarrhea, malaise, and an 8-lb weight gain around Day 32. Study medication was discontinued on Day 28. This likely represents a hypersensitivity reaction to study medication.

Pancreatitis: Please see the discussion regarding cases of pancreatitis below.

Skin and subcutaneous tissue disorders: A small proportion (<1%) of alogliptin-treated patients discontinued due to potential allergic type reactions, such as rash and urticaria. Please see the discussion on hypersensitivity reactions below.

Common adverse events: Table 10 summarizes the common adverse events (incidence $\geq 3\%$ in the all alogliptin group) and occurring more frequently with alogliptin than with placebo for each of the phase 3 trials. There are no adverse events that consistently meet these criteria across all 5 phase 3 trials. Nasopharyngitis, headache, and hypertension were the only adverse events showing some consistency, meeting the above criteria in three of the 5 phase 3 trials. Of note, the objective blood pressure data do not support an adverse effect of alogliptin on blood pressure and are more reliable than the somewhat subjective reporting by investigators of adverse events of hypertension.

Table 10. Common adverse events (incidence $\geq 3\%$ in the all alogliptin group) and occurring more frequently with alogliptin than with placebo				
System Organ Class Preferred term	Placebo	Alogliptin		
		All doses	12.5 mg	25 mg
Monotherapy trial	N=64	N=329	N=133	N=132
≥ 1 event	45 (70.3)	225 (68.4)	91 (68.4)	89 (67.4)
Nasopharyngitis	5 (7.8)	27 (8.2)	12 (9.0)	10 (7.6)
Headache	3 (4.7)	22 (6.7)	10 (7.5)	9 (6.8)
Hypertension	1 (1.6)	10 (3.0)	4 (3.0)	5 (3.8)
Add-on to sulfonylurea trial	N=99	N=500	N=203	N=198
≥ 1 event	53 (53.5)	307 (61.4)	129 (63.5)	125 (63.1)
Urinary tract infection	3 (3.0)	22 (4.4)	9 (4.4)	10 (5.1)
Hypertension	2 (2.0)	20 (4.0)	7 (3.4)	11 (5.6)
Headache	3 (3.0)	19 (3.8)	5 (2.5)	11 (5.6)
Nasopharyngitis	2 (2.0)	18 (3.6)	8 (3.9)	8 (4.0)
Hypertriglyceridemia	2 (2.0)	18 (3.6)	8 (3.9)	8 (4.0)
Diarrhea	0	17 (3.4)	8 (3.9)	9 (4.5)
Back pain	3 (3.0)	16 (3.2)	4 (2.0)	9 (4.5)
Add-on to metformin	N=104	N=524	N=213	N=207
≥ 1 event	69 (66.3)	321 (61.3)	134 (62.9)	118 (57.0)
Urinary tract infection	4 (3.8)	24 (4.6)	14 (6.6)	6 (2.9)
Bronchitis	2 (1.9)	17 (3.2)	9 (4.2)	6 (2.9)
Add-on to thiazolidinedione	N=97	N=494	N=198	N=199
≥ 1 event	63 (64.9)	345 (69.8)	138 (69.7)	144 (72.4)
Upper respiratory tract infection	5 (5.2)	26 (5.3)	11 (5.6)	10 (5.0)
Headache	4 (4.1)	22 (4.5)	8 (4.0)	10 (5.0)
Nausea	2 (2.1)	17 (3.4)	9 (4.5)	6 (3.0)
Hypertension	2 (2.1)	16 (3.2)	6 (3.0)	8 (4.0)
Add-on to insulin	N=129	N=389	N=131	N=129
≥ 1 event	95 (73.6)	270 (69.4)	89 (67.9)	86 (66.7)
Nasopharyngitis	6 (4.7)	19 (4.9)	5 (3.8)	8 (6.2)
Arthralgia	3 (2.3)	16 (4.1)	9 (6.9)	4 (3.1)
Edema peripheral	4 (3.1)	15 (3.9)	4 (3.1)	7 (5.4)
Upper respiratory tract infection	4 (3.1)	14 (3.6)	6 (4.6)	4 (3.1)
Nausea	3 (2.3)	13 (3.3)	4 (3.1)	6 (4.7)

Adverse events of interest:

Major adverse cardiovascular events: As discussed in Section 2, the Division has requested that sponsors of new pharmacologic treatments for type 2 diabetes show that these treatments do not result in an unacceptable increase in cardiovascular risk. The 2008 guidance on this topic asks sponsors to do the following during the planning stage of their drug development programs for therapies for type 2 diabetes:

- Establish an independent cardiovascular endpoints committee to prospectively and blindly adjudicate major cardiovascular events during phase 2 and 3 clinical trials.
- Ensure that the phase 2 and 3 clinical trials are appropriately designed so that a pre-specified meta-analysis of major cardiovascular events can reliably be performed. The sponsor should provide a protocol describing the statistical methods for the proposed meta-analysis of all placebo-controlled trials, add-on trials, and active-comparator trials. The guidance states that it is likely that the controlled trials will need to last longer than the typical 3-6 months duration to obtain a sufficient number of events and to provide data on longer-term cardiovascular risk for these chronically used therapies.
- To enroll patients at increased cardiovascular risk, such as elderly patients and those with renal impairment.

The guidance states that to support approvability from a cardiovascular standpoint, the sponsor should compare the incidence of major cardiovascular events with the investigational agent to the incidence of the same types of events occurring with the control group and show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8 with a reassuring point estimate. If this upper bound is between 1.3 and 1.8 and the overall risk-benefit analysis supports approval then a postmarketing cardiovascular trial generally will be needed to definitively show that this upper bound is less than 1.3. If the premarketing data show that this upper bound is less than 1.3 and the overall risk-benefit analysis supports approval then a postmarketing cardiovascular trial generally may not be necessary.

Although the alogliptin development program was completed well in advance of this guidance, the Division has publicly communicated that all pending NDAs will be held to the 1.3 and 1.8 goalposts described above. This decision affected two other NDAs (saxagliptin and liraglutide) submitted to FDA prior to the publication of the guidance. To standardize the approach for assessing cardiovascular safety for all three products, the Division requested that the sponsors of these applications perform similar post-hoc analyses of cardiovascular events, as summarized below and discussed in detail in Dr. Pratt's clinical review. Of note, none of the programs had pre-specified definitions or prospective adjudication of major cardiovascular events and, because of the retrospective nature of these analyses, some events have insufficient information to definitively determine whether a cardiovascular event of interest had occurred.

The Division requested that the main cardiovascular analysis be conducted on the randomized, controlled periods for all completed phase 2 and phase 3 clinical trials. The Division requested two cardiovascular endpoints. The first endpoint, termed "Broad SMQ MACE" was defined as a composite endpoint of cardiovascular death and all preferred terms in the Standardised

MedDRA Queries (SMQs) for “Myocardial Infarction” and “Central Nervous System Haemorrhages and Cerebrovascular Accidents.” Although some of the preferred terms in the “Broad SMQ MACE” could be consistent with cardiovascular events of interest, there may be an alternate explanation in some patients. For example, “blood creatine phosphokinase increased” is a preferred term in the Myocardial Infarction SMQ, but could be related to exercise, muscle trauma, medications, or a variety of other causes. Therefore, the SMQ analyses will detect all patients with reported preferred terms that could be consistent with, but not necessarily diagnostic of, the condition of interest.

A second endpoint, called “Custom MACE”, was also analyzed. The “Custom MACE” endpoint is a subset of “SMQ MACE” and was created as follows. Without considering which events had occurred, the 3 clinical reviewers for alogliptin, saxagliptin, and liraglutide independently reviewed the list of all preferred terms included in the “Broad SMQ MACE” endpoint with the following question in mind: “If I had a patient who actually had a myocardial infarction or a stroke, is this a Preferred Term that I might actually have chosen for such an event?” The goal was to select only those preferred terms that seemed more likely to represent events of myocardial infarction or stroke as reported by investigators. The lists generated by the 3 clinical reviewers were compared and consensus was reached regarding inclusion or exclusion for all preferred terms. A listing of the preferred terms included in the “Broad SMQ MACE” and “Custom MACE” endpoints are shown in the January 2009 information request in the Division Files System (DFS).

Tables 11 and 12, adapted from Dr. Derr’s analyses, summarize the MACE findings. Event rates were low (<1%). The incidence rate (events per 100-patient years) of Broad SMQ MACE is similar for alogliptin and placebo, whereas the incidence rate of Custom MACE is numerically higher with alogliptin. When the incidence of MACE with alogliptin is compared to the incidence of MACE with placebo, the upper bound of the 95% confidence interval for the incidence ratio exceeds 1.8 for both the broad and custom endpoints. Dr. Derr has demonstrated this to be the case using three different statistical approaches (Table 12). Therefore, the currently available data do not meet the 1.8 goalpost to support approvability as recommended in the diabetes cardiovascular guidance. The low event rate and only 26-week controlled treatment periods limited data available for these analyses.

Table 11. MACE analyses – phase 2/3 trials (including OPI-001 and OPI-002)					
	N	Exposure (patient-years)	Number of events	Incidence (%) Events/N	Incidence Rate Events/100 pt-yrs
Broad SMQ MACE					
Alogliptin	3,489	1,537	24	0.69%	1.56
Placebo	1,213	505	8	0.66%	1.59
Custom MACE					
Alogliptin	3,489	1,539	14	0.40%	0.91
Placebo	1,213	505	4	0.33%	0.79

Table 12. Incidence ratios (with 95% confidence intervals) for the MACE analyses		
Method	Broad SMQ MACE	Custom MACE
Stratified, asymptotic (MH) ¹	1.09 (0.5, 2.5)	1.4 (0.4, 4.3)
Stratified, exact ²	1.09 (0.5, 2.8)	1.3 (0.4, 5.7)
Stratified, fixed effects MH meta-analysis ³	0.9 (0.4-1.9)	0.8 (0.3, 2.0)
MH = Mantel-Haenszel ¹ This analysis excludes studies with zero MACE events in the comparator group. The assumptions of this analysis may not apply well in circumstances where events are rare. ² This analysis excludes studies with zero MACE events in the comparator group. This analysis tends to yield conservative (wider) confidence intervals. ³ This analysis adds a continuity correction of 0.5 to groups with zero MACE events. The continuity correction can be influential in estimating the confidence interval in circumstances where events are rare.		

Dr. Pratt reviewed all narratives for the 35 events meeting the criteria for Broad SMQ MACE. She notes that approximately one-half of these events were not classified as serious and that several of these events could have represented myocardial infarction or stroke based on her review of the limited data available. Dr. Pratt notes that even if some of these events were miscoded they would still be included in the MACE analysis and not change overall conclusions. Nonetheless, these questionable diagnoses demonstrate the limitations of cardiovascular data that are not derived from trials that have been prospectively designed to collect such data.

Hypoglycemia: Patients were educated about the signs and symptoms of hypoglycemia and were instructed to record events in diaries. These events were entered onto dedicated case report forms, but were not summarized as adverse events unless they met the criteria for serious adverse events. The sponsor used two definitions for hypoglycemia:

- Mild to moderate hypoglycemia – blood glucose <60 mg/dL with symptoms or <50 mg/dL even if asymptomatic.
- Severe hypoglycemia – requiring assistance of another person to actively administer carbohydrate, glucagon, or other “resuscitative actions” associated with blood glucose <60 mg/dL unless the clinical situation affects the ability to obtain a blood glucose measurement (e.g., coma, seizure). A more specific definition for severe hypoglycemia should have required resolution of symptoms with treatment in those patients without a documented blood glucose.

In the pooled phase 2/3 database, the incidence of hypoglycemia was numerically lower in the alogliptin 12.5 mg and 25 mg groups compared to the placebo group (5.6-5.7% vs. 6.0% for symptomatic blood glucose <60 mg/dL; 3.7-3.8% vs. 4.5% for blood glucose <50 mg/dL; and 0.1-0.2% vs. 0.6% for severe hypoglycemia as defined above).

Table 13 summarizes the hypoglycemia data by phase 3 trial. As expected, reports of hypoglycemia were lowest in the monotherapy, add-on to metformin, and add-on to thiazolidinedione trials, intermediate in the add-on to sulfonylurea trial, and highest in the add-on to insulin trial. In each trial, the incidence of mild-moderate hypoglycemia (as defined

above) was generally comparable in the alogliptin groups and placebo groups, except in the add-on to insulin trial. In this trial, a numerically greater proportion of alogliptin-treated patients reported symptomatic blood glucose <60 mg/dL (21% with alogliptin 12.5 mg and 23% with alogliptin 25 mg vs. 16% with placebo) and blood glucose <50 mg/dL (16% with alogliptin 25 mg vs. 10% with placebo). Reports of severe hypoglycemia only occurred in the add-on to sulfonylurea trial and add-on to insulin trials, although event rates were low (3 cases per trial) and not more frequent in the alogliptin groups than in the placebo groups.

Table 13. Hypoglycemia data					
	Overall	Symptomatic blood glucose <60 mg/dL	Blood glucose <50 mg/dL¹	Severe²	Symptoms only³
Monotherapy					
Placebo (N=64)	1 (1.6)	0	1 (1.6)	0	0
12.5 mg (N=133)	4 (3.0)	2 (1.5)	3 (2.3)	0	1 (0.8)
25 mg (N=132)	2 (1.5)	1 (0.8)	1 (0.8)	0	1 (0.8)
Add-on to sulfonylurea					
Placebo (N=99)	11 (11.1)	8 (8.1)	6 (6.1)	1 (1.0)	2 (2.0)
12.5 mg (N=203)	32 (15.8)	18 (8.9)	10 (4.9)	2 (1.0)	6 (3.0)
25 mg (N=198)	19 (9.6)	16 (8.1)	8 (4.0)	0	0
Add-on to metformin					
Placebo (N=104)	3 (2.9)	1 (1.0)	0	0	0
12.5 mg (N=213)	2 (0.9)	1 (0.5)	1 (0.5)	0	0
25 mg (N=207)	0	0	0	0	0
Add-on to thiazolidinedione					
Placebo (N=97)	5 (5.2)	1 (1.0)	2 (2.1)	0	2 (2.1)
12.5 mg (N=198)	10 (5.1)	4 (2.0)	1 (0.5)	0	2 (1.0)
25 mg (N=199)	14 (7.0)	5 (2.5)	5 (2.5)	0	2 (1.0)
Add-on to insulin					
Placebo (N=129)	31 (24.0)	21 (16.3)	13 (10.1)	2 (1.6)	4 (3.1)
12.5 mg (N=131)	35 (26.7)	28 (21.4)	15 (11.5)	0	6 (4.6)
25 mg (N=129)	35 (27.1)	29 (22.5)	20 (15.5)	1 (0.8)	8 (6.2)
¹ with or without symptoms					
² see definition in text					
³ no blood glucose measurement available					

Hypersensitivity reactions: Because of postmarketing reports of hypersensitivity reactions with Januvia, the sponsor conducted analyses for angioedema using the angioedema SMQ.

In the controlled phase 2/3 program, 18 (3.4%) placebo-treated patients and 88 (4.5%) alogliptin-treated patients (4.8% with 6.25 mg, 3.9% with 12.5 mg, 4.9% with 25 mg, and 5.7% with 50/100 mg) reported an event that mapped to a preferred term in the sponsor's angioedema analysis. Some preferred terms (e.g., drug hypersensitivity, face edema, swelling

face, swollen tongue, tongue edema) were reported in 1-4 alogliptin-treated patients but in none of the placebo-treated patients. Two patients in the phase 2/3 program (including the open-label extension study and the 120-day safety update) reported a serious adverse event that mapped to a preferred term in the sponsor's angioedema analysis. One of these patients developed difficulty breathing and swallowing with edema of the uvula, face, and neck. Alogliptin 25 mg had been started 3 days earlier and an angiotensin receptor blocker had been started 10 days earlier. Both medications were temporarily interrupted then restarted. On Study Day 174 in the open-label extension, this patient again developed difficulty swallowing and speaking and was diagnosed with probable angioedema. The angiotensin receptor blocker was discontinued and the alogliptin was only temporarily interrupted. The patient had no recurrent events while taking only alogliptin. The second patient who reported a serious adverse event developed allergic edema on the right side of the face on Day 230 during the open-label extension but the event resolved despite continued treatment with alogliptin.

Three alogliptin-treated patients in the phase 2/3 program (including the open-label extension study and the 120-day safety update) withdrew due to an adverse event that mapped to a preferred term in the sponsor's angioedema analysis. Two of these patients developed generalized urticaria (one after 99 days of exposure to alogliptin and the other after 184 days of exposure to alogliptin). The remaining patient developed peripheral edema on Day 135 (body location not described) but alogliptin was not discontinued.

Skin: Some DPP-4 inhibitors cause dose- and treatment duration-dependent skin lesions in monkeys, sometimes at or near clinical exposures. Importantly, alogliptin is one of the few DPP-4 inhibitors that does not cause skin lesions in monkeys (at tested exposures up to 31-fold higher than clinical exposures with the maximum recommended clinical dose of 25 mg). Nonetheless, the sponsor conducted analyses of potential cutaneous drug reactions using MedDRA high-level terms from the Immune System Disorders and Skin and Subcutaneous Tissue Disorders System-Organ-Classes for allergic conditions, anaphylactic responses, angioedemas, urticaria, dermal and epidermal conditions, dermatitis and eczema, erythemas, exfoliative conditions, papulosquamous conditions, pruritis, rashes and eruptions.

In the controlled phase 2/3 program, a similar proportion of placebo-treated patients (10.3%) and alogliptin-treated patients (11.5%) reported at least one event in the Skin and Subcutaneous Tissue Disorders System-Organ-Class. However, 37 (6.9%) placebo-treated patients and 188 (9.6%) alogliptin-treated patients (2.4% with 6.25 mg, 8.8% with 12.5 mg, 11.0% with 25 mg, and 6.9% with 50/100 mg) reported an event that mapped to a preferred term in the sponsor's skin analysis. These differences were predominantly driven by the higher incidence of pruritis (0.4% of placebo-treated patients vs. 1.6% of alogliptin-treated patients) and rash (0.7% of placebo-treated patients and 1.6% of alogliptin-treated patients) with alogliptin.

Three alogliptin-treated patients in the phase 2/3 program (including the open-label extension study and the 120-day safety update) reported serious adverse events that mapped to a preferred term in the sponsor's skin analysis. One patient was reported to have serum sickness (see the section above on withdrawals due to adverse events). The symptoms likely represent a hypersensitivity reaction. The second patient is the patient described above who developed two

bouts of probable angioedema while on an angiotensin receptor blocker and alogliptin. The third patient developed facial and lip edema after a wasp bite.

Fifteen patients (1 treated with placebo and 14 treated with alogliptin) in the phase 2/3 program (including the open-label extension study and the 120-day safety update) discontinued due to an adverse event that mapped to a preferred term in the sponsor's skin analysis. Only one of these adverse events was reported as serious (the patient with serum sickness described above). Seven of the remaining 13 discontinuations with alogliptin were due to rash (Day 11-266), 2 were due to urticaria (Day 3 and 99), 1 was due to worsening eczema (Day 5), 2 were due to pruritis (Day 2 and 22), and 1 was due to skin reaction (Day 114).

One feature of the skin lesions in monkeys treated with some of the other DPP-4 inhibitors is necrosis in distal locations like the tail. Reports of blistering or ulceration were infrequent in the controlled phase 2/3 program. Specifically, there was one report of traumatic ulcer in an alogliptin 25 mg-treated patient. Blister was reported as an adverse event in 4 (0.7%) placebo-treated patients and 15 (0.8%) alogliptin-treated patients. Skin ulcer was reported as an adverse event in 5 (0.9%) placebo-treated patients and 8 (0.4%) alogliptin-treated patients. Decubitus ulcer was reported in one alogliptin 12.5 mg-treated patient. These findings do not support an association between alogliptin and skin ulceration.

Infections: DPP-4 has many substrates other than GIP and GLP-1, including chemokines involved in immune development and function. In addition, DPP-4 is expressed on a subset of CD4+ and CD8+ T-cells and natural killer cells. There is a theoretical concern that DPP-4 inhibition may increase the risk for infections. However, as discussed by Dr. Pratt, the alogliptin-treated patients had a numerically lower incidence of serious and non-serious adverse events compared to placebo in the Infections and Infestations System-Organ-Class (serious: 0.8% vs. 0.9%; non-serious 29% vs. 31%). Unusual infections included one report of scrotal abscess on Day 84 in a patient with no relevant medical history and 3 reports of hemorrhagic fever. Information is very limited to know whether the 3 reports are true cases of viral hemorrhagic fever. All 3 cases of hemorrhagic fever were reported at one clinical site in India and two of these cases occurred very soon after study drug initiation (Study Day 1 and Study Day 3), which weakens the likelihood of drug-relatedness because viral hemorrhagic fevers have incubation periods of at least several days.

Pancreatitis: Serum amylase and lipase were not routinely measured in the phase 3 trials. There are 4 reports of pancreatitis (3 serious, 1 non-serious) in the controlled phase 2/3 program, including OPI-001 and OPI-002. All 4 reports occurred in alogliptin-treated patients, which is consistent with the randomization scheme. Three of the 4 patients had other risk factors for pancreatitis. There were no reports of the necrotizing/hemorrhagic form.

- One alogliptin 12.5 mg-treated patient in the add-on to insulin trial was diagnosed with pancreatitis approximately 3 months after starting study medication. Risk factors for pancreatitis included concomitant use of hydrochlorothiazide and an angiotensin-converting enzyme inhibitor. The patient was diagnosed with concurrent cholecystitis. An intraoperative cholangiogram was unrevealing, but gallbladder pathology showed active chronic inflammation without gallstones.

- One alogliptin 25 mg-treated patient in the add-on to insulin trial was diagnosed with a non-serious adverse event of pancreatitis on Day 73, leading to study drug discontinuation. She did not appear to have other risk factors for pancreatitis.
- One alogliptin 12.5 mg-treated patient in OPI-001 was diagnosed with pancreatitis approximately 3 months after starting study medication. The patient had a history of pancreatitis and pancreas divisum.
- One alogliptin 25 mg+pioglitazone 30 mg-treated patient in OPI-002 was diagnosed with pancreatitis approximately one month after starting study medication. Risk factors for pancreatitis include concurrent use of hydrochlorothiazide. The patient was also diagnosed with acalculus cholecystitis. Intraoperative cholangiogram showed a normal biliary system without retained stones, but gallbladder pathology showed chronic inflammation.

Laboratory data: This section focuses on the pooled laboratory data for the controlled phase 2/3 program. I concur with Dr. Pratt that mean changes in laboratory parameters were small and are not expected to be clinically relevant. For example, mean baseline lymphocyte count was approximately 30% and declined by an absolute 0-2% with alogliptin 6.25 mg-100 mg relative to no change with placebo. Mean platelet count was approximately 250-260 x 10³/mm³ at baseline and declined by 2-3 x 10³/mm³ with alogliptin 6.25-25 mg and by 9 x 10³/mm³ with the 50/100 mg doses. Alogliptin was associated with small mean reductions from baseline in serum ALT (0-2 U/L) and alkaline phosphatase (1-2 U/L), whereas mean values were unchanged with placebo. The mean change in serum creatinine from baseline was 0.0 mg/dL in all alogliptin treatment groups and with placebo.

Few patients met the criteria for markedly abnormal hematology values.

Table 14 summarizes the proportion of patients developing markedly abnormal values for select chemistry values. A similar proportion of patients in the placebo and alogliptin groups reported post-baseline ALT >3x ULN. One placebo-treated patient and 7 alogliptin-treated patients reported post-baseline ALT >5x ULN. None of these 7 patients had treatment-emergent total bilirubin above the upper limit of the reference range. Four (one on 12.5 mg and three on 25 mg) of these 7 alogliptin-treated patients had a transient rise in ALT that returned to baseline despite continued treatment with alogliptin. Narratives for the remaining 3 alogliptin-treated patients with ALT >5x ULN are summarized below:

- One patient (25 mg) with ALT >5x ULN had a history of biliary colic. ALT increased from a baseline value of 26 U/L to 199 U/L (8x ULN) on Day 147. This patient had an adverse event of biliary colic reported on Day 147. Total bilirubin was normal. ALT declined to 60 U/L on Week 26 despite continued treatment.
- Another patient (25 mg) with ALT >5x ULN actually had ALT >10x ULN both at baseline (430 U/L) and at Week 1 (357 U/L), leading to study medication discontinuation.
- The remaining patient (12.5 mg+pioglitazone) with ALT >5x ULN actually had ALT >10x ULN. This patient (311-9003) had a baseline ALT of 14 U/L but the ALT increased to 66 U/L on Day 1 and 646 U/L on Day 32 then declined to 46 U/L on Day 42 and 25 U/L on Day 49. The sponsor reports that the patient used 11 alogliptin tablets instead of 24 tablets between Day 32 and 56. The investigator attributed the elevation in serum transaminases to alcohol, although, as Dr. Pratt notes, the AST:ALT ratio is usually 2:1 in the setting of

alcohol whereas in this patient ALT was always greater than AST. Of note, the patient was also on fluoxetine and trazadone, which have also been associated with ALT elevations.

Nineteen patients developed treatment-emergent serum creatinine $>1.5\times$ baseline (2 or 0.4% of placebo-treated patients, 8 or 0.9% of alogliptin 12.5 mg-treated patients, and 9 or 1.0% of alogliptin 25 mg-treated patients). Both placebo patients and 12 of the 17 alogliptin-treated patients had isolated, transient elevations in serum creatinine. For these 14 patients, the last available serum creatinine value was at baseline or was at most 0.1-0.2 mg/dL above the baseline value. The remaining 6 alogliptin-treated patients (0.3%) had serum creatinine values at study end that were 0.3-0.6 mg/dL higher than the baseline value. No explanation was noted for these findings but information on these cases is limited. Additional information on renal safety will be forthcoming from clinical trials involving patients with moderate and severe renal impairment.

Table 14. Patients meeting the postbaseline markedly abnormal criteria for select serum chemistry parameters in the controlled phase 2/3 program						
Serum chemistry test	Placebo N=534	Alogliptin				
		All doses N=1961	6.25 mg N=42	12.5 mg N=922	25 mg N=910	50/100 mg N=87
Liver						
ALT >3x ULN	6 (1.1)	23 (1.2)	0	11 (1.2)	12 (1.3)	0
AST >5x ULN	1 (0.2)	7 (0.4)	0	2 (0.2)	5 (0.6)	0
ALT >10x ULN	0	2 (0.1)	0	1 (0.1)	1 (0.1)	0
Total bilirubin >2 mg/dL	2 (0.4)	10 (0.5)	0	2 (0.2)	8 (0.9)	0
Alkaline phosphatase >3x ULN	1 (0.2)	1 (0.1)	0	0	1 (0.1)	0
Serum creatinine >1.5x baseline	2 (0.4)	17 (0.9)	0	8 (0.9)	9 (1.0)	0
ULN = upper limit of normal						

In the controlled phase 2/3 program, the mean urine albumin/creatinine ratio was 71 mcg/mg in the placebo group, 85 mcg/mg in the alogliptin 12.5 mg group, and 81 mcg/mg in the alogliptin 25 mg group. The mean change from baseline in urine albumin/creatinine ratio was -8 mcg/mg with placebo, +22 mcg/mg with alogliptin 12.5 mg, and +15 mcg/mg with alogliptin 25 mg. However, these mean changes are unreliable because of outliers as reflected in the accompanying large standard deviations (184-469 mcg/mg). A more appropriate measure in this circumstance is the median, which yielded reassuring results. The median change from baseline in urine albumin/creatinine ratio was -1 mcg/mg with placebo, -2 mcg/mg with alogliptin 12.5 mg, and -3 mcg/mg with alogliptin 25 mg.

Vital signs: I concur with Dr. Pratt that alogliptin has no clinically meaningful effects on blood pressure and heart rate.

Dr. Derr notes that 84-94% of patients in each phase 3 trial remained within $\pm 5\%$ of their baseline body weight at Week 26 (FAS population with last-observation-carried-forward). In the add-on to sulfonylurea trial, the mean baseline body weight was approximately 80 kg, and

the mean change in body weight from baseline to Week 26 in the FAS population with last-observation-carried-forward was +0.6 kg with alogliptin 12.5 mg, +0.7 kg with alogliptin 25 mg, and -0.2 kg with placebo. Therefore, in this trial, alogliptin 12.5 mg resulted in a mean weight gain of +0.8 kg relative to placebo ($p=0.02$) and alogliptin 25 mg resulted in a mean weight gain of +0.9 kg relative to placebo ($p=0.01$). In the remaining phase 3 clinical trials, alogliptin had no effect on body weight (p -values 0.29-1.00 for comparisons to placebo).

Electrocardiograms: Standard 12-lead electrocardiograms were obtained in the controlled phase 2 and 3 trials at screening, baseline, Week 12, and the end of treatment visit. The electrocardiograms were reviewed by the investigator or his/her designee and were not read centrally by a cardiologist, which limits conclusions. However, alogliptin does not have a clinically meaningful effect on the QT interval based on results from the Thorough QT Study. In addition, non-clinical findings do not raise concerns for an effect of alogliptin on the heart. Based on the available data, I concur with Dr. Pratt that alogliptin 12.5 mg and 25 mg doses are not associated with clinically meaningful changes in electrocardiogram parameters. Please see Dr. Pratt's review of mean changes from baseline and outlier analyses for further details.

Uncontrolled extension trial 012: Interim results from this extension trial (cutoff date of August 29, 2007) were included in the original NDA. The 120-day safety update provides additional data accrued in this trial through the cutoff date of January 31, 2008. All data in this trial are uncontrolled, which substantially limits conclusions. This section will focus on select serious adverse events, withdrawals due to adverse events, and marked outliers in select laboratory data (deaths are discussed above). Please see Dr. Pratt's review for further details.

Serious adverse events included one report of coccidioidomycosis (after approximately 3 months of treatment with alogliptin), one report of typhoid fever (after approximately 6 months of treatment with alogliptin), and one report of tuberculosis (after approximately 8 months of treatment with alogliptin). These types of unusual infections are of interest because DPP-4 is expressed on a subset of CD4+ and CD8+ T-cells and natural killer cells. Conclusions are limited based on these isolated cases.

Withdrawals due to adverse events included one report of elevated liver tests that was attributed to alcohol. Up to the January 31, 2008 cutoff date, there have been eight alogliptin-treated patients who have developed ALT >5x ULN during Study 012. Three of these cases resolved despite continued treatment with alogliptin. An alternate explanation was provided for two cases (cholangitis and viral infection). In two other cases, ALT values declined with interruption or discontinuation (peak ALT 142 U/L) of alogliptin. In the remaining case, ALT exceeded 10x ULN (peak 333 U/L) but declined to 186 U/L one week later without interruption of study medication, and the elevation was attributed to excessive alcohol intake during the holiday season. None of these patients had elevated total bilirubin.

Findings with higher alogliptin doses: Phase 1 studies tested single alogliptin doses as high as 800 mg (5 healthy males) and repeat alogliptin doses up to 400 mg (45 healthy subjects dosed for 6 days and 64 healthy subjects dosed for 7 days). The 12-week, phase 2 dose finding tested alogliptin doses as high as 50 mg (44 enrolled; 35 completed) and 100 mg (45 enrolled; 38 completed). Therefore, these phase 1 and phase 2 studies tested alogliptin doses that are 2-

32-fold higher than the proposed maximum recommended human dose of 25 mg, providing an opportunity to assess for exaggerated pharmacologic effects and safety signals.

There were no deaths, serious adverse events, or discontinuations due to adverse events in the single-dose study testing alogliptin 25 mg (n=5), 50 mg (n=5), 100 mg (n=5), 200 mg (n=5), 400 mg (n=5), and 800 mg (n=5), and placebo (n=6). No adverse events were reported in the 800 mg group. Hypoglycemia was the only adverse event reported by more than 1 subject in the study (1 subject in the 50 mg group, 2 subjects in the 200 mg group, 1 subject in the 400 mg group, and 1 subject in the placebo group). One subject in the 200 mg, 400 mg, and 800 mg groups experienced a shift in bilirubin from normal to high. Two of these subjects had elevated bilirubin at screening and the sponsor notes that none of the increased bilirubin values were accompanied by increases in serum transaminases.

There were no deaths, serious adverse events, or reports of hypoglycemia among the subjects dosed with alogliptin 100 mg (n=46) or alogliptin 400 mg (n=45) once daily for 6 days in the first Thorough QT Study. Similarly, there were no deaths, serious adverse events, or reports of hypoglycemia among the subjects dosed with alogliptin 50 mg (n=64) and alogliptin 400 mg (n=64) once daily for 7 days in the second Thorough QT Study. There were no adverse events consistently associated with alogliptin when data from the two Thorough QT Studies were compared. Only one alogliptin-treated subject in each Thorough QT Study discontinued due to an adverse event (premature ventricular contractions in one study and streptococcal pharyngitis in the other study). In the second Thorough QT Study, a shift in serum calcium from normal to low occurred in one placebo-treated subject, two alogliptin 50 mg-treated subjects, and five alogliptin 400 mg-treated subjects. The lowest recorded post-treatment serum calcium value in these seven alogliptin-treated subjects was 8.6 mg/dL (lower limit of the reference range is 8.9 mg/dL). A shift in serum creatinine from normal to high occurred in three placebo-treated subjects, two alogliptin 50 mg-treated subjects, and six alogliptin 400 mg-treated subjects. All eight alogliptin-treated subjects had a post-dose serum creatinine value of 1.4 mg/dL (upper limit of the reference range is 1.3 mg/dL).

There were no deaths in the 12-week phase 2 dose-ranging study. There was a single serious adverse event (angina) in the alogliptin 100 mg group (n=44) and no serious adverse events in the alogliptin 50 mg group (n=43). Discontinuations due to adverse events included rash (n=2, both in the 50 mg group), headache (n=3, one patient each in the 25 mg, 50 mg, and 100 mg groups), and “disturbance in attention” (n=1, in the 100 mg group). The alogliptin 100 mg-treated group had a numerically greater proportion of patients who reported adverse events (66% vs. 51% with alogliptin 50 mg and 58% with placebo), driven predominantly by a higher incidence of nausea in the alogliptin 100 mg dose group (11% vs. 2-5% in the other treatment groups). No patients receiving alogliptin 50 mg or 100 mg developed serum transaminase elevations. Symptomatic hypoglycemia associated with a documented blood glucose <70 mg/dL perhaps occurred slightly more frequently with alogliptin 100 mg (n=3) compared with placebo (n=1), and alogliptin 12.5 mg (n=1), 25 mg (n=1), and 50 mg (n=1) groups, although there were two events in the alogliptin 6.25 mg dose group and the overall event rates are low, which limit conclusions.

9. Advisory Committee Meeting

An advisory committee meeting was not held because the application cannot be approved in its current form (see below).

10. Pediatrics

The sponsor has requested a deferral for children ≥ 10 years old and a waiver for children < 10 years old. The Pediatric Review Committee (PeRC) agrees with this proposal, which is consistent with our approach to other oral treatments for type 2 diabetes (there are too few children less than 10 years of age with type 2 diabetes; therefore, studies in this population are highly impractical). The sponsor's submitted pediatric plan proposes two studies: The first proposed study is a phase 1, single-dose pharmacokinetic and pharmacodynamic study testing 12.5 mg and 25 mg [REDACTED] (b) (4)

[REDACTED] The purpose of this study is to confirm that the pharmacokinetic and pharmacodynamic profiles are similar between children and adults and that dose selection for children is appropriate. The sponsor has recently submitted a study protocol that is under review. The second proposed study is a phase 3, [REDACTED] (b) (4) efficacy and safety study of alogliptin in children with type 2 diabetes between 10-17 years of age. Further discussions regarding the phase 3 pediatric study design should be postponed until the single-dose pediatric clinical pharmacology data are available and, possibly, until the sponsor has demonstrated cardiovascular safety in adults given the imbalance in serious cardiovascular events in the current NDA database.

11. Other Relevant Regulatory Issues

Tradename: The primary reviewer in the Division of Medication Error Prevention and Analysis (DMEPA) found the proposed tradename "Nesina" to be unacceptable because of potential confusion with "Lessina-28", an oral contraceptive. However, the team leader, deputy director, and director of DMEPA determined that the tradename "Nesina" is acceptable because there are sufficient differentiating characteristics between the two products. Please see the reviews of Drs. Jinhee Lee and Kellie Taylor dated September 23, 2008, for further details. The tradename will need to be re-reviewed by DMEPA within 90 days prior to approval of the NDA to ensure there is no risk for confusion with new tradenames approved after DMEPA's September 23, 2008 review.

The sponsor submitted revised carton and container labels based on comments from DMEPA. Because the NDA cannot be approved in its current form, these revised labels and all other labeling reviews will be deferred until the next review cycle.

Financial disclosures: Dr. Pratt reviewed the financial disclosure statements for investigators involved in the phase 3 trials and noted that only 2 principal investigators reported significant payments from the sponsor. [REDACTED]

[REDACTED] I concur with Dr. Pratt that findings from these 2 investigators are not expected to meaningfully impact the conclusions of the trials because few patients were involved [REDACTED] (b) (6). In addition, the double-blind study designs and objective primary efficacy endpoint limit bias.

Division of Scientific Investigations (DSI): Most investigators randomized less than 10 patients per protocol. The three sites that randomized the largest number of patients in the phase 3 program were identified. DSI inspected two of these sites, limiting inspection to two studies per site (29 patients for one site and 37 patients for the other site). One investigator, Dr. Phillips, was found to have inadequate source documents to verify eligibility [REDACTED] (b) (7)(A)

However, DSI has determined that the findings at both inspected sites do not negatively impact data acceptability. DSI also inspected the sponsor's monitoring reports, training records, and drug shipping records for the phase 3 clinical trials and determined the data to be acceptable. Please see Dr. Susan Leibenhaut's memorandum for further details.

12. Labeling

Labeling is deferred because the NDA cannot be approved in its current form.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Complete Response.

- Risk Benefit Assessment

Based on 26-week controlled data, alogliptin has modest efficacy but is generally well-tolerated with neutral effects on body weight (except as add-on to sulfonylurea) and minimal risk of hypoglycemia. However, all submitted data beyond Week 26 are uncontrolled, which limits conclusions regarding long-term safety for this medication that will be used chronically, if approved.

In addition, there is a numerical imbalance not favoring alogliptin in serious cardiovascular events, which may be related to the randomization scheme, differential dropout rates in the alogliptin and placebo treatment groups, lack of long-term controlled data, and low event rates. However, an adverse effect of alogliptin on cardiovascular risk cannot be excluded. Therefore, I concur with Dr. Pratt that the NDA cannot be approved in its current form because the sponsor has not ruled out an unacceptable increase in cardiovascular risk as recommended in the December 2008 diabetes cardiovascular guidance. The sponsor has been involved in active

discussions with the Division regarding the design of a cardiovascular safety trial that will satisfy the recommendations described in the diabetes cardiovascular guidance. During the discussions, the Division has stressed the importance of controlled data beyond 26 weeks at the time of submission of the interim cardiovascular data. The sponsor has stated that full results from two 1-year controlled trials will be available by that time. One of these trials is comparing alogliptin 25 mg vs. titration of pioglitazone in patients on background metformin + pioglitazone therapy. Approximately 280 patients per treatment arm will be exposed to study medication for 1 year. The second trial is comparing alogliptin to sulfonylurea in elderly patients (>65 years old) and is adjudicating cardiovascular events. Approximately 170 patients per treatment arm will be exposed to study medication for 1 year. The Complete Response letter should explicitly state that data should be available on at least 500 patients exposed to alogliptin for at least 1-year in controlled trials to support approvability. These data will complement the 1,400 patients already exposed to alogliptin for at least 1-year in uncontrolled trials and provide further assurance regarding longer-term safety.

The adverse events of interest for all drugs in the DPP-4 inhibitor class (e.g., hypersensitivity reactions, hepatotoxicity, pancreatitis, infections, skin reactions, and renal safety) should be included as adverse events of interest in the planned cardiovascular trial and future alogliptin trials. An updated analysis of these adverse events of interest based on all available controlled data should be included in the Complete Response.

I concur with the other reviewers that the 25 mg dose of alogliptin is not consistently more efficacious than the 12.5 mg dose across the phase 3 trials. However, based on the available data, it is probable that 25 mg may be more efficacious than 12.5 mg in some patients. Importantly, there are no safety or tolerability concerns unique to the 25 mg dose and there are large safety margins based on the non-clinical data. Therefore, in my opinion, both 12.5 mg and 25 mg are acceptable from an efficacy viewpoint.

One issue pertaining to dose selection is whether there should be an adjustment to 12.5 mg for all patients with mild renal impairment (as recommended by clinical pharmacology) or whether an adjustment for this patient population is not needed (as recommended by the sponsor and Dr. Pratt). Based on the large safety margins in animals, the 25 mg dose may be acceptable in these patients with mild renal impairment and could simplify the dosing regimen. The sponsor is proposing 25 mg in the cardiovascular safety trial for patients with mild renal impairment, which should provide additional data in this regard. Also, the sponsor should perform analyses of the controlled phase 2/3 data comparing the safety and tolerability of alogliptin in patients with normal renal function to those with mild renal impairment, as estimated using Cockcroft-Gault and the MDRD formula. These findings should be included in the Complete Response.

- Recommendation for Postmarketing Risk Management Activities

Not applicable. The application cannot be approved in its current form.

- Recommendation for other Postmarketing Study Commitments

Not applicable. The application cannot be approved in its current form.

- Recommended Comments to Applicant

Information to convey in the Complete Response letter:

- A description of the cardiovascular deficiency. The sponsor should rule out an unacceptable increase in cardiovascular risk as recommended in the December 2008 diabetes cardiovascular guidance. The adverse events of interest for all drugs in the DPP-4 inhibitor class (e.g., hypersensitivity reactions, hepatotoxicity, pancreatitis, infections, skin reactions, and renal safety) should be included as adverse events of interest in the cardiovascular trial and future alogliptin clinical trials. An updated analysis of these adverse events of interest based on all available controlled data should be included in the Complete Response.
- The need for controlled data beyond 26 weeks (at least 500 patients with at least 1 year total exposure to alogliptin) to provide additional assurance regarding safety for this therapy that will be used chronically, if approved. These data can be derived from the cardiovascular safety trial and/or the two 1-year trials described above.
- Clinical pharmacology is questioning whether there should be a dosage adjustment from 25 mg to 12.5 mg in all patients with mild renal impairment. The sponsor should perform analyses of their controlled phase 2/3 program comparing safety and tolerability in patients with normal renal function to those with mild renal impairment, as assessed using Cockcroft-Gault and MDRD, and include the findings in the Complete Response.
- A statement per CMC that the (b) (4) dosage strength was not reviewed as part of the NDA.
- A statement that labeling reviews have been deferred (including the sponsor's response to DMEPA's recommendations on the carton and container labels)

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Mary Parks
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MEDICAL OFFICER

**Medical Officer Safety Review
Division of Metabolism and Endocrinology Products**

NDA 22-271

Name of drug: Alogliptin (SYR-322, NESINA, a DPP-4 inhibitor)

Sponsor: Takeda

Relevant INDs: 69,707; 73,193; and 101,628

Relevant NDA: 22-426

Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)

Date of Submission: April 9, 2009

Date of Internal Meeting: April 22, 2009

Date of External Meeting: April 27, 2009

Medical Reviewer: Valerie Pratt, M.D.

Medical Team Leader: Hylton Joffe, M.D.

Background: NDA 22-271 proposes the use of alogliptin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). A complete response will be requested because (1) the sponsor has not ruled out an unacceptable increase in cardiovascular risk (based on the December 2008 diabetes cardiovascular guidance), (2) there is a numerical imbalance against alogliptin in cardiovascular serious adverse events, and (3) there are inadequate data regarding long-term exposure. (Please also refer to my review of NDA 22-271.) To address these deficiencies, the sponsor submitted study SYR-322_402, a CV outcomes trial which is reviewed below, along with 17 questions, which will be discussed at a meeting with the sponsor on April 27, 2009.

Sponsor's Questions:

Protocol Design

1. Does the Agency agree that the protocol is appropriately designed to assess the CV risk associated with alogliptin?
2. Does the Agency agree that the higher risk T2DM population chosen for this study is appropriate?

Study Endpoints

3. Does the Agency agree with the proposed primary endpoint of time from randomization to the first occurrence of any of the events in the primary MACE

composite of CV death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina (with or without urgent revascularization)?

4. Does the Agency agree that the secondary endpoint adequately supports the primary endpoint?

General Safety Evaluation

5. Does the Agency agree with the safety data that Takeda plans to collect and analyze in the proposed CV outcomes study?

Dose Selection

6. Does the Agency agree with the proposed dose selection for this study?

Evaluation of Subjects with Renal Impairment

7. Does the Agency agree that the proposed CV outcomes study can be used to provide additional safety data on the use of alogliptin in patients with renal impairment (in place of conducting the 2 separate renal safety studies which are currently pending review by the FDA)?

Statistical Methods

8. Does the Agency agree with a single trial incorporating an adaptive Bayesian design to satisfy the Agency requirements to rule out excess CV risk greater than 1.3 and 1.8?
9. Does the Agency agree with the statistical methods proposed for the interim analyses and for the final analysis?
10. Does the Agency agree with the proposed statistical assumptions for this study?
11. Takeda currently does not plan to conduct a meta-analysis combining this study with any other previously completed controlled studies. Does the Agency agree that this study can stand-alone to satisfy the guidance criteria for both the interim analysis and the primary analysis?

Long-Term Exposure

12. Does the Agency find this acceptable to support the long-term safety of alogliptin?

Regulatory

13. If the Agency determines Takeda must collect additional data to satisfy the 1.8 criterion prior to approval, does the Agency agree that the proposed submission contents as outlined above would be adequate for the Agency to determine the approvability of alogliptin?
14. If these data are submitted to address a complete response letter, Takeda anticipates that these data would be subject to a 6-month review cycle. Is Takeda's understanding correct? Additionally, does the Agency agree that this focused data package could undergo an expedited review cycle of less than 6 months?
15. If the results of the interim analysis show that the upper bound of the confidence interval for the estimated risk ratio is less than 1.8, Takeda would expect (1) alogliptin to be approved for general use in patients with T2DM, and (2) that a statement be included in the product labeling such as, (b) (4)

Does the Agency agree?

16. If the final analysis satisfies a non-inferiority margin of 1.3, Takeda would expect a labeling statement such as, (b) (4)
? Does the Agency agree?
17. It is Takeda's expectation that the current proposed study will rule out excess CV risk with alogliptin. Coupled with the knowledge that pioglitazone does not increase CV risk, can Takeda anticipate that a separate CV safety study will not be required for marketing approval of the alogliptin/pioglitazone fixed-dose combination (FDC) product? Also, if Takeda must collect additional data to satisfy the 1.8 criterion with alogliptin prior to approval, and assuming adequacy of the interim analysis, can Takeda expect a concurrent action on the alogliptin (NDA 22-271) and FDC (NDA 22-426) applications?

Proposed Clinical Study: SYR-322_402: A multicenter, randomized, double-blind, placebo-controlled study to evaluate cardiovascular (CV) outcomes following treatment with alogliptin in addition to standard of care in subjects with type 2 diabetes (T2D) and acute coronary syndromes (ACS)

NOTE: This reviewer will defer review of the CV and statistics-specific details to cardiologist Dr. Karen Hicks and statistician Dr. Janice Derr, respectively.

Objectives: (Reproduced from the sponsor)

Primary:

- To demonstrate that no excess risk of MACE exists following treatment with alogliptin compared with placebo when given in combination with Standard of Care in subjects with T2DM and ACS. For purposes of this study, the primary MACE composite comprises CV death, MI, nonfatal stroke, (b) (4)

Secondary:

- (b) (4)

Schedule/Design: This will be a multicenter, randomized, double-blind, placebo-controlled, 2-arm study to evaluate CV outcomes following treatment with alogliptin in addition to standard of care in subjects with T2D and ACS. The study will be conducted in approximately 1000 sites in North America, South/Central America, Europe, and the rest of the world. Approximately 5400 subjects will be randomly assigned to treatment, approximately 2700 subjects exposed to alogliptin and placebo. Subjects must have a diagnosis of T2D and be either receiving monotherapy or combination therapy (with the exception of a DDP-4 inhibitor or GLP-1 analogue) or have failed diet and exercise therapy alone. (Please see other inclusion/exclusion criteria below.) The duration of the study is dependent on the number of Major Adverse Cardiovascular Events (MACE) events; however the maximum length is 4-5 years. Study duration will vary for each participant but is expected to be a minimum of 2 years.

After screening on day 1 (baseline), subjects will be randomly assigned in a 1:1 ratio to alogliptin or placebo QD. Randomization will be stratified based on screening renal

function (normal function/mild impairment vs. moderate/severe renal impairment according to the Modification of Diet in Renal Disease [MDRD] formula). Study medication will be assigned as follows:

- Normal function/mild renal impairment (estimated glomerular filtration rate [eGFR] ≥ 50 ml/min): alogliptin 25 mg or placebo daily
- Moderate renal impairment (eGFR between ≥ 30 and < 50 ml/min): alogliptin 12.5 or placebo daily
- Severe renal impairment (eGFR < 30 ml/min): alogliptin 6.25 or placebo daily

Changes in renal function as measured by the MDRD formula after randomization warranting dose reductions are as follows:

- If a subject's renal function declines from normal function/mild impairment to moderate renal impairment based upon the MDRD formula during the study, the study medication will be reduced to 12.5 mg or placebo daily.
- If a subject's renal function declines to severe impairment based upon the MDRD formula during the study, the study medication will be reduced to 6.25 mg or placebo daily

INTERNAL COMMENT: Clinical pharmacology previously also recommended dose adjustment to 12.5 mg for subjects with mild renal impairment due to a mean exposure increase of 69% in these subjects.

According to Dr. David Carlson's review of alogliptin (NDA 22-271):

- **Alogliptin did not cause any remarkable skin lesions in mice, rats, dogs, or monkeys.**
- **Immune/skin (hypersensitivity/pseudoallergy) (~10-20x MRHD at NOAEL; ~20-30x MRHD at LOAEL)**
 - **Dog: flushing, swelling, hypersensitivity/pseudoallergy (as early as skin dose)**
 - **No skin lesions any species**
 - **No phototoxicity**
- **The reaction in dogs seems to be separate from DPP4-inhibitor induction of necrotic skin lesions. The risk of skin lesions from prolonged alogliptin treatment cannot be ruled out, but there was no evidence of skin lesions in any species in the nonclinical program.**
- **No remarkable skin lesions or skin-related toxicity were noted in rodent studies.**
- **Four- and 13-week monkey studies were designed specifically to examine the potential for drug induced skin lesions. There was no evidence of drug-related skin lesions in clinical observations, macroscopic analyses at necropsy, or histological analyses at necropsy in either monkey study. The NOAEL for skin-related toxicity in the 13 week monkey study was 30 mg/kg/d, which provided approximately 31x expected human exposure.**

COMMENTS:

- **The sponsor may consider dose adjustment to 12.5 mg for subjects with mild renal impairment due to a mean exposure increase of 69% in these subjects.**
- **Please clarify approximately how many patients will have moderate and severe renal failure in the CV study SYR-322_402.**
- **Your approach using MDRD for estimation of GFR for inclusion criteria seems reasonable. It is recommended that you use the standardized creatinine assay (refer Miller G. Am J Kidney Dis. 2008:645-648).**
- **In your study reports, you should present the analysis of GFR estimation, efficacy, and safety data using both MDRD and Cockcroft-Gault (CG) equations.**
- **With regards to dose reductions for changes in renal function as measured by the MDRD after randomization:**
 - **For the primary analysis of safety and tolerability endpoints, subjects in the safety dataset should be analyzed in the renal severity subgroup in which they were randomized. For example, if a subject enters the study in the “moderate” renal status subgroup and then experiences a deterioration of renal function during the course of the study such that s/he progresses from “moderate” to “severe” renal impairment, this subject should still be included in the “moderate” status subgroup for purposes of the primary safety analysis. The rationale behind this request is to conduct the primary analysis in the same way that the randomization was established. If a substantial percentage of subjects experience a change in severity status during the course of the study, you should conduct a secondary analysis by renal severity subgroup according to the actual severity status of patients at the time period in which the study endpoint is measured.**
 - **Similarly, for the analysis of efficacy endpoints, subjects in the intention-to-treat data set should be included in the renal severity subgroup that they were classified upon entry into the study. An additional analysis could be conducted by the actual severity status of patients at the time period in which the efficacy endpoint is measured.**

Following the day 1 visit, subjects will return for visits at months 1, 3, 6, 9, and 12 during the first year and every 4 months during subsequent years of participation. Subjects will be followed until the study is completed even if they experience a nonfatal MACE composite event or if they discontinue study drug. If the subject refused to return for study visits, then a telephone visit may be conducted, although this is not preferred nor recommended.

When a sufficient number of events in the primary MACE composite has occurred, the sponsor will notify sites that the study will conclude and all subjects will be requested to return to the clinic for an end of study visit and 2 week subsequent follow up visit.

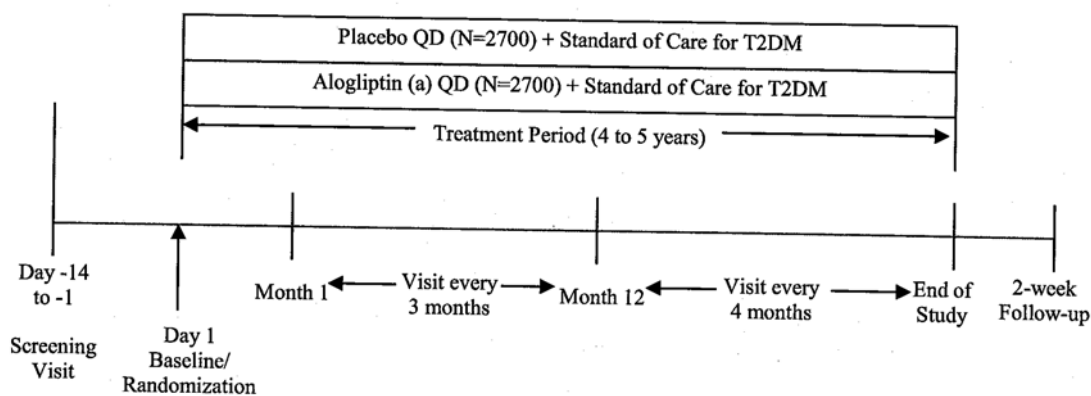
A Steering Committee will oversee the study’s conduct. A Data Monitoring Committee (DMC) will oversee the safety data for this study and a separate independent

Cardiovascular Endpoints Committee (CEC) will adjudicate all suspected MACE composite events. Each committee will develop a charter to describe their activities and responsibilities prior to study initiation.

The study will be completed unless it is determined that 1) the risk/benefit is no longer acceptable for participating subjects or 2) significant violation of Good Clinical Practice (GCP) compromises safety or the ability to achieve the primary study objectives. A study site may be terminated if 1) it is found to be in violation of GCP, protocol, or contractual agreement; 2) it is unable to ensure adequate performance of the study, or 3) as otherwise permitted by the contractual agreement.

INTERNAL COMMENT: The sponsor should submit committee charters for review.

NDA 22-271. Study design (Reproduced from the sponsor)



(a) At randomization, subjects will be assigned 25 mg, 12.5 mg, or 6.25 mg QD depending on renal function. Following randomization, dose adjustments will be allowed based on changes in renal function.

NDA 22-271. Study schedule (Reproduced from the sponsor)

	Screening Period	Treatment Period Visit Schedule							Follow-Up Visit (a)
Procedure	Screening / Visit 1	Baseline / Random- ization Visit 2	Month 1/ Visit 3	Month 3/ Visit 4	Month 6/ Visit 5	Month 9/ Visit 6	Month 12 & Every 4 Months until EOS	End of Study Visit/ Early Termin- ation	2 Weeks after Final Visit (a)
Day	-14 to -1	1							
Visit Window			±5	±7	±14	±14	±14	±14	±3
Informed consent/HIPAA Authorization (if required)	X (b)								
Inclusion/exclusion	X								
Demographics, medical history (including medication history)	X								
Overnight fast	X	X	X	X	X	X	X	X	
Diabetes education	X	X	X						
Randomization		X							
Complete physical exam	X							X	
Vital signs	X	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X	X	
Height	X								
12-lead ECG (c)		X			X		X	X	
Ask questions about recent diagnoses and concomitant medications (d).	X	X	X	X	X	X	X	X	X
Laboratory tests (hematology and serum chemistry (e)	X	X	X	X	X	X	X	X	
Serum Pregnancy tests (f)	X							X	
Urine pregnancy tests (f)		X							
HbA1c	X	X	X	X	X	X	X	X	
FPG (g)	X	X	X	X	X	X	X	X	

	Screening Period	Treatment Period Visit Schedule							Follow-Up Visit (a)
Procedure	Screening / Visit 1	Baseline / Random- ization Visit 2	Month 1/ Visit 3	Month 3/ Visit 4	Month 6/ Visit 5	Month 9/ Visit 6	Month 12 & Every 4 Months until EOS	End of Study Visit/ Early Termin- ation	2 Weeks after Final Visit (a)
Day	-14 to -1	1							
Visit Window			±5	±7	±14	±14	±14	±14	±3
hsCRP (h)	X	X					X	X	
IVRS	X	X	X	X	X	X	X	X	X
Dispense study medication		X	X	X	X	X	X		
Document drug accountability		X	X	X	X	X	X	X	
Collection of unused study drug			X	X	X	X	X	X	

Key: HIPAA= Health Insurance Portability and Accountability Act of 1996; EOS=end of study.

(a) Subjects will complete a 2-Week Follow-Up Visit after completing study drug treatment or following Early Termination from the study.

(b) Subjects may be consented at any time following an ACS event.

(c) A 12-lead ECG will be completed at Screening, at the End of Month 6 and the End of Month 12. Thereafter, a 12-lead ECG will be completed at the end of each study year (ie, every 12 months and at the End of Study Visit).

(d) The specific questions to be asked are listed in Section 10.2.1.

(e) The samples will be obtained under fasting conditions (ie, overnight fast) at each study visit.

(f) Pregnancy tests will be completed only on women of childbearing potential. Serum pregnancy tests (Screening) will be completed by the central lab. Urine pregnancy tests will be performed at the site at Baseline prior to dosing.

(g) FPG is always drawn in a separate tube for this study.

(h) hsCRP levels will be determined at Screening, Baseline Visit, and at the End of Month 12. Thereafter, hsCRP levels will be determined every 12 months and at the End of Study Visit.

NOTE: Vital signs will be measured in duplicate in accordance with American Heart Association guidelines after subjects have been seated for at least 5 minutes.

Serum pregnancy tests will be obtained at screening and end of study. Urine pregnancy tests will be obtained as baseline.

At each visit, answers to targeted questions will be captured as AEs.

INTERNAL COMMENT: The division generally recommends development of a boxed check-list for cardiovascular outcome events so investigators can review the check list at each study visit. The list should be submitted prospectively to the FDA for review. Please see cardiologist Dr. Karen Hick's review for full details.

COMMENT: Women of childbearing potential should be educated to contact the investigator for a possible pregnancy test if changes in menstrual bleeding are observed.

NDA 22-271. Clinical laboratory tests (Reproduced from the sponsor)

Hematology	Serum Chemistry	Other
White blood cell count with autodifferential	Alanine aminotransferase	HbA1c
Platelet count	Aspartate aminotransferase	Fasting plasma glucose (a)
Hemoglobin	Blood urea nitrogen	High-sensitivity C-reactive protein
Red blood cell count	Creatinine	
	Potassium	
	Sodium	
	Total bilirubin	
	Lipid panel (total cholesterol, high-density lipoproteins, low-density lipoproteins, and triglycerides)	
Diagnostic Screening:		
Serum	Urine	
hCG	hCG	
(only for female subjects of childbearing potential)	(only for female subjects of childbearing potential)	
(a) Always drawn in a separate tube for this study.		

Proposed dose: 6.25, 12.5, and 25 mg daily

Subjects: Approximately 5400 subjects worldwide (500 sites in North and Latin America and 500 sites in Europe and the rest of the world). Approximately 2700 subjects would receive alogliptin and 2700 would receive placebo.

Inclusion Criteria: (Reproduced from the sponsor)

1. Male or female subjects 18 years of age or older who have a historical diagnosis of T2DM, who either are receiving monotherapy or combination antidiabetic therapy (with the exception of a DPP-4 inhibitor or GLP-1 analogue) or have failed diet and exercise therapy alone, prior to Screening.
2. Subjects must meet the following HbA1c requirements based the following baseline therapy:
 - If a subject's antidiabetic regimen includes diet and exercise, oral monotherapy, or oral combination therapy, the subject must have an HbA1c level between 6.5 and 9%, inclusive, at Screening.
 - If the subject's antidiabetic regimen includes insulin, the subject must have an HbA1c level between 6.5 and 8.5%, inclusive, at Screening.
3. Subject has a history of ACS (acute MI or unstable angina requiring hospitalization as defined in Appendix E) within 15 days to 6 months prior to randomization.
4. Female subjects of childbearing potential and males who are sexually active who agree to routinely use adequate contraception from Screening throughout the duration of the study.

NOTE: Women NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy, tubal ligation) or who are postmenopausal (defined as at least 1 year since last regular menses). Acceptable methods of contraception are defined in Section 9.1.9, Contraception and Pregnancy Avoidance Procedure.
5. Subject or the subject's legally acceptable representative is able and willing to provide written informed consent prior to the initiation of any study procedures.
6. The subject is capable of understanding and complying with protocol requirements, including scheduled clinic appointments.

Exclusion Criteria: (Reproduced from the sponsor)

1. Subject has signs of type 1 diabetes mellitus, including any history of ketoacidosis or requirements for insulin within 1 year of first diagnosis of diabetes mellitus.
2. Subject is currently receiving a GLP-1 analogue for glycemic control of T2DM at Screening.
3. Subject has received a DPP-4 inhibitor for either more than 14 days total or within the 3 months prior to Screening.
4. Subject has any hemodynamically unstable CV disorder including uncompensated heart failure, refractory angina, uncontrolled arrhythmias, critical valvular heart disease, and severe hypertension (as further defined in Appendix F) at Screening.
5. Subject has had an ACS event less than 15 days prior to randomization according to the definition outlined in Appendix E.
6. Subject has received dialysis within 14 days prior to Screening.
7. Subject has a history of infection with human immunodeficiency virus.
8. Subject has a history of alcohol or substance abuse within the 6 months prior to the Screening Visit.
9. Subject has received any investigational drug within the 30 days prior to the Screening Visit or has received an investigational antidiabetic drug within the 3 months prior to the Screening Visit.
10. Subject has any major illness or debility that, in the investigator's opinion, prohibits the subject from participating in the study.
11. The subject is a study site employee, or is an immediate family member (ie, spouse, parent, child, and sibling) of a study site employee who is involved in conduct of this study.
12. Subject is pregnant (confirmed by laboratory testing, ie, serum/urine human chorionic gonadotropin [hCG]), or in females of childbearing potential], intends to become pregnant during the study, or is lactating.

Discontinuation and Withdrawal Criteria: Subjects will not be discontinued from the study for discontinuing study drug. The primary reason for discontinuation or withdrawal should be as follows: lost to follow up (must be documented with 2 telephone calls and 1 certified letter), voluntary withdrawal (underlying reason should be recorded), and study termination.

Endpoints and Study Procedures: (Reproduced from the sponsor)

The primary endpoint will be the time from randomization to the first occurrence of any event in the primary MACE composite:

- CV death.
- Nonfatal MI.
- Nonfatal stroke.

(b) (4)

The secondary endpoint will be the time from randomization to the first occurrence of any event in the core MACE composite:

(b) (4)

Exploratory endpoints will include:

- Time from randomization to the occurrence of each event counted in the primary MACE composite endpoint:
 - CV death.
 - Nonfatal MI.
 - Nonfatal stroke.

(b) (4)

- Time from randomization to the first occurrence of any event in the exploratory MACE composite (1):
 - All-cause mortality.
 - Nonfatal MI.
 - Nonfatal stroke.
 - Hospitalization for unstable angina (with or without urgent revascularization).
- Time from randomization to the first occurrence of any event in the exploratory MACE composite (2):
 - All-cause mortality.
 - Nonfatal MI.
 - Nonfatal stroke.
 - Hospitalization for unstable angina (with or without urgent revascularization).
 - Hospitalization for heart failure.
- Time from randomization to CV death.
- Recurrence of each of the following:
 - Nonfatal MI.
 - Nonfatal stroke.
 - Hospitalization for unstable angina (with or without urgent revascularization).

Safety variables will include the following:

- SAEs.
- Vital sign measurements (blood pressure and heart rate).
- Clinical laboratory evaluations (hematology and serum chemistry).

Required and excluded medications and treatments: Any medications deemed necessary for the management of AEs may be given at the discretion of the investigator. However, details regarding the medications should be recorded in electronic case report forms (eCRFs).

Provided medication: In addition to study treatment, subjects will be able to receive metformin, sulfonylureas (SUs), insulin, voglibose, and acarbose to ensure they have adequate medications available to maintain glycemic control per protocol.

Medications and treatments not provided directly by the sponsor or excluded: Investigators should manage subjects according to regional guidelines for the Standard of Care in the management of CV comorbidities (including blood pressure and lipids) and T2D. However, DPP-4 inhibitors and GLP-1 analogues are excluded.

Contraception and pregnancy: The acceptable methods of contraception are shown below. “Acceptable” is defined as i.e. $\leq 1\%$ failure rate. Women of child bearing

potential will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy during the course of the study.

If a female becomes pregnant during treatment or within 30 days of the last dose, she will be educated of her right to receive treatment information. If a subject becomes pregnant during treatment, she will be requested to discontinue study medication immediately. However, she will be followed as per the protocol schedule until the study is completed despite drug discontinuation.

All pregnancies, including those in a partner of a male subject, will be followed to final outcome and the outcome will be reported.

NDA 22-271. Acceptable methods of contraception (Reproduced from the sponsor)

Hormonal methods	Barrier methods	Intrauterine Devices (IUDs):
Implants	Male condom PLUS spermicide	Copper T
Hormone shot/injection	Cap (plus spermicide) PLUS male condom	Progesterone T PLUS condom or spermicide
Combined pill	Diaphragm (plus spermicide) PLUS male condom	
Minipill		
Patch		

Adjudication of potential CV events: Additional information will be requested for serious and nonserious CV AEs. The information required and the process will be described in a procedure manual for the adjudication of CV events. These events will be sent by the sponsor to an independent CEC to determine if the event meets criteria for MACE composite. Details of the CEC are provided in the CEC charter. Adjudicated events will be categorized as follows: death (CV or non-CV), nonfatal MI, nonfatal stroke, hospitalization for unstable angina (with or without urgent revascularization), and hospitalization for heart failure.

NOTE: Please refer to cardiologist Dr. Karen Hick's review of the CV analysis plan.

Study-specific committees:

- **Steering:** External medical experts involved in the study and with the sponsor. This committee will remain blinded to treatment assignments, will oversee study conduct and reporting to ensure quality, and make protocol modifications as necessary.
- **Independent DMC:** This committee will assess study progress and safety data at specified intervals and recommend to the sponsor to continue, modify, or stop the study.
- **CEC:** Independent experts with experience and training appropriate for MACE reviews. This committee will review blinded data. Its assessment will be documented in the clinical database and used in endpoint analysis.

NOTE: Please also refer to Dr. Janice Derr's Statistics review.

COMMENT: The sponsor should follow adverse events of angioedema and pancreatitis as events of special interest.

Sponsor's Questions and Agency's Responses (in bold):
Protocol Design

1. Does the Agency agree that the protocol is appropriately designed to assess the CV risk associated with alogliptin?
2. Does the Agency agree that the higher risk T2DM population chosen for this study is appropriate?

Internal comment: This reviewer will defer Questions 1-2 to cardiologist Dr. Karen Hicks.

Study Endpoints

3. Does the Agency agree with the proposed primary endpoint of time from randomization to the first occurrence of any of the events in the primary MACE composite of CV death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina (with or without urgent revascularization)?
4. Does the Agency agree that the secondary endpoint adequately supports the primary endpoint?

Internal comment: This reviewer will defer Questions 3 and 4 to cardiologist Dr. Karen Hicks.

General Safety Evaluation

5. Does the Agency agree with the safety data that Takeda plans to collect and analyze in the proposed CV outcomes study?

Response: No.

- **Women of childbearing potential should be educated to contact the investigator for a possible pregnancy test if changes in menstrual bleeding are observed.**
- **The sponsor should follow adverse events of angioedema and pancreatitis as events of special interest.**
- **The trial should include prespecified renal safety endpoints.**

Dose Selection

6. Does the Agency agree with the proposed dose selection for this study?

Response: Consider dose adjustment to 12.5 mg for patients with mild renal impairment due to a mean exposure increase of 69% in these subjects.

Evaluation of Subjects with Renal Impairment

7. Does the Agency agree that the proposed CV outcomes study can be used to provide additional safety data on the use of alogliptin in patients with renal impairment (in place of conducting the 2 separate renal safety studies which are currently pending review by the FDA)?

Internal comment: The sponsor is referring to studies SYR-322_302 and 304.

Response:

- **Yes, provided that the renal substudy included in SYR-322_402 provides the same duration of exposure as was originally planned in the 2 proposed renal studies.**
- **Please clarify approximately how many patients will have moderate and severe renal failure in the CV study SYR-322_402.**
- **Your approach using MDRD for estimation of GFR for inclusion criteria seems reasonable. It is recommended that you use the standardized creatinine assay (refer Miller G. Am J Kidney Dis. 2008:645-648).**
- **In your study reports, you should present the analysis of GFR estimation, efficacy, and safety data using both MDRD and Cockcroft-Gault (CG) equations.**
- **As stated above, the trial should include prespecified renal safety endpoints.**
- **With regards to dose reductions for changes in renal function as measured by the MDRD after randomization:**
 - **For the primary analysis of safety and tolerability endpoints, subjects in the safety dataset should be analyzed in the renal severity subgroup in which they were randomized. For example, if a subject enters the study in the “moderate” renal status subgroup and then experiences a deterioration of renal function during the course of the study such that s/he progresses from “moderate” to “severe” renal impairment, this subject should still be included in the “moderate” status subgroup for purposes of the primary safety analysis. The rationale behind this request is to conduct the primary analysis in the same way that the randomization was established. If a substantial percentage of subjects experience a change in severity status during the course of the study, you should conduct a secondary analysis by renal severity subgroup according to the actual severity status of patients at the time period in which the study endpoint is measured.**
 - **Similarly, for the analysis of efficacy endpoints, subjects in the intention-to-treat data set should be included in the renal severity**

subgroup that they were classified upon entry into the study. An additional analysis could be conducted by the actual severity status of patients at the time period in which the efficacy endpoint is measured.

Statistical Methods

8. Does the Agency agree with a single trial incorporating an adaptive Bayesian design to satisfy the Agency requirements to rule out excess CV risk greater than 1.3 and 1.8?
9. Does the Agency agree with the statistical methods proposed for the interim analyses and for the final analysis?
10. Does the Agency agree with the proposed statistical assumptions for this study?
11. Takeda currently does not plan to conduct a meta-analysis combining this study with any other previously completed controlled studies. Does the Agency agree that this study can stand-alone to satisfy the guidance criteria for both the interim analysis and the primary analysis?

Response: This reviewer will defer Questions 8-11 to Dr. Janice Derr of Statistics.

Long-Term Exposure

12. Does the Agency find this acceptable to support the long-term safety of alogliptin?

Response: Although the final decision remains a review-issue, study SYR-322_402 should be adequate to support the long-term safety of alogliptin, provided it incorporates the listed comments.

Regulatory

13. If the Agency determines Takeda must collect additional data to satisfy the 1.8 criterion prior to approval, does the Agency agree that the proposed submission contents as outlined above would be adequate for the Agency to determine the approvability of alogliptin?

Response: Although the final decision remains a review-issue, study SYR-322_402 should be adequate to determine the approvability of alogliptin based on the 1.8 criterion, provided the study incorporates the listed comments. The current protocol may need to be amended or other studies may be needed if safety issues are identified in the alogliptin NDA that is currently under review.

14. If these data are submitted to address a complete response letter, Takeda anticipates that these data would be subject to a 6-month review cycle. Is Takeda's understanding correct? Additionally, does the Agency agree that this focused data package could undergo an expedited review cycle of less than 6 months?

Response: A submission to address a complete response letter is subject to a 6-month review cycle regardless of the amount of data included in the submission. Therefore, the sponsor should anticipate a 6 month review cycle if these data are submitted to address a complete response letter. Clinical reviews of the alogliptin NDA are still ongoing; therefore, a final action and a complete list of deficiencies (if applicable) have not been determined.

15. If the results of the interim analysis show that the upper bound of the confidence interval for the estimated risk ratio is less than 1.8, Takeda would expect (1) alogliptin to be approved for general use in patients with T2DM, and (2) that a statement be included in the product labeling such as, (b) (4)

Does the Agency agree?

Response: Clinical reviews of the alogliptin NDA are still ongoing; therefore, a decision on approvability and, if applicable, a list of deficiencies have not been determined. Antidiabetic drugs that meet the 1.8 or 1.3 criteria would likely have standard language about cardiovascular safety in the package insert but the exact wording has not yet been decided upon. (b) (4)

16. If the final analysis satisfies a non-inferiority margin of 1.3, Takeda would expect a labeling statement such as, (b) (4)
? Does the Agency agree?

Response: Please see response above.

17. It is Takeda's expectation that the current proposed study will rule out excess CV risk with alogliptin. Coupled with the knowledge that pioglitazone does not increase CV risk, can Takeda anticipate that a separate CV safety study will not be required for marketing approval of the alogliptin/pioglitazone fixed-dose combination (FDC) product? Also, if Takeda must collect additional data to satisfy the 1.8 criterion with alogliptin prior to approval, and assuming adequacy

of the interim analysis, can Takeda expect a concurrent action on the alogliptin (NDA 22-271) and FDC (NDA 22-426) applications?

Response: Clinical reviews of the alogliptin + pioglitazone NDA are still ongoing. Therefore, a decision on approvability and, if applicable, a list of deficiencies have not been determined. If individual components of a FDC product do not increase CV risk, then the FDC product will not likely need a separate dedicated CV safety trial provided there is not pharmacological basis for a detrimental interaction between the 2 components on CV safety. However, you should include a reasonable number of patients on background pioglitazone therapy in your planned CV trial. Please provide an estimate of the number of alogliptin and comparator-treated patients you propose to enroll who will be on background pioglitazone therapy. A similar comment applies if you develop a FDC tablet of alogliptin and metformin.

APPENDIX E. Inclusion criteria definition for Acute Coronary Syndromes
(Reproduced from the sponsor)

Myocardial Infarction (MI)

The term MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. For this definition of MI, there must be a rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia as indicated by at least one of the following:

1. Symptoms of ischemic chest pain or its clinical equivalent for 10 minutes or longer.
2. ECG changes indicative of new ischemia (new ST-T wave manifestations of acute myocardial ischemia or new left bundle branch block). For the purposes of diagnosing an MI, ST-T wave manifestations are defined as:
 - a) ST injury pattern: New ST elevation at the J-point in two contiguous leads with the cut-off points: ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.
 - b) ST depression and T wave changes: The term ST depression and T wave changes should be used when there is new horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1 .
3. Development of pathological Q waves in the ECG. For the purposes of diagnosing an MI, a pathologic Q-wave is defined as:
 - a) Any Q-wave in leads V2-V3 ≥ 0.02 s or QS complex in leads V2 and V3.
 - b) Q-wave ≥ 0.03 s and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF).
 - c) R-wave ≥ 0.04 s in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect.
4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Unstable Angina Requiring Hospitalization

The term Unstable Angina should be used when hospitalization is required to treat one or more episodes of ischemic discomfort at rest lasting ≥ 5 minutes and supported by one or more of the following:

- ST depression of > 0.5 mm.
- ST elevation > 0.5 mm.
- Persistent (> 30 minutes) ST elevation < 0.5 mm.

APPENDIX F. Definitions of hemodynamically unstable CV disorders (Reproduced from the sponsor)

Uncompensated heart failure: Evidence of volume overload despite appropriate treatment as evidenced by moderate to severe dyspnea at rest or with minimal exertion.

Refractory angina: Daily chest pain consistent with angina despite appropriate anti-ischemic therapy.

Uncontrolled arrhythmias: Atrial fibrillation with uncontrolled ventricular response (>100 beats/minute) or ventricular tachycardia, or high-grade second degree AV block or higher.

Critical valvular heart disease: Known mitral or aortic valvular heart disease associated with heart failure, syncope, or angina or requiring imminent surgical repair or replacement.

Severe hypertension: Blood pressure is greater than 180/110 mm Hg or lesser number if associated with ongoing target organ injury or symptoms.

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/s/

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6/1/2009 02:10:02 PM
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CLINICAL REVIEW

Application Type	NDA
Submission Number	22-271
Submission Code	N

Letter Date	12-21-07
Stamp Date	12-27-07
PDUFA Goal Date	10-27-08

Reviewer Name	Valerie S. W. Pratt, M.D.
Review Completion Date	5-12-09

Established Name	Alogliptin (SYR-322)
(Proposed) Trade Name	Nesina
Therapeutic Class	DPP-4 inhibitor
Applicant	Takeda

Priority Designation	S
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Formulation	Tablet
Dosing Regimen	6.25, 12.5, or 25 mg daily
Indication	Treatment of type 2 diabetes
Intended Population	Adult type 2 diabetics

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, I recommend a complete response to this NDA because the sponsor has not ruled out an unacceptable increase in cardiovascular risk (based on the December 2008 diabetes cardiovascular guidance) and there is a numerical imbalance against alogliptin in cardiovascular serious adverse events. These limitations, in part, arise because of low event rates and inadequate controlled data regarding long-term exposure.

The sponsor will need to do the following to address the identified deficiencies and support approvability:

- Rule out unacceptable cardiovascular risk as described in the December 2008 Final Guidance titled *Diabetes mellitus: Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes*. This may be done by conducting study SYR-322_402 *A multicenter, randomized, double-blind, placebo-controlled study to evaluate cardiovascular (CV) outcomes following treatment with alogliptin in addition to standard of care in subjects with type 2 diabetes (T2D) and acute coronary syndromes (ACS)*, which was discussed at the type A meeting on April 27, 2009.

Although it is not a condition for approval, the sponsor should also conduct either 1) dedicated renal safety studies in patients with moderate and severe renal impairment or 2) a renal substudy as part of the cardiovascular outcomes trial.

1.2 Risk Benefit Assessment

The sponsor proposes that alogliptin be indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2D) (b) (4)

This review focused on the controlled phase 2 and 3 clinical studies pertinent to the claimed indication that were originally submitted to NDA 22-271 (i.e. SYR-322 studies 003, SULF-007, MET-008, TZD-009, PLC-010, INS-011). Due to early concerns about cardiovascular safety, the sponsor also submitted 2 studies of alogliptin + pioglitazone (study 01-05-TL-322OPI-001 and 01-06-TL-322OPI-002), which were originally intended for the fixed dose combination NDA 22-426. The adverse events (AEs) in these studies were also reviewed. The uncontrolled extension study OLE-012 was used to support durability of effect and long-term safety, although the uncontrolled design limits conclusions.

The primary efficacy variable for all 5 controlled, pivotal, phase 3 studies was the difference in hemoglobin A1c (HbA1c) at study endpoint (after 26 weeks of treatment) compared to baseline. Both the 12.5 and 25 mg doses achieved statistically significant least square (LS) mean reductions in HbA1c from baseline to week 26 compared to placebo, regardless of the add-on therapy. The net effect of alogliptin 25 mg ranged from an average improvement of 0.4 - 0.5% across the 5 studies. In all but the MET-008 trial, the LS mean difference was slightly greater in the 25 mg group compared to the 12.5 mg group. The net effect of the alogliptin 12.5 and 25 mg doses was very similar and not statistically separable, although this was not an objective of the studies.

The use of HbA1c for hyperglycemic rescue from weeks 12 – 26 resulted in an unusually high level of rescue after week 12. Subjects who entered a study in the higher baseline HbA1c stratification level were more likely to receive hyperglycemic rescue, compared to subjects in the lower HbA1c stratification level. The high rate of discontinuation limits our confidence in the HbA1c results, due to the imputation of missing value. Estimates of the placebo-adjusted effect of alogliptin from the 2 subjects of completers and noncompleters were influenced by the differential rescue rate in the alogliptin and placebo arms, thus complicating data interpretation. Subjects with higher baseline HbA1c also generally had greater HbA1c reductions compared to subjects with lower baseline HbA1c values when the alogliptin arms were compared to placebo.

The insulin add-on study INS-011 was different from the 4 other studies in the larger percentage of subjects in each arm who were rescued or discontinued (58% placebo, 37% alogliptin 12.5 mg, 40% alogliptin 25 mg). The large percentage of subjects who were rescued or discontinued makes it difficult to ascertain the quantity of change in HbA1c when alogliptin was added-on to insulin, although statistical analysis supported an improvement in HbA1c.

The major secondary efficacy parameters were the percentage of alogliptin-treated subjects achieving HbA1c < 6.5% and < 7%, FPG, and body weight.

- All alogliptin study groups, except the SULF-007 alogliptin 12.5 mg and INS-011 25 mg groups, had a statistically significantly greater number of subjects who achieved HbA1c $\leq 7.0\%$ ($p < 0.05$) compared to placebo. Only the MET-008 and TZD-009 studies had a statistically significantly greater number of alogliptin subjects who achieved HbA1c levels $\leq 6.5\%$ ($p < 0.05$) compared to placebo.
- The LS mean decreases in fasting plasma glucose (FPG) observed in alogliptin-treated subjects were statistically significant compared with the placebo group in studies MET-008, TZD-009, PLC-010, and INS-011 (alogliptin 25 mg dose group only in INS-011). In SULF-007, both alogliptin 12.5 and 25 mg groups had LS mean decreases from baseline in FPG values compared with placebo. However, in this study, the differences between alogliptin and placebo-treated subjects were not statistically significant. No difference was observed between the alogliptin 12.5 mg dose group and placebo in study INS-011.
- No consistent effect on the change from baseline in weight at week 26 was seen in the 5 pivotal studies.

No titration of 12.5 to 25 mg or vice versa was performed during phase 3 clinical studies. Thus, no data exist to provide clinical recommendations for dosage adjustment beyond the general comment that alogliptin should be titrated in individual patients based on glycemic response.

Although the application meets the agency's current recommendations regarding the extent and duration of exposure, it must be noted that all studies excluding uncontrolled OLE-012 had a controlled, 26 week treatment period. Thus, all exposure data beyond 6.5 months is uncontrolled and its interpretation limited. Due to the cardiovascular safety concern that has arisen in the data submitted, the lack of long term controlled safety data is a significant deficiency.

In the controlled clinical trials, there were 4 deaths among the alogliptin-treated patients and 1 death in a non-alogliptin-treated patient. These 5 deaths were all cardiovascular-related. The 4:1 ratio of deaths in the controlled portions of the trial is generally consistent with the randomization scheme for these trials.

Approximately 4% of alogliptin subjects and 3.7% of placebo subjects experienced a treatment emergent serious adverse event (TESAE) in phase 2 or 3 trials of the drug, whereas 2.5% of Alo+ Pio subjects, 2.9% of alogliptin subjects, and 3.5% of pioglitazone subjects experienced a TESAE in the fixed dose combination (FDC) trials. In controlled phase 2 and 3 trials of alogliptin, cardiac events were most common (1.2%) followed by infections and infestations (0.8%). In controlled phase 3 studies of the FDC, TESAEs occurred less frequently, but were most common in the infection and infestation disorders SOC (0.5%) followed by cardiac, gastrointestinal, and nervous system disorders (0.4% each).

In controlled phase 2 and 3 studies originally submitted to the NDA, the percentage of subjects who withdrew due to AEs was similar in the placebo, all alogliptin, and the alogliptin 12.5 mg and alogliptin 25 mg groups (2.1%, 2.8%, 2.7%, and 2.6%, respectively). The percentage of subjects who experienced hypoglycemia was similar between the placebo and alogliptin 12.5 and 25 mg treatment groups (mild-moderate hypoglycemia: 3.7-6.0%; severe hypoglycemia 0.1-0.6%).

The sponsor analyzed the phase 2 and 3 AEs with 2 different cluster analyses:

- The angioedema standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ)
- A customized MedDRA query of potential cutaneous drug reaction (PCDR) events

A deficiency of this analysis was that the customized MedDRA query of PCDR events did not include most ulcers (only venous ulcer pain was included), although there was no evidence of drug-related skin lesions in 2 monkey studies designed to assess this.

Although the percentages of subjects experiencing angioedema cluster events in the placebo (3.4%) and alogliptin groups (4.5%) were similar, the number of events per 100 subject-years of exposure was approximately 25% greater in the all alogliptin group (13.0) compared to the placebo group (9.8). The most common angioedema cluster event was peripheral edema, which occurred similarly in the alogliptin and placebo groups. Eleven angioedema cluster events, however, were reported in alogliptin but not placebo subjects. The preferred term,

hypersensitivity, occurred slightly more often in the alogliptin group, especially when events per 100 subject-years exposure was compared (1.4 vs. 0.5). Angioedema-like events and hypersensitivity reactions have been seen with other DPP4 inhibitors and are labeled in the Warnings and Precautions section for Januvia, the only FDA-approved DPP4 inhibitor.

The percentage and number of PCDR events per 100 subject-years of exposure were slightly higher in the all alogliptin dose group when compared to placebo (9.6% and 28.4 vs. 6.9% and 24.9). This was also true when alogliptin 12.5 and 25 mg were compared to placebo. The most common AEs in the PCDR cluster were pruritis and rash, which occurred in a higher percentage of subjects in the all alogliptin group than placebo group (pruritis 1.6% vs. 0.4%; rash 1.6% vs. 0.7%). More subjects experienced AEs of contact dermatitis, dermatitis, allergic dermatitis, and atopic dermatitis in the all alogliptin group than in the placebo group (27/1961 [1.4%] vs. 3/534 [0.6%], respectively).

Although sponsors of some other DPP-4 inhibitors evaluated infections as an AE of special interest, alogliptin's sponsor did not. However, the incidence of infection and infestation TESAEs in controlled phase 2/3 trials of alogliptin was similar in the alogliptin and placebo groups (0.8% vs. 0.9%); the incidence of infection and infestation TEAEs was less in the alogliptin group when compared to placebo (28.8% vs. 31.3%).

After carefully considering the recommendations of the Endocrinologic and Metabolic Drugs Advisory Committee on July 1 and 2, 2008 and the data submitted, it was decided that NDAs currently under review must meet the cardiovascular safety standards recommended in the December 2008 final diabetes cardiovascular guidance. This meant that, prior to approval, the incidence of important cardiovascular events occurring with the investigational agent should be compared to the incidence of important cardiovascular events occurring with the control group and that the upper bound of the 2-sided 95% confidence interval (CI) for the estimated risk ratio should be < 1.8. If the integrated analysis approach did not show this, then a single large safety trial should be conducted alone or added to other trials to satisfy this upper bound. On January 21, 2009, the sponsor submitted the requested major adverse cardiovascular event (MACE) information, which is described in section 7.3.5 Submission Specific Primary Safety Concerns.

The analysis shows that the upper bound of the 2-sided 95% CI for the estimated risk ratio is > 1.8 in pooled SMQ and custom analyses and in all individual studies, when it was estimable. The high upper bound of the 2-sided 95% CI is likely due to low MACE event rates. Nonetheless, NDA 22-271 does not meet current cardiovascular risk safety guidelines for approval. The large fixed dose combination study of alogliptin + pioglitazone (study OPI-001) also likely drove the results of the pooled study comparison.

In total, 10 of 35 (28.6%) cases were coded as MI or acute MI. Sixteen of the 35 (45.7%) MACE events were adverse events (AEs), not serious adverse events (SAEs). Three of the 16 (18.8%) AEs (725/3005, 716/3021, and 728/3008) were coded as myocardial infarction. Based on the limited information present, this reviewer considers it possible that as many as an additional 6 myocardial infarctions (MIs) and 6 cerebrovascular accidents (CVAs) (2 placebo and 4 alogliptin in each group) may have occurred in the 16 AEs cases. Case 716/3021 is

especially concerning as it describes an AE of myocardial infarction with subject discontinuation on the same day for “lack of efficacy”. This reviewer believes the AE should have been listed as the reason for discontinuation.

Aside from the fact that several of the AEs described in the MACE analysis may have met criteria for an SAE, MI, and/or CVA, there is also an imbalance in the events the sponsor labeled as SAEs when the alogliptin cardiac system organ class (SOC) is compared to placebo. As shown in section 7.3.2 Nonfatal Serious Adverse Events, in the controlled phase 2 and 3 trials in NDA 22-271, the sponsor described 23 cardiovascular TESAES in alogliptin subjects versus 2 events in the placebo population. However, NDA 22-271 Integrated Analysis of Safety’s table 10.b Listing of Subjects who Experienced an SAE indicates there were 24 cardiac SAEs. As one would expect the SAE table to have a greater or equal number of SAEs as the TESAES table, the sponsor was asked to clarify this point. The sponsor responded that 2 cases (hypertensive heart disease MET-008 520/8010 and palpitations PLC-010 440/4008) were inadvertently not included in table 10.b. Subject 520/8010 died from hypertensive heart disease and is included in the Deaths section. Subject 440/4008 experienced atrial fibrillation with a positive troponin and was included in the review of CV SAEs. When these 25 cardiovascular (CV) SAE cases were internally adjudicated, two possible cases of MI were identified (422/9009 angina pectoris and coronary artery disease; 440/4008 palpitations). Overall, the ratios of CV SAE exceeded the expected 3.7:1 ratio based on randomized patients in the safety population of NDA 22-271. When Dr. Janice Derr of statistics calculated the incidence ratio for CV SAEs, it also exceeded 1.8 with the stratified asymptotic and exact methods (2.31 and 2.24, respectively). The 95% confidence intervals (CIs) were again broad.

In controlled phase 2 and 3 studies originally submitted to NDA 22-271, there was an increase in cardiovascular TEAEs when alogliptin was compared to placebo (4.0% vs. 2.4%). The most common AE in this SOC was angina pectoris (0.7% vs. 0%, respectively). A slight increase in immune system disorders was also seen when alogliptin was compared with placebo (1.3% vs. 0.4%). The most common events in this SOC were seasonal allergy (0.5% vs. 0.2%) and hypersensitivity (0.4% vs. 0.2%). Nervous system disorders also occurred more frequently in the alogliptin group (13.0% vs. 9.7%). Headache and dizziness, which occurred at similar rates in the alogliptin and placebo groups, were the most common events in the SOC. Upper respiratory infection, nasopharyngitis, and headache, which are AEs associated with sitagliptin, occurred more commonly in placebo than the all alogliptin doses treatment group (5.2% vs. 3.6%; 5.1% vs. 4.9%; and 3.9% vs. 4.9%).

Standard safety laboratory data were obtained in all studies at baseline, during the treatment period, and at study end. Serum CPK, amylase, and lipase were not measured in the phase 3 studies. The mean changes from baseline to endpoint in laboratory results were small and generally similar between placebo and alogliptin treatment groups. In the controlled phase 2 and 3 studies originally submitted to NDA 22-271, the mean change in serum creatinine in the alogliptin treatment groups from baseline to endpoint was 0 mg/dl. Small increases from baseline in the alogliptin groups’ urine albumin/creatinine ratios were seen when compared to placebo (30 and 15 mcg/mg versus 5 mcg/mg). The median changes were more similar (-1, -2, and -3 for the placebo and alogliptin 12.5 and 25 mg groups). A greater percentage of alogliptin

12.5 and 25 mg subjects experienced markedly abnormal creatinine values when compared to placebo (0.9% and 1.0% vs. 0.4%).

A consistent effect of alogliptin on liver enzymes was not seen. Transaminase elevation > 5x ULN usually resolved without study drug interruption and may have been due to alternative etiologies. The change from baseline to endpoint in alkaline phosphatase in the placebo and alogliptin 12.5 and 25 mg groups was also -0.3, -1.8, and -1.4 mU/ml respectively.

The results of special PK and safety studies were as follows:

- In subjects with mild, moderate, and severe renal impairment and end stage renal disease (ESRD), the AUC_{0-t} increased by 69%, 108%, 219%, and 281%, respectively. (Please refer to section 7.4.5 Special Safety Studies for more information.)
- Moderate hepatic impairment did not significantly alter alogliptin exposure. (Alogliptin PK was not studied in patients with mild or severe hepatic renal impairment.)
- Elderly white women had a 97% increase in exposure compared to young white men. The creatinine clearance in elderly white women was approximately half that of young white men, suggesting the renal function decrease resulted in the increased exposure in elderly white women. Sex and race, however, did not affect alogliptin exposure.
- There was no significant effect of alogliptin on QT prolongation.
- Metabolic modulators did not significantly affect exposure.
- Alogliptin did not significantly affect exposure of P450 probe substrates.

Although the sponsor should have used more rigorous criteria for defining abnormal blood pressure, no significant differences were seen in blood pressure, heart rate, and ECG parameters between treatment groups.

Alogliptin poses minimal carcinogenic risk to humans based on high exposure multiples at the NOAEL (32x) for rat thyroid C-cell tumors, very high exposure multiples ($\geq 288x$) at doses that caused increased combined thyroid C-cell adenomas and carcinomas in male rats, and absence of any other drug-related tumors in rats ($> 400x$ female MRHD) or mice (60x MRHD).

There were no remarkable effects on pregnancy or fetal development except at maternally toxic doses that were generally greater than 200x higher than expected human exposure. There was a slight increase in sperm abnormalities in males (NOAEL approximately 67x MRHD). However, rat sperm abnormalities did not affect fertility. Alogliptin crosses the placenta and is secreted in rat milk at 2x the concentration of maternal plasma.

Two pregnancies were reported in the phase 1 program. Both subjects had completed study drug administration at the time of their first positive pregnancy test and both subjects terminated their pregnancies via induced abortion. Four pregnancies were reported in the alogliptin phase 2 and 3 programs. Two of the 4 subjects delivered healthy, full-term infants. The other 2 subjects experienced spontaneous abortions.

No cases of alogliptin overdose were reported during clinical development. Over a 3 hour hemodialysis session, approximately 7% of the drug was removed. Therefore, hemodialysis is unlikely to benefit an overdose situation.

In conclusion, while the efficacy of alogliptin 12.5 and 25 mg was demonstrated after 26 weeks of treatment, the net effect of the doses (-0.4% to -0.5% HbA1c improvement) was very similar and not statistically separable. The use of HbA1c for hyperglycemic rescue from weeks 12 – 26 resulted in an unusually high level of rescue after week 12. The high rate of discontinuation limits our confidence in the HbA1c results due to the imputation of missing value, especially in study INS-011. Estimates of the placebo-adjusted effect of alogliptin from the 2 subsets of completers and noncompleters were influenced by the differential rescue rate in the alogliptin and placebo arms, thus complicating but not prohibiting data interpretation.

The safety data, however, is compromised by a lack of controlled, longterm data. The data available does not meet the division's current guidelines on acceptable cardiovascular risk, thus prohibiting alogliptin's approval.

1.3 Recommendations for Postmarketing Risk Management Activities

Not applicable.

1.4 Recommendations for other Post Marketing Study Commitments

Not applicable.

2 Introduction and Regulatory Background

2.1 Product Information

Takeda Global Research and Development Center, Inc. (TGRD) has submitted this new drug application for the new molecular entity (NME), dipeptidyl peptidase-4 (DPP4) inhibitor alogliptin (SYR-322), trade name Nesina. The sponsor is proposing use of 6.25, 12.5, or 25 mg alogliptin daily as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D). The recommended dose of alogliptin is 25 mg daily, taken with or without food as mono- or combination therapy. The sponsor recommends dosage adjustment in patients with moderate or severe renal insufficiency and in patients with end stage renal disease (ESRD) requiring dialysis as follows:

NDA 22-271. The sponsor's recommended dosage adjustment for moderate, severe, and ESRD			
Degree of renal insufficiency	Serum creatinine levels (mg/dl)	Creatinine clearance (ml/min)	Recommended dosing
Moderate	Men > 1.7 to ≤ 3.0 Women > 1.5 to ≤ 2.5	≥ 30 to < ^(b) ₍₄₎	12.5 mg once daily
Severe/ESRD	Men > 3.0	< 30	6.25 mg once daily*

	Women > 2.5		
*Without regard to timing of dialysis in patients with ESRD			

However, clinical pharmacology recommended dose adjustment to 12.5 mg for subjects with mild renal impairment due to a mean exposure increase of 69% in these subjects. Please refer to section 7.4.5 Special Safety Studies for more information.

2.2 Currently Available Treatments for Proposed Indications

Medications currently approved for the treatment of type 2 diabetes mellitus include the following:

- Insulin
- Sulfonylureas (SFU)
 - Tolazamide (Tolinase)
 - Chlopropramide (Diabinese)
 - Glyburide (Micronase)
 - Glipizide (Glucotrol and Glucotrol XL)
 - Glimepiride (Amaryl)
- Meglitinide analogs: Repaglinide (Prandin)
- D-Phenylalanine: Nateglinide (Starlix)
- Biguanides: Metformin (e.g., Glucophage and Glucophage XR)
- Thiazolidinediones (TZD)
 - Rosiglitazone (Avandia)
 - Pioglitazone (Actos)
- α -Glucosidase inhibitors
 - Acarbose (Precose)
 - Miglitol (Glyset)
- Incretin-mimetics
 - Exenatide (Byetta)
- Amylinomimetics
 - Pramlintide (Symlin)
- Dipeptidyl peptidase 4 inhibitors
 - Sitagliptin (Januvia)
- Bile acid sequestrants
 - WelChol (colesevelam)
- Dopamine receptor agonists
 - Cycloset (bromocriptine mesylate)

2.3 Availability of Proposed Active Ingredient in the United States

The new molecular entity alogliptin is not currently approved in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

The only DPP-4 inhibitor currently approved in the United States is sitagliptin. Dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with end stage renal disease. When sitagliptin is used with a sulfonylurea (SFU), a lower dose of the SFU may be required to reduce the risk of hypoglycemia. There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Adverse reactions reported in $\geq 5\%$ of patients treated with sitagliptin and more commonly than patients treated with placebo are: upper respiratory tract infection, nasopharyngitis, and headache.

Monkeys develop necrotic skin lesions after exposure to some DPP-4 inhibitors, which is thought to result from cross-reactivity with DPP-8 and DPP-9. Vildagliptin, which is currently in development, may cause hepatotoxicity. Vildagliptin's sponsor has been asked to conduct a dedicated hepatic safety study.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

End of phase 2 (EOP2) meetings were held on November 28, 2005 and April 30, 2007. At the first EOP2 meeting, the clinical discussion centered on the dose selection (12.5, 25, and/or 50 mg) for phase 3 studies. The agency encouraged the sponsor to include 12.5 and 25 mg doses in the development program, based on the efficacy seen in phase 2 trials and the then not as yet fully characterized safety profile of DPP-4 inhibitors. The division also encouraged the sponsor to conduct a 3 month monkey study in parallel with phase 3 at doses 1, 3, and 10x clinical AUC exposures to investigate for the possible development of skin lesions. The agency also recommended a transporter based drug interaction study to examine the effects of cyclosporine on the pharmacokinetics of alogliptin.

At the April 30, 2007 EOP2 meeting, the clinical section agreed that the approvability of (b) (4) dose strengths of (b) (4) 6.25 mg, for the purpose of dose reduction in patients with impaired renal function, would be supported by the following. (The sponsor, however, is not seeking approval of the (b) (4) dose.)

- Dose proportionality of alogliptin AUC in healthy subjects and patients with T2D
- Similar systemic exposure to alogliptin between healthy subjects and subjects with T2D receiving the same dose
- No dose limiting toxicities at single doses up to alogliptin 800 mg in healthy subjects and multiple doses of alogliptin 100 mg daily for 12 weeks and alogliptin 400 mg daily for 14 days in T2D subjects

The sponsor was also reminded that it must submit patient profiles for phase 2 and 3 subjects who die, experience serious adverse events, or discontinue use due to adverse events.

2.6 Other Relevant Background Information

Alogliptin is not currently approved in the United States or abroad. One DDP4 inhibitor, sitagliptin, is currently marketed in the United States. Another DDP4 inhibitor, vildagliptin, is currently marketed in a few countries outside of the United States.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The 7 controlled, phase 3 studies (SYR-322 studies SULF-007, MED-008, TZD-009, PLC-010, INS-011 as well as 01-06-TL-322OPI-002 and 01-05-TL-322OPI-001) pertinent to the claimed indication that are reviewed here were each conducted in multiple countries (average 17 countries, range 13-23 countries).

No study site enrolled large numbers of subjects in any one of the studies. Most investigators randomized less than 10 subjects per protocol. Investigators who participated with the greatest number of randomized subjects in all studies were selected for inspection. The protocols inspected included SYR-322-MET-008, SYR-322-TZD-009, SYR-322-PLC-010, and SYR-322-INS-011. Site inspections for studies 01-06-TL-322OPI-002 and 01-05-TL-322OPI-001 are currently ongoing. Based on preliminary findings, the data from these sites appear acceptable in support of the indication.

Of the 3 sites investigated thus far by the Division of Scientific Investigations (DSI), Dr. Marc Rendell's Omaha, NE and Deerfield, IL offices had no deviations from regulations. Dr. Fatima Phillips' Merritt Island, FL site, however, was preliminarily classified as having significant deviations from regulations. Records for 14 of 19 (74%) of subjects randomized to SYR-322-TZD-009 and 10 of 11 (91%) subjects enrolled in study SYR-322-PLC-010 were reviewed for completeness, accuracy, protocol deviations, and compliance with applicable regulations. The inspection found that Dr. Phillips did not maintain adequate and accurate records, and she may not have obtained adequate informed consent. However, DSI determined that neither of these observations adversely impact data acceptability.

3.2 Compliance with Good Clinical Practices

The sponsor reports that the 9 clinical studies pertinent to the claimed indication that are reviewed here (SYR-322 studies 003, SULF-007, MED-008, TZD-009, PLC-010, INS-011, OLE-012 as well as 01-06-TL-322OPI-002 and 01-05-TL-322OPI-001) were conducted in accordance with the principles of good clinical practice (GCP), including use of the institutional review board/ethics committee (IRB/EC) and informed consent.

Protocol violations in the 7 controlled, phase 3 clinical studies pertinent to the claimed indication were as follows:

- Study SULF-007: 4/500 (0.8%) subjects were discontinued due to major protocol violations (12.5 mg group 3; 25 mg group 1). Deviations included 1 subject each who took excluded metformin, had inadequate consumption of study drug, had received concomitant treatment with systemic steroids, and was provided with a mistaken bottle of medication at the week 16 visit.
- MET-008: 8/527 (1.5%) subjects were discontinued due to a protocol violation (placebo group 2; 12.5 mg group 2; 25 mg group 4). Deviations included 2 subjects each who took excluded medications or did not have retests of their laboratory values and 1 subject each who was given the wrong study drug bottle, went more than 7 days without study drug, did not meet the BMI criterion, or violated another inclusion/exclusion criterion.
- TZD-009: 4/493 (0.8%) subjects were discontinued due to a protocol deviation (placebo group 1; 12.5 mg group 1; 25 mg group 2). Deviations included 2 subjects with changes in their metformin dose during the stabilization period, 1 subject who received a prohibited medication, and 1 subject who stopped her add-on SFU.
- PLC-010: 2/329 (0.6%) subjects were discontinued due to protocol deviations. One placebo group subject did not meet inclusion criteria. One 12.5 mg group subject began an oral hypoglycemic drug during the study.
- INS-011: 12/390 (3.1%) subjects were discontinued due to protocol deviations (placebo group 3; 12.5 mg group 5; 25 mg group 4). Deviations included 8 subjects with substantial changes in their insulin dose, and 1 subject each who was unable to come in for study visits, given the wrong study drug, received another antidiabetic drug, or went 15 days without study drug.
- OPI-002: 18/655 (2.7%) subjects were discontinued due to protocol deviations (25 mg alogliptin [A] 2; 30 mg pioglitazone [P] 3; A12.5+P30 group 7; A25+P30 group 6). Deviations included 3 subjects who received incorrect study drug allocations, 2 subjects who received an incorrect bottle but still received the correct study drug, 5 subjects who violated inclusion/exclusion criteria, 4 subjects who were noncompliant, 2 subjects who took excluded medications, 1 subject who was incorrectly randomized due to a lost glucose result, and 1 subject who did not fully disclose medical and medication history at screening.
- OPI-001: 46/1554 (3.0%) subjects were discontinued due to a protocol deviation.
 - Placebo group 2 subjects; P15 group 8 subjects; P30 group 6 subjects; P45 group 4 subjects
 - A12.5 group 3 subjects; A12.5+P15 group 5 subjects; A12.5+P30 3 subjects; A12.5+P45 group 6 subjects
 - A25 group 2; A25+P15 group 5; A25+P45 group 2 subjectsDeviations included 10 subjects who received incorrect study drug, 10 subjects with violations of inclusion/exclusion criterion, 18 subjects who were noncompliant with study drug or metformin dose, 1 subject who was noncompliant with study visits, 2 subjects who took excluded medications, and 5 subjects with visits outside the specified window.

In addition, 7 subjects should have been labeled as having a major protocol deviation for receiving a treatment different from the randomized treatment (SULF-007: 1 alogliptin; MET-

008: 3 alogliptin subjects; OPI-002: 3 A+P subjects). Please see section 6.1.3 Patient Disposition for more information. However, discontinuations due to protocol violations in each trial are not expected to impact the study results because the rates of discontinuation were low.

3.3 Financial Disclosures

Only 2 principal investigators, Drs. (b) (6) certified that financial interests or arrangements existed during the conduct of the clinical study. They each disclosed that, "I or the institution with which I am affiliated, has or will receive significant payment from Takeda (e.g., a grant to fund ongoing research, compensation in the form of equipment, retainers for ongoing consultation or honoraria that have a cumulative monetary value in excess of \$25,000) in support of my activities, exclusive of the cost of conducting the clinical study or other clinical studies." As of March 2008, Drs. (b) (6) received \$295,000 (b) (6) and \$202,700 (b) (6) respectively. (u) (6)

The number of subjects contributed by each investigator was small. Therefore, the data submitted by Drs. (b) (6) did not impact the overall conclusions of the trials.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The drug substance and drug product are acceptable. The chemistry reviewer is recommending approval of the NDA. The sponsor agreed to follow the stability of the first 3 packaged lots of different bulk batches of each strength of product and submit the results to the annual report. The applicant agreed to place at least one commercial production lot of the drug product per year aside for stability testing for each strength and package configuration following the approved stability protocol.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Alogliptin exhibits a benign toxicological profile in rats, dogs, mice, and monkeys over a considerable range of drug exposure relative to anticipated clinical exposure. Drug-related mortality was only seen in multiple dose studies and only at high exposures in mice, rats, and rabbits (generally > 50x the maximum recommended human dose [MRHD]). Body weights were typically lower than controls after repeat dosing at very high exposure multiples (generally > 100x MHRD). Very large exposures (≥ 200 fold excess vs. clinical exposure) were required to

identify target organs in animals, which included kidney, lung, liver, and male reproductive organs. The kidney is the major route of excretion. As kidney toxicity occurred at very high concentrations in animals ($\geq 200\times$ MRHD), the risk of kidney toxicity in humans is minimal. A slightly higher kidney exposure in patients with renal impairment is not likely to significantly increase the risk of kidney toxicity.

Dogs showed clinical signs of reddened/flushing ears and face, along with body and facial swelling. These signs were tolerated for up to 9 months (100 mg/kg [133x] and 200 mg/kg [267x]) and were not dose limiting. Although the sponsor did not investigate the mechanism of the reddening/edema, another DPP4 inhibitor showed the reactions to be due to histamine release, suggesting pseudoallergy and not a true, immunoglobulin-mediated allergic reaction. Although hypersensitivity-type reactions were not observed with sitagliptin in animals prior to approval, similar reactions were observed clinically postmarketing and prompted a labeling change. Because alogliptin produced hypersensitivity reactions in animals and humans premarketing (see the safety section of this review), such reactions could potentially occur with greater frequency and severity with alogliptin. There was no evidence of phototoxicity in a dedicated study.

Cutaneous toxicity, which has been observed with other DPP4 inhibitors, was not seen in alogliptin studies in mice, rats, dogs, or monkeys. No remarkable skin lesions or skin-related toxicity were noted in rodent studies. Four- and 13-week monkey studies were designed specifically to examine the potential for drug induced skin lesions. There was no evidence of drug-related skin lesions in clinical observations, macroscopic analyses at necropsy, or histological analyses at necropsy in either monkey study. The NOAEL from skin-related toxicity in the 13 week monkey study was 30 mg/kg/d, which provided approximately 31x expected human exposure. The lack of cutaneous toxicity may be due to alogliptin's high selectivity for DPP4, as opposed to DPP8 and/or DPP9.

No cardiac signals or potential mechanisms for preliminary clinical cardiac findings were seen in animal studies. However, it must be noted that healthy animals are used in toxicology studies, thus risks specific to the T2D population cannot be fully assessed in nonclinical studies.

Alogliptin poses minimal carcinogenic risk to humans based on high exposure multiples at the NOAEL (32x) for rat thyroid C-cell tumors, very high exposure multiples ($\geq 288\times$) at doses that caused increased combined thyroid C-cell adenomas and carcinomas in male rats, and absence of any other drug-related tumors in rats ($> 400\times$ female MRHD) or mice (60x MRHD). Of note, two glucagon-like peptide 1 (GLP-1) analogues (exenatide and liraglutide) increase thyroid C-cell adenomas in rats, but there is no evidence to suggest the finding with alogliptin (which increases GLP-1) is due to a common mechanism. There is no evidence of increased C-cell tumors with 3 other DPP4 inhibitors, sitagliptin, (b) (4) and saxagliptin.

Alogliptin was not teratogenic at doses greater than 200x higher than expected human exposure. There were no remarkable effects on pregnancy or fetal development except at maternally toxic doses that were generally greater than 200x higher than expected human exposure. There was a

slight increase in sperm abnormalities in males (NOAEL approximately 67x MRHD). However, rat sperm abnormalities did not affect fertility.

Alogliptin crosses the placenta and is secreted in rat milk at 2x the concentration of maternal plasma. Fetal exposure was confirmed in rats and assumed in nursing rats. Although no specific risks to fetuses, neonates, or nursing infants are predicted from reproductive toxicity studies, human fetuses and nursing infants will be exposed to alogliptin from maternal drug use.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Alogliptin is a DPP4 inhibitor, which increases incretin hormones including GLP-1 and glucose dependent insulintropic polypeptide (GIP). DPP4 inactivates GLP-1 by N-terminal cleavage. GLP-1 is released from L-cells in the ileum and colon after meals and increases glucose-dependent insulin secretion from pancreatic β cells, resulting in increased hepatic glucose metabolism and low risk for hypoglycemia. GLP-1 also reduces glucagon secretion.

Alogliptin showed no inhibition of DPP2, DPP8, DPP9, or related DASH enzymes (PREP, FAP/seprase, tryptase). Alogliptin's DPP4 selectivity is similar to sitagliptin and superior to vildagliptin.

4.4.2 Pharmacodynamics

Alogliptin has been studied at doses ranging from 6.25 to 800 mg. Peak DPP-4 inhibition exceeded 93% for most doses. Maintaining higher than 80% DPP-4 inhibition over 24 hours is targeted by many sponsors of DPP-4 inhibitors in order to achieve desirable chronic glucose lowering in T2D and 25 mg was the minimum dose achieving this DPP-4 inhibition goal. In healthy subjects, peak and total exposure to GLP-1 across all doses was 2-4x greater than placebo, and dose related elevations of GLP-1 persist 24 hours after dosing.

The HbA1c lowering effect of 12.5 and 25 mg alogliptin were statistically significant compared to placebo in study 003, a 12 week randomized, double blind, placebo controlled, dose-finding, comparison of HbA1c using alogliptin doses 6.25, 12.5, 25, 50, and 100 mg. The treatment effect of 25 mg was slightly greater than that of 12.5 mg in 3 of 5 phase 3 trials (see the table below). According to Drs. Sang Chung's and Luke Bi's clinical pharmacology review, there was no dose effect relationship for alogliptin's reducing serum HbA1c, thus there is no clear benefit in starting with 25 over 12.5 mg for serum HbA1c reduction.

NDA 22-271. Placebo-corrected change from baseline in HbA1c at week 26 by treatment (Reproduced from the sponsor)

Add-on Therapy	Alogliptin vs Placebo		Difference Between Alogliptin 12.5 mg and 25 mg.
	Alogliptin 12.5 mg	Alogliptin 25 mg	
As monotherapy (010)	-0.54%***	-0.57%***	-0.03%
Add-on to metformin (008)	-0.50%***	-0.48%***	0.02%
Add-on to a TZD (009)	-0.47%***	-0.61%***	-0.14%
Add-on to a sulfonylurea (007)	-0.39%***	-0.53%***	-0.14%
Add-on to insulin (011)	-0.51%***	-0.59%***	-0.08%

***P<0.001 compared with placebo. Difference between alogliptin doses derived by subtracting alogliptin 12.5 mg from the alogliptin 25 mg dose.

The effect of alogliptin on QT interval was assessed in a single blind, randomized, placebo, and positive controlled Thorough QT study testing two parallel supratherapeutic multiple doses (50 or 400 mg x 7 days; study 019). The QT IRT concluded there was no significant effect of alogliptin on QT prolongation. Alogliptin (50 and 400 mg) was not positively associated with QTcF > 450 ms while moxifloxacin was.

4.4.3 Pharmacokinetics

As 68% of the oral alogliptin dose is excreted in urine, renal excretion is the major excretion pathway. Alogliptin is metabolized to N-dealkylated alogliptin (M1) by CYP2D6 and acetylated alogliptin (M2), although these metabolites are minor (< 1% and < 4% of alogliptin exposure, respectively).

Alogliptin exposure increase was proportional to the dose increase after multiple dosing (25-400 mg). Mean time to reach C_{max} (T_{max}), clearance (CL/F), volume of distribution (V_d/F), and elimination half-life following a 25 mg single dose were 1-2 h, 16.9L/h, 609.6 L, and 25.6 h, respectively. The terminal elimination half-life is 22 hours. Food did not significantly affect exposure. The mean AUC_{0-t} increased in elderly and women by 28% and 19%, respectively. The mean AUC_{0-t} increased by 28% in white subjects when compared to black subjects. In subjects with mild, moderate, and severe renal impairment and end stage renal disease (ESRD), the mean AUC_{0-t} increased by 69%, 108%, 219%, and 281%, respectively. Moderate hepatic impairment did not significantly alter alogliptin exposure. The PK of alogliptin was not evaluated in subjects with mild or severe hepatic impairment. Please also refer to section 7.4.5 Special Safety Studies.

Metabolic modulators, including fluconazole, ketoconazole, gemfibrozil, cyclosporine, pioglitazone, cimetidine, metformin, atorvastatin, and digoxin, did not significantly affect exposure. Alogliptin did not significantly affect exposure of P450 probe substrates (i.e. caffeine, tolbutamine, dextromorphan, and midazolam), fexofenadine, glyburide, (S)-warfarin, (R)-warfarin, ethinyl estradiol, norethindrone, cimetidine, metformin, pioglitazone, atorvastatin, and digoxin.

About 68% of the oral dose was excreted in the urine as alogliptin, indicating that renal excretion is the major elimination pathway for alogliptin.

5 Sources of Clinical Data

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5.1 Tables of Clinical Studies

NDA 22-271. Tabular listing of submitted clinical studies				
Study No. No. Centers-Country	Study Design Primary Objective	Population No. and Type	Treatment Duration	Treatment (enrolled/completed)
5.3.1.1 Bioavailability studies				
SYR-322-026 1-United States	Open label, randomized, 2 period crossover Food effect, safety (PK)	24 healthy subjects	2d (7d washout for crossover)	Alogliptin 25 mg (24/24)
SYR-322/CPH-006 1-Japan	Single dose, open label, randomized, 2 period, 2 way crossover Food effect, safety (PK)	10 healthy males	2d (7d washout for crossover)	Alogliptin 50 mg (10/9)
5.3.1.2 Comparative bioavailability and bioequivalence studies				
SYR-322-027 1-United States	Open label, randomized, 2 period crossover Bioequivalence (PK)	72 healthy subjects	2d (7d washout for crossover)	1-12.5 mg alogliptin phase 3 tablet + 1-12.5 mg alogliptin commercial tablet (36/33) 1-25 mg alogliptin phase 3 tablet + 1-25 mg alogliptin commercial tablet (36/36)
5.3.3.1 Healthy subject pharmacokinetic and initial tolerability study reports				
SYR-322-001 1-United States	Single and ascending dose, randomized, double blind, placebo controlled Safety, tolerability (PK/PD)	36 healthy males	1d	Alogliptin 25, 50, 100, 200, 400, and 800 mg (each 5/5) Placebo (6/6)
SYR-322-014 1-United States	Open label, single dose PK, mass balance, and total radioactivity (ADME)	8 healthy subjects	1d	Oral solution containing 25 mg equivalent of [14C]SYR- 322 (100 µCi) (8/8)
SYR-322/CPH-001 1-Japan	Single ascending dose, randomized, double blind, placebo controlled, parallel group comparison Safety, tolerability (PK/PD)	60 healthy males	1d	Alogliptin 6.25, 12.5, 25, 50, 100, and 200 mg (each 8/8) Placebo (12/12)
SYR-322/CPH-002 1-Japan	Multiple ascending dose, randomized, double blind,	30 healthy males	7d	Alogliptin 25, 50, and 100 mg (each 8/8)

	placebo controlled Safety, tolerability (PK/PD)			Placebo (6/6)
5.3.3.2 Patient pharmacokinetic and initial tolerability studies				
SYR-322-002 9-United States and Mexico	Randomized, double blind, placebo controlled, repeat dose Safety, efficacy (PK/PD)	56 T2Ds	14 d	Alogliptin 25 (15/15), 100 (14/14), and 400 (16/14) mg Placebo (11/11)
5.3.3.3 Intrinsic factor pharmacokinetic studies				
SYR-322-006 3-United States	Open label, parallel group, comparison, single dose Effect of renal impairment (PK)	48 subjects (24 healthy subjects, 6 with mild renal impairment, 6 with moderate renal impairment, 6 with severe renal impairment, and 6 with ESRD on hemodialysis)	1d	Alogliptin 50 mg (48/48)
SYR-322-022 2-United States	Single blind, placebo controlled, randomized, parallel group, single and multiple dose Effects of age, gender, and race (Safety, PK/PD)	64 healthy subjects	8d	Alogliptin 25 mg (48/48) Placebo (16/16)
SYR-322-023 1-United States	Open label, single dose Effect of hepatic impairment (PK)	16 subjects (8 healthy, 8 with moderate hepatic impairment)	1d	<u>Alogliptin 25 mg:</u> Hepatically impaired (8/8) Healthy (8/8)
5.3.3.4 Extrinsic factor pharmacokinetic studies				
SYR-322-005 1-United States	Randomized, open label, 2 phase, single dose (2 period crossover), and multiple dose (3 period crossover) Effects of food and drug-drug interactions: metformin and cimetidine (PK)	36 healthy subjects	2d for food effect phase with 4d washout; 6d for each treatment in DDI with 4d washouts	<u>Food effect phase:</u> Alogliptin 100 mg (36/36) <u>DDI phase:</u> Metformin arm (17/16): Alogliptin 100 mg QD, metformin 1000 mg BID, alogliptin 100 mg QD + metformin 1000 mg BID Cimetidine arm (18/18): Alogliptin 100 mg QD, cimetidine 400 mg QD, alogliptin 100 mg QD + cimetidine 400 mg QD

SYR-322-015 1-United States	Open label, multiple dose, single sequence Drug-drug interaction: caffeine, tolbutamide, dextromorphan, midazolam, and fexofenadine administered as a cocktail (PK)	18 healthy subjects	8d	Drug cocktail (caffeine 200 mg + tolbutamide 500 mg + dextromorphan 30 mg + midazolam 4 mg + fexofenadine 60 mg) (18/18) Alogliptin 100 mg (18/18) Alogliptin 100 mg + drug cocktail (18/18)
SYR-322-016 1-United States	Open label, multiple dose, nonrandomized, drug interaction Drug interaction: fluconazole, ketoconazole, and gemfibrozil (PK)	48 healthy subjects	8d (with 3d washout separating reference treatment and drug-interactions treatments)	Alogliptin 25 mg (48/48) <u>Fluconazole arm (16/16):</u> Fluconazole 200 mg Alogliptin 25 mg + fluconazole 200 mg <u>Ketoconazole arm (16/16):</u> Ketoconazole 400 mg Alogliptin 25 mg + ketoconazole 400 mg <u>Gemfibrozil arm (16/14):</u> Gemfibrozil 600 mg Alogliptin 25 mg + gemfibrozil 600 mg
SYR-322-017 1-United States	Randomized, multiple dose, open label, 6 sequence, 3 period crossover Drug interaction: pioglitazone (PK)	30 healthy subjects	36 d (with 9d washouts separating treatments)	Alogliptin 25 mg Pioglitazone 45 mg Alogliptin 25 mg + pioglitazone 45 mg (30/27)
AYR-322-018 1-United States	Open label, nonrandomized, single sequence, multiple dose, drug interaction Drug interaction: glyburide (PK)	24 healthy subjects	10d (with 1d washout after reference treatment)	Glyburide 5 mg Alogliptin 25 mg Alogliptin 25 mg + glyburide 5 mg (24/24)
SYR-322-020 1-United States	Open label, randomized, single dose, 2 sequence, 2 period crossover, drug interaction Drug interaction: cyclosporine (PK)	24 healthy males	2d (with 14d washout separating treatments)	Alogliptin 25 mg Alogliptin 25 mg + cyclosporine 600 mg (24/23)
SYR-322-021	Randomized, single blind,	36 healthy males	7d (with a 9d titration period)	Warfarin 1-10 mg titration

1-United States	placebo controlled, multiple dose Drug interaction: warfarin (PK: PT/INR)			(36/31) Warfarin + placebo (16/15) Alogliptin 25 mg + warfarin (15/15)
SYR-322-024 1-United States	Single blind, randomized, placebo controlled, multiple dose, 2 sequence, 2 period crossover Drug interaction: ethinyl estradiol and norethindrone (PK/PD)	28 healthy women who had taken ≥ 2 complete cycles of an oral contraceptive prior to randomization	42 d (with 7d washout between treatments)	Placebo + Ortho-Novum 1/35 Alogliptin 25 mg + Ortho-Novum 1/35 (28/24)
SYR-322-025 1-United States	Randomized, open label, multiple dose, 3 sequence, 3 period crossover Drug-drug interaction: atorvastatin (PK)	24 healthy subjects	21 d (with two 7d washout intervals)	Alogliptin 25 mg Atorvastatin 80 mg Alogliptin 25 mg + atorvastatin 80 mg (24/23)
SYR-322-029 1-United States	Multiple dose, open label, randomized, 3 sequence, 3 period crossover Drug interaction: digoxin (PK)	24 healthy subjects	30d (with two 12d washout intervals between treatments)	Alogliptin 25 mg Digoxin 200 mcg Alogliptin 25 mg + digoxin 200 mcg (24/22)
5.3.5.1 Study reports of controlled clinical studies pertinent to the claimed indication				
SYR-322-003 62-United States and Chile	Randomized, double blind, placebo controlled, comparison Efficacy (HbA1c)	265 T2Ds	12 weeks	Alogliptin 6.25 (44/34), 12.5 (44/37), 25 (45/40), 50 (44/35), and 100 mg (45/38) Placebo (43/39) (265/223)
SYR-322-SULF-007 125-16 countries	International, randomized, double blind, placebo controlled, 3 treatment arm Efficacy (HbA1c)	500 T2Ds receiving sulfonylurea (SFU) alone ≥ 3 months	26 weeks	Alogliptin 12.5 mg + SFU 2.5 mg (203/153) Alogliptin 25 mg + SFU 5 mg (198/148) Placebo + SFU 2.5 or 5 mg (99/62)
SYR-322-MET-008 115-15 countries	International, randomized, double blind, placebo controlled, 3 treatment arm design	527 T2Ds receiving metformin alone	26 weeks	Alogliptin 12.5 mg + metformin 500 mg (213/176) Alogliptin 25 mg + metformin 850 mg (210/165)

				Placebo + metformin 500 or 850 mg (104/72)
SYR-322-TZD-009 125-13 countries	International, randomized, double blind, placebo controlled, 3 treatment arm Efficacy (HbA1c)	493 T2Ds treated with pioglitazone alone or in combination with metformin or SFU	26 weeks	Pioglitazone + SFU or metformin with: Alogliptin 12.5 mg (197/153) Alogliptin 25 mg (199/160) Placebo (97/71)
SYR-322-PLC-010 117-16 countries	International, randomized, double blind, placebo controlled, 3 treatment arm Efficacy (HbA1c)	329 T2Ds	26 weeks	Alogliptin 12.5 mg (133/105) Alogliptin 25 mg (131/107) Placebo (65/40)
SYR-322-INS-011 110-13 countries	International, randomized, double blind, placebo controlled, 3 treatment arm in combination with insulin Efficacy (HbA1c)	390 subjects with T2Ds treated with insulin alone or in combination with metformin	26 weeks	Insulin with/without metformin with: Alogliptin 12.5 mg (131/83) Alogliptin 25 mg (129/77) Placebo (130/55)
01-06-TL-322OPI-002 268-23 countries	Randomized, double blind, placebo controlled, parallel group, factorial Efficacy (HbA1c)	655 T2Ds	26 weeks	Alogliptin (ALO) 25 mg + Placebo (PBO) (164/126) Pioglitazone (PIO) 30 mg + Placebo (163/126) ALO 12.5 mg + PIO 30 mg (164/126) ALO 25 mg + PIO 30 mg (164/136) Total (655/514)
01-05-TL-322OPI-001 327-20 countries	Randomized, double blind, placebo controlled, parallel group factorial Efficacy (HbA1c)	1554 T2Ds on metformin \geq 1500 mg (or maximum tolerated dose)	26 weeks	PBO + PBO (129/70) PBO + ALO 12.5 mg (128/97) PBO + ALO 25 mg (129/101) PIO 15 mg + PBO (130/93) PIO 15 mg + ALO 12.5 mg (130/115) PIO 15 mg + ALO 25 mg (130/110) PIO 30 mg + PBO (129/94) PIO 30 mg + ALO 12.5 (130/116) PIO 30 mg + ALO 25 mg

				(130/113) PIO 45 mg + PBO (129/97) PIO 45 mg + ALO 12.5 mg (130/112) PIO 45 mg + ALO 25 mg (130/114) Total (1554/1232)
5.3.5.2 Study reports of uncontrolled clinical studies				
SYR-322-OLE-012 246-22 countries	International, long term, open label, extension of 7 controlled phase 3 studies Safety (AEs, laboratories, ECGs, vital signs, temperature, physical examinations, and hypoglycemic events)	1749 T2Ds previously enrolled in SULF-007, MET-008, TZD-009, PLC-010, INS-011, 322OPI-001, or 322OPI-002	2y	Alogliptin 12.5 mg (680/pending) Alogliptin 25 mg (1069/pending)
5.3.5.4 Other clinical studies				
SYR-322-004 1-United States	Evaluator blinded, active and placebo controlled, multiple dose, 4 period crossover Safety (QTc)	48 healthy subjects	28d	Alogliptin 100 mg Alogliptin 400 mg Moxifloxacin 400 mg Placebo (48/45)
SYR-322-019 1-United States	Single blind, randomized, 4 arm, parallel group, placebo and positive controlled Safety (QTc)	257 healthy subjects	7d	Alogliptin 50 mg (64/63) Alogliptin 400 mg (64/64) Moxifloxacin 400 mg (65/60) Placebo (64/63)

5.2 Review Strategy

This reviewer focused her review on the controlled clinical studies pertinent to the claimed indication that were originally submitted to the NDA, including SYR-322 studies 003, SULF-007, MED-008, TZD-009, PLC-010, and INS-011. During the review process, concern arose about the cardiovascular safety of alogliptin. Thus, the sponsor also submitted to this NDA controlled studies 01-06-TL-322OPI-002 (OPI-002) and 01-05-TL-322OPI-001 (OPI-001), which were originally intended for the alogliptin + pioglitazone (A+P) fixed dose combination (FDC) NDA 22-426. Studies OPI-002 and OPI-001's AEs were also reviewed. The deaths, serious AEs, and marked abnormalities in serum chemistry values that occurred in uncontrolled, long term extension study OLE-012 were reviewed, as well.

Clinical study reports were first reviewed, including the selected case report forms and datasets. The author then reviewed the Integrated Summary of Efficacy, Integrated Summary of Safety, 120-day Safety Update (April 24, 2008), as well as other responses to clinical information requests.

5.3 Discussion of Individual Studies

The sponsor conducted one 12-week, dose finding phase 2 study (SYR-322-003) and five 26-week phase 3 studies (SULF-007, MET-008, TZD-009, PLC-010, and INS-011) to evaluate the safety and efficacy of alogliptin. All of these studies were double blind, randomized, and placebo controlled. The 12-week trial compared several doses of alogliptin versus placebo in patients who were treatment naïve or receiving a SFU, metformin, or a combination of a SFU and metformin. The 26 week trials tested alogliptin versus placebo as monotherapy and as add-on to SULF, metformin, pioglitazone, or insulin.

Due to early concerns about cardiovascular safety, the sponsor also submitted 2 studies of alogliptin + pioglitazone, which were originally intended for the fixed dose combination NDA 22-426. Study 01-05-TL-322OPI-001 and 01-06-TL-322OPI-002 were 26-week, randomized, double blind, placebo controlled studies in diabetics with and without metformin, respectively. The decision was made not to classify these 2 studies as a major amendment but to review their AEs as part of this NDA.

Uncontrolled, open label extension study OLE-012 was also conducted in subjects previously enrolled in studies SULF-007, MET-008, TZD-009, PLC-010, INS-011, 322OPI-001, and 322OPI-002.

The section below provides a detailed description of the study designs.

NOTE: Please refer to section 6 Review of Efficacy for a discussion of the individual studies' findings and conclusions and patient disposition and demographic information.

1) SYR-322-003: A multicenter, randomized, double blind, placebo controlled comparison study to determine the efficacy and safety of SYR110322 in patients with T2D, who are either receiving no current treatment or currently treated with diet and exercise, a SFU, metformin, or a combination of a SFU and metformin

Study phase and dates conducted: Phase 2 study completed March 21, 2005-October 3, 2005

Objectives:

Primary: To determine the benefit of SYR-322 on HbA1c after 12 weeks of treatment

Secondary:

- To evaluate the efficacy of SYR-322 on fasting plasma glucose (FPG), fasting fructosamine, and lipid profile after 12 weeks of treatment
- To evaluate the effect on HbA1c after 6 weeks of treatment
- To evaluate treatment effect on daily glycemic instability in a subset of subjects as measured by a continuous glucose monitoring system (CGMS; Medtronic MiniMed CGMS System Gold) for 72 h at baseline and after 6 and 12 weeks of treatment

Safety: To determine the safety of SYR-322 by evaluating adverse events (AEs), laboratory results, ECGs, physical examinations, vital signs, and hypoglycemic events

Pharmacokinetic (PK)/Pharmacodynamic (PD): To determine plasma levels and DPP4 percent inhibition after 12 weeks of treatment and at 1- and 2-week follow up visits

Study design: This was an international, multicenter, randomized, double blind, placebo controlled, parallel group study using 5 dose levels of SYR-322 in 265 subjects with T2D. Subjects were assigned (1:1:1:1:1) to SYR-322 at 6.25, 12.5, 25, 50, or 100 mg or placebo. The population was stratified by baseline HbA1c (< or ≥ 8%), antidiabetic treatment (yes or no), and antidiabetic treatment class (3 levels: SFU, metformin, or a combination of SFU and metformin). Subjects using SFU, metformin, or a combination were screened from day -14 to -1 and underwent a 14 day washout prior to randomization. Subjects not on antidiabetic medication were screened from day -7 to -1. All subjects received glucose monitoring and dietary education. Subjects took the assigned medication daily for 12 weeks followed by a 14 day follow up; study visits were on days 1, 8, 15, 22, 29, 43, 57, 71, 85, 92, and 99. A subset of sites required study visits on days -3, 40, and 82 for the application of CGMS, which was worn for 72 hours at a time. Subjects who met hyperglycemic rescue criteria (random blood glucose ≥ 270 mg/dl on 3 consecutive days between days 8–28, or fasting blood glucose ≥ 250 mg/dl on 2 consecutive days within a 7 day period between days 29–85) were classified as having reached a study endpoint, at which time the study drug was stopped and day 85 assessments completed. Day 92 and 95 follow up assessments were then completed 7-14 days later.

SYR-322 plasma concentrations and assessment of DPP4 percent inhibition were obtained in a subset of subjects at US sites on days 85, 92, and 99; DPP4 inhibition was also measured on day 1.

COMMENT: The study design, which included a 14 day washout prior to randomization and included subjects on a stable dose of nonexcluded medication for at least 4 weeks, was not ideal as the recent changes are not accurately reflected in the baseline HbA1c.

Main inclusion criteria:

- Age 18-75 years
- Signed informed consent form
- Diagnosed with T2D (ADA criteria) and either receiving no treatment (i.e. newly diagnosed or inadequately controlled with diet and exercise for 3 months) or inadequately controlled with a SFU, metformin, or a combination of both
- Niacin, weight loss drugs, investigational antidiabetic drugs, and nonincidental glucocorticoids were not allowed from 3 months prior to screening until study end, although topical and nasal steroids were allowed
- Body mass index (BMI) ≥ 23 kg/m² and ≤ 40 kg/m²

- Fasting c-peptide ≥ 0.8 ng/ml
- HbA1c 6.8-11.0% on a stable dose of nonexcluded medications for at least 4 weeks
- Diastolic blood pressure (BP) ≤ 110 mmHg and systolic BP ≤ 180 mmHg
- Neither pregnant or lactating
- Using adequate contraception if a woman is of childbearing potential (i.e. not surgically sterile and/or not postmenopausal) for at least 3 months prior and throughout the study
- Able and willing to monitor blood glucose concentrations with a home glucose monitor
- No major illness or debility that would prohibit study completion
- Hemoglobin ≥ 12 g/dl for males and ≥ 10 g/dl for women
- Hepatic transaminase levels $\leq 2x$ the upper limit of normal (ULN)

Exclusion criteria:

- History of cancer, other than squamous or basal cell carcinoma of the skin, that had not been in remission for ≥ 1 year
- History of proteinuria > 100 mg/d on a 12 or 24 hour urine collection or urine albumin/creatinine ratio > 1000 mcg/mg at screening. If elevated, the subject was to be rescreened within 1 week
- Serum creatinine ≥ 2 mg/dl
- History of proliferative diabetic retinopathy or laser treated retinopathy
- History of peripheral or autonomic neuropathy
- History of systolic dysfunction congestive heart failure
- History of myocardial infarction (MI) within 1 year prior to screening
- History of ulcerative colitis or Crohn's disease
- History of hepatitis B, hepatitis C, or human immunodeficiency virus
- History of a psychiatric disorder that would affect the subject's ability to participate
- History of anaphylactic reaction(s) to any drug
- History of angioedema
- History of alcohol or substance abuse within the last 2 years
- History of any surgery which could affect the absorption of study drug
- Receipt of any investigational drug within the preceding 30 days or a history of receipt of any investigational antidiabetic drug within the preceding 90 days

Treatments and management: SYR-322 (6.25, 12.5, 25, 50, or 100 mg) or placebo daily oral doses. Subjects were instructed to take the study drug 30 minutes prior to the first meal of the day with 8 ounces (240 ml) water.

The use of over the counter medications and herbals was discouraged from 7 days prior to the first dose through study completion. Niacin, weight loss drug, investigational antidiabetics, or regular treatment with glucocorticoids was not allowed from 3 months prior to screening through study completion. Topical and nasal steroids were acceptable.

Subjects met with a diabetes educator at screening and received instruction on the signs and symptoms of hypoglycemia as well as treatment with glucose, if necessary. Subjects were to use the provided glucometer to test blood glucose any time they experienced signs and symptoms of hypoglycemia and to record the glucose value along with the signs and symptoms.

Study sites including enrollment: There were 62 study sites in the United States and Chile. No study site enrolled large numbers of subjects in any one of the studies.

Efficacy (exposure/response) assessments:

Primary: Change in HbA1c from baseline (day 1) to 85

Secondary:

- Change from baseline in average daily blood glucose on days 43 and 85 in the subset of subjects wearing CGMS

- Change from baseline in HbA1c on day 43
- Change from baseline in FPG on days 43 and 85
- Change from baseline in fasting fructosamine on days 43 and 85
- Change from screening in lipid panel on days 43 and 85
- The incidence of hyperglycemia (proportion of self monitored blood glucose measurements ≥ 200 mg/dl)

Safety assessments: Adverse events, clinical laboratory test results, ECG results, physical examination findings, oral temperature, seated vital signs, and hypoglycemic events

All hypoglycemic events were recorded in the CRF. Symptomatic events were transcribed from diary data and glucometer readings were reviewed for additional readings < 70 mg/dl, which were also recorded in the CRF.

Hypoglycemic events were classified as follows:

- Mild to moderate: any glucose values < 70 mg/dl with or without symptoms, OR the subject's typical hypoglycemic symptoms without a glucose measurement
- Severe: any episode requiring assistance from another person to resolve or involved coma or seizure

2) SYR-322-SULF-007: A multicenter, randomized, double blind, placebo controlled study to determine the efficacy and safety of SYR110322 (SYR-322) when used in combination with a SFU in subjects with T2D

Study phase and dates conducted: Phase 3 study completed April 4, 2006-June 20, 2007.

Objectives:

Primary: To determine the efficacy of alogliptin administered with a SFU as compared to SFU alone on HbA1c change from baseline

Secondary:

- To evaluate other measures of glycemic control after treatment with alogliptin with SFU as compared to SFU alone, including FPG, incidence of FPG ≥ 200 mg/dl, and incidence of glycemic rescue
- To evaluate the changes in biomarkers of pancreatic function after treatment with alogliptin and a SFU as compared to a SFU alone, determined by changes in fasting proinsulin, insulin, and C-peptide
- To evaluate changes in body weight following treatment with alogliptin with SFU as compared to a SFU alone
- To evaluate the safety of alogliptin in combination with SFU as compared to SFU alone by evaluating adverse events (AEs), clinical laboratory parameters, ECGs, physical examinations, and hypoglycemic events
- To evaluate plasma concentrations of alogliptin using a sparse sampling approach
- To evaluate clinically meaningful levels of response in HbA1c after treatment with alogliptin in combination with a SFU as compared with a SFU alone

Study design: This was a phase 3, international, multicenter, randomized, double blind, placebo controlled, 3 treatment arm study which evaluated the efficacy and safety of 2 doses of alogliptin in combination with a SFU versus placebo in combination with a SFU. The study included a screening period of up to 2 weeks, a 4 week run in/stabilization period, a 26 week treatment period with an end of treatment visit, and a 2 week follow up period. Eligible subjects were then allowed to enter open label extension study OLE-012.

During the run in/stabilization period, eligible subjects were switched (open label) from their own SFU to an equivalent dose of glyburide and were given placebo study drug (single blind). The minimum glyburide dose permitted was 10 mg, unless there was documentation at screening that the subject could not tolerate this dose. Subjects who were $< 75\%$ compliant with the single blind placebo regimen during the run in/stabilization period were not randomized. Subjects were randomized as follows: placebo with glyburide (n=100), 12.5 mg alogliptin with glyburide (n=200), or alogliptin 25 mg with glyburide (n=200). Subjects were stratified by HbA1c at week -1 ($<$ or $\geq 8\%$) and geographic region.

SYR-322-SULF-007. Study design (Reproduced from the sponsor)

Screening Period Week -6 through -5 Prior to randomization		Run-in/Stabilization Weeks -4 through -1 Prior to randomization				Treatment Period Weeks 1 through 26 after randomization										End-of- treatment	Follow- up Period
Week																	
Screening Visit		-4	-3	-2	-1	Baseline Visit (Day 1)	1	2	4	8	12	16	20	26		28	

SYR-322-SULF-007. Study schedule (Reproduced from the sponsor)

	Screening Period Weeks -6 through -5 prior to randomization	Run-in/ Stabilization Weeks -4 through -1 prior to randomization				Treatment Period Weeks 1 through 26 after randomization										End-of- Treatment (or ET)	Follow -up Period
	Week (a)																
	Screening Visit (a)	-4	-3	-2	-1	Baseline Visit (Day 1)	1	2	4	8	12	16	20	26	28		
Informed consent	X																
Inclusion/ exclusion	X																
Demographics and medical history	X																
Overnight fast	X				X	X	X	X	X	X	X	X	X	X			
Diabetes education (b)	X	X	X	X	X	X	X	X									
Randomization						X											
Complete physical examination	X													X			
Brief physical examination						X					X						
Clinical examination of skin and digits	X					X	X	X	X	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Oral temperature	X													X			
Body weight	X					X				X	X		X	X			
Height and BMI	X																
12-lead ECG	X					X					X			X			
Issue subject diary		X	X	X	X	X	X	X	X	X	X	X	X				
Review diaries and glucometer readings			X	X	X	X	X	X	X	X	X	X	X	X			
Review concomitant medications and AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood sample for alogliptin plasma level									X(c)	X(c)							
Laboratory tests																	
Hematology, serum chemistry (d)	X				X(e)	X	X(e)	X (f)	X	X	X	X	X	X			
Urinalysis (g)	X (g)					X					X			X (g)			
Proinsulin						X			X	X	X	X	X	X			

	Screening Period Weeks -6 through -5 prior to randomization	Run-in/ Stabilization Weeks -4 through -1 prior to Randomization				Treatment Period Weeks 1 through 26 after randomization										End-of- Treatment (or ET)	Follow -up Period
Week (a)																	
Assessment	Screening Visit (a)	-4	-3	-2	-1	Baseline Visit (Day 1)	1	2	4	8	12	16	20	26	28		
Insulin						X			X	X	X	X	X	X			
C-peptide	X					X			X	X	X	X	X	X			
HbA1c	X				X(h)	X			X	X	X	X	X	X			
CRP						X					X			X			
TSH	X																
Serum pregnancy test (i)	X													X			
Urine pregnancy test (i)						X					X						
Dispense single-blind placebo study drug		X	X	X	X												
Dispense glyburide		X (j)	X (j)	X (j)	X (j)	X (j)	X (j)	X (j)	X (j)	X (j)	X (j)	X (j)	X (j)				
Dispense blinded study drug						X	X	X	X	X	X	X	X				
Document drug accountability			X	X	X	X	X	X	X	X	X	X	X	X			

BMI=body mass index; CRP=C-reactive protein; ET=early termination; TSH=thyroid-stimulating hormone.

(a) The Screening visit was scheduled within the 2 weeks prior to the start of the Run-in/Stabilization Period. During the Run-in/Stabilization period, subjects were to visit the study center weekly at the start of Weeks -4, -3, -2, and -1 prior to randomization. Subjects were randomized on Day 1 (Baseline) of the 26-week treatment period. After randomization, visits were scheduled the day following 1, 2, 4, 8, 12, 16, 20, and 26 weeks of treatment, respectively, and at 2 weeks after the end-of-treatment (or early termination) visit.

(b) Subjects were instructed on proper nutrition and exercise (at all visits), how to recognize signs and symptoms of hypoglycemia (at all visits after Screening), and the use of the glucometer (at all visits after Screening).

(c) Two blood samples were obtained during the treatment period for assessment of alogliptin plasma concentrations (1 trough and 1 nontrough level). The trough sample was obtained at the Week 4 visit, approximately 24 hours (22 to 28 hours) after taking the study drug and prior to taking the next dose. The nontrough sample was scheduled for the Week 8 visit. The exact timing of this pharmacokinetic sample could have varied based on subject preferences for scheduling. It was permissible to obtain this sample on another day within the randomized treatment period, provided that the subject had received blinded treatment for at least 4 weeks.

(d) The samples were obtained under fasting conditions. In addition to the glucose samples as part of serum chemistry, a fasting blood sample for plasma glucose was obtained at Week -1 and Week 1.

(e) Plasma glucose only at Week -1 and Week 1. Fasting plasma glucose must have been <275 mg/dL (<15.27 mmol/L) at the Week -1 visit. If this criterion was not met at Week -1, the assessment could have been repeated on a weekly basis, for a maximum of 4 additional weeks.

(f) No lipid panel was obtained at the Week 2 visit.

(g) In addition to urinalysis, an albumin/creatinine ratio was determined at Screening and at the end-of-treatment (or early termination) visit.

(h) HbA1c concentration was to be between 7.0% and 10.0%, inclusive at Week -1 to qualify for randomization. If this criterion was not met at Week -1, the assessment could have been repeated on a weekly basis, for a maximum of 4 additional weeks.

(i) Women of childbearing potential only.

(j) Glyburide was dispensed at the start of the Run-in/Stabilization period. Additional glyburide was dispensed as needed at subsequent visits.

SYR-322-SULF-007. Clinical laboratory tests (Reproduced from the sponsor)

Hematology	Serum Chemistry	Urinalysis
White blood cell count with autodifferential	Albumin	<u>Qualitative:</u>
Platelet count	Alkaline phosphatase	Appearance
Hemoglobin	ALT	Color
Hematocrit	Aspartate aminotransferase	pH
Red blood cell count	Blood urea nitrogen	Specific gravity
Mean corpuscular volume	Carbon dioxide	Ketones
Mean corpuscular hemoglobin	Calcium	Protein
Mean corpuscular hemoglobin concentration	Magnesium	Glucose
	Chloride	Nitrite
	Creatinine	Urobilinogen
	Glucose	Blood
	Lactate dehydrogenase	
	Phosphorus	<u>Quantitative:</u>
Other	Potassium	Albumin/creatinine ratio
C-reactive protein	Sodium	
C-peptide	Total bilirubin	
HbA1c	Total protein	
Proinsulin	Uric acid	
Insulin	γ -Glutamyl transferase	
	Lipid panel (total cholesterol, high-density lipoproteins, low-density lipoproteins, and triglycerides)	
Diagnostic Screening:		
Serum	Urine	
Thyroid-stimulating hormone	hCG (for pregnancy)	
hCG (for pregnancy) (women of childbearing potential)	(women of childbearing potential)	
hCG=human chorionic gonadotropin.		

Main inclusion criteria which differed from study SYR-322-003:

- Age 18-80 years (as opposed to 18-75 years)
- Receiving current treatment with a SFU alone for at least 3 months prior to screening with inadequate glycemic control. Dose must be equivalent to at least 10 mg glyburide, except if documented maximum tolerated dose was equivalent to < 10 mg but ≥ 5 mg, for at least 8 weeks prior to randomization.
- Body mass index (BMI) ≥ 23 kg/m² and ≤ 45 kg/m² (as opposed to < 40 kg/m²)
- HbA1c between 7.0-10.0% at screening (as opposed to 6.8-11.0%)
- ALT ≤ 3 x ULN (as opposed to ≤ 2 x ULN)
- TSH \leq ULN and the subject clinically euthyroid

Additional inclusion criteria prior to randomization:

- HbA1c between 7-10% at week -1 visit (Assessment may have been repeated weekly for a maximum of 4 additional weeks.)
- FPG < 275 mg/dl at week -1 (Assessment may have been repeated weekly for a maximum of 4 additional weeks.)
- Compliance $\geq 75\%$ with single blind placebo regimen during run in/stabilization
- No use of oral or systemically injected glucocorticoids or use of weight loss drugs within 3 months prior to randomization (Inhaled corticosteroids were allowed.)

Exclusion criteria which differed from study SYR-322-003:

- History of cancer, other than squamous or basal cell carcinoma of the skin that had not been in full remission for at least 5 years prior to screening. A history of treated cervical intraepithelial neoplasia I (CIN 1) or II was allowed (as opposed to history of cancer, other than squamous or basal cell carcinoma of the skin, that had not been in remission for ≥ 1 year)
- History of proliferative diabetic retinopathy or laser treated retinopathy within 6 months prior to screening (as opposed to a history of proliferative diabetic retinopathy or laser treated retinopathy)
- History of treated diabetic gastroparesis
- History of New York Heart Association Class III or IV heart failure regardless of therapy (as opposed to a history of systolic dysfunction congestive heart failure)

- History of coronary angioplasty, coronary stent placement, coronary bypass surgery, or myocardial infarction within 6 months prior to screening (as opposed to a history of myocardial infarction (MI) within 1 year prior to screening)
- History of hemoglobinopathy that could affect HbA1c
- History of angioedema in association with ACE inhibitors or angiotensin-II receptor blockers (ARBs) (as opposed to a history of angioedema)

NOTE: Subjects with a history of any surgery which could affect the absorption of study drug were not excluded.

Treatments and management: Subjects were randomized (1:2:2) to placebo, 12.5 mg alogliptin, or 25 mg alogliptin with glyburide 10 mg daily (or maximum tolerated glyburide dose). Subjects were to take their study drug prior to the first meal of the day with 8 ounces of water.

Like in study SYR-322-003, subjects received dietary, exercise, and hypoglycemia education. If randomized subjects met any of the following criteria relating to efficacy, there were removed from the study and completed an early termination visit. If subject had been kept in the trial despite starting rescue therapy, more complete controlled data would have been obtained.

- Weeks 1-4: a single fasting glucose ≥ 275 mg/dl as determined by the central laboratory and confirmed by a second sample drawn within 5 days after the first sample and analyzed by the central laboratory
- Weeks 4-8: a single fasting glucose ≥ 250 mg/dl as determined by the central laboratory and confirmed by a second sample drawn within 5 days after the first sample and analyzed by the central laboratory
- Weeks 8-12: a single fasting glucose ≥ 225 mg/dl as determined by the central laboratory and confirmed by a second sample drawn within 5 days after the first sample and analyzed by the central laboratory
- Week 12 to end of treatment: HbA1c $\geq 8.5\%$ and $\leq 0.5\%$ reduction in HbA1c as compared with the baseline HbA1c, confirmed by a second sample drawn within 5 days after the first and analyzed by the central laboratory

Subjects who met the criteria for rescue were considered to have completed the study and were eligible to enter open label extension study OLE-012. For these subjects, the end of treatment (week 26) assessments served as screening assessments for the open label extension study. Laboratory values collected at early termination were carried forward to week 26. Rescued subjects who did not continue into study OLE-012 also underwent week 28 follow up procedures. Also for any subject who received at least 1 dose of study drug and discontinued without requiring rescue, effort was made to complete the week 26 and 28 visit assessments.

After randomization, if a subject experienced hypoglycemia, the glyburide dose could be reduced by 2.5 mg/week (or 5 mg/wk in countries where 2.5 mg tablets were unavailable) until recurrent hypoglycemia was resolved.

Reasons for removal from the study included but were not limited to a significant AE, major protocol deviation, loss to follow up, voluntary withdrawal, study termination, pregnancy, lack of efficacy, and at the discretion of the principal investigator.

Study sites including enrollment: There were 125 study sites in the United States, Argentina, Brazil, Chile, Dominican Republic, Guatemala, Mexico, Peru, Australia, New Zealand, United Kingdom, India, Poland, and South Africa. No study site enrolled large numbers of subjects in any one of the studies. Most investigators randomized less than 10 subjects per protocol.

Efficacy (exposure/response) assessments:

Primary: Change in HbA1c from baseline (day 1) to week 26. The primary analysis was performed for the full analysis set using analysis of covariance (ANCOVA). The primary model included study treatment and geographic region as class variables and diabetes duration and baseline HbA1c as continuous variables. For the primary analysis, the 25 mg dose was compared with placebo at the 2-sided 0.05 significance level using a contrast derived from the primary model. If this test was statistically significant, the 12.5 mg dose was evaluated in a similar

fashion. Using this step down strategy, no significance level adjustment was necessary for the multiple comparisons. Please refer to the Dr. Janice Derr's statistical review for full details.

Secondary:

- Glycemic control variables
 - Change from baseline in HbA1c at weeks 4, 8, 12, 16, and 20
 - Change from baseline in FPG at weeks 1, 2, 4, 8, 12, 16, 20, and 26
 - Incidence of marked hyperglycemia (FPG \geq 200 mg/dl)
 - Incidence of rescue
- Biomarkers of pancreatic function variables
 - Change from baseline in fasting proinsulin at weeks 4, 8, 12, 16, 20, and 26
 - Change from baseline in insulin at weeks 4, 8, 12, 16, 20, and 26
 - Change from baseline in proinsulin/insulin ratio at weeks 4, 8, 12, 16, 20, and 26
 - Change from baseline in C-peptide at weeks 4, 8, 12, 16, 20, and 26
- Clinical response variables
 - Incidence of week 26 HbA1c \leq 6.5, 7.0, and 7.5%
 - Incidence of week 26 HbA1c decrease from baseline \geq 0.5, 1.0, 1.5, and 2.0%
- Change from baseline in body weight at weeks 8, 12, 20, and 26

Safety assessments: Adverse events, clinical laboratory test results, ECG results, physical examination findings (including examination of the skin and digits), oral temperature, seated vital signs, and hypoglycemic events (mild to moderate: blood glucose $<$ 60 mg/dl with symptoms or blood glucose $<$ 50 mg/dl regardless of symptoms; severe: any episode requiring assistance of another person associated with blood glucose $<$ 60 mg/dl unless the clinical situation prohibited the measurement of blood glucose).

3) SYR-322-MET-008: A multicenter, randomized, double blind, placebo controlled study to determine the efficacy and safety of SYR110311 (SYR-322) when used in combination with metformin in subjects with T2D

Study phase and dates conducted: Phase 3 study completed March 10, 2006-June 12, 2007.

Objectives: The objectives were similar to those of study SULF-007, except that they compared treatment with alogliptin in combination with metformin as compared with metformin alone.

Study design: The design of study MET-008 was similar to that of SULF-007, except that it evaluated the efficacy and safety of 2 doses of alogliptin in combination with metformin versus metformin alone. During the run in/stabilization period, subjects received a minimum of 1500 mg/day metformin. If there was documentation at screening to indicate that the subject did not tolerate this dose, the subject could participate at their maximum tolerated dose (MTD).

Main inclusion criteria which differed from study SULF-007:

- Receiving current treatment with metformin alone with inadequate glycemic control. The subject had to have received metformin monotherapy for at least 3 months prior to screening with a stable dose of \geq 1500 mg for at least 8 weeks prior to randomization. Subjects with an MTD $<$ 1500 mg could have been enrolled if this dose was stable for 8 weeks prior to randomization.
- Serum creatinine $<$ 1.5 mg/dl for men and $<$ 1.4 mg/dl for women

Exclusion criteria: The exclusion criteria were similar to study SULF-007.

Treatments and management which differed from SULF-007: Subjects were randomized (1:2:2) to placebo, 12.5 mg alogliptin, or 25 mg alogliptin as add-on to immediate release metformin (dose \geq 1500 mg/day, unless the MTD was less). Once established, the metformin dose was not changed for the remainder of the study.

Reasons for removal from the study included but were not limited to a significant AE, major protocol deviation, loss to follow up, voluntary withdrawal, study termination, pregnancy, lack of efficacy, and at the discretion of the principal investigator.

Study sites including enrollment: There were 115 sites in 15 countries (United States, Brazil, Germany, New Zealand, the United Kingdom, South Africa, Argentina, Australia, India, Chile, Netherlands, Hungary, Guatemala, Spain, and Mexico). No study site enrolled large numbers of subjects in any one of the studies. Most investigators randomized less than 10 subjects per protocol.

Efficacy (exposure/response) and safety assessments: These assessments were similar to those in study SULF-007.

4) SYR-322-TZD-009: A multicenter, randomized, double blind, placebo controlled study to determine the efficacy and safety of SYR110322 (SYR-322) when used in combination with pioglitazone in subjects with T2D

Study phase and dates conducted: Phase 3 study completed February 24, 2006-August 2, 2007

Objectives: The objectives were similar to those of study SULF-007, except that they compared treatment with alogliptin in combination with pioglitazone as compared with pioglitazone alone.

Study design: The design of study TZD-009 was similar to that of SULF-007, except that it evaluated the efficacy and safety of 2 doses of alogliptin in combination with pioglitazone versus pioglitazone alone. During the run in/stabilization period, subjects treated with pioglitazone continued this medication at the same daily dose, but it was provided by the study center. Subjects treated with rosiglitazone were switched to a comparable dose of pioglitazone, provided by the study center.

Main inclusion criteria which differed from study SULF-007:

- Subjects were treated with a thiazolidinedione (TZD) either alone or in combination with metformin or a SFU but who were experiencing inadequate glycemic control. Subjects received TZD (rosiglitazone or pioglitazone) either alone or in combination with metformin or SFU for at least 3 months prior to screening and must have been on a stable dose for all their antidiabetic treatments for at least the month prior to screening.
- No treatment with antidiabetic agents other than a TZD alone or in combination with either metformin or a SFU within 3 months prior to screening. (Exception: if a subject had received other antidiabetic therapy for less than 7 days within the 3 months prior to screening.)
- ALT \leq 2.5x ULN

Exclusion criteria: The exclusion criteria were similar to study SULF-007.

Treatments and management which differed from study SULF-007: Subjects were randomized (1:2:2) to the following groups:

- Placebo (with pioglitazone with or without metformin or a SULF)
- 12.5 mg alogliptin (with pioglitazone with or without metformin or a SULF)
- 25 mg alogliptin (with pioglitazone with or without metformin or a SULF)

Subjects were stratified with regard to HbA1c at week -1, geographic region, and baseline treatment regimen (pioglitazone, pioglitazone + metformin, or pioglitazone + SULF). Rescue criteria were similar to that of study SULF-007. As in study SULF-007, subjects who met the criteria for rescue were considered to have completed the study and were eligible to enter uncontrolled, open label extension study OLE-012.

Study sites including enrollment: There were 117 study sites in 16 countries (United States, Argentina, Brazil, Guatemala, Peru, Australia, Germany, Netherlands, New Zealand, Spain, Hungary, India, and South Africa).

Efficacy (exposure/response) and safety assessments: These assessments were similar to those in study SULF-007.

5) SYR-322-PLC-010: A multicenter, randomized, double blind, placebo controlled study to determine the efficacy and safety of SYR110322 (SYR-322) compared with placebo in subjects with T2D

Study phase and dates conducted: Phase 3 study completed February 24, 2006-July 5, 2007.

Objectives: The objectives were similar to those of study SULF-007, except that they compared treatment with alogliptin to placebo in treatment-naïve patients.

Study design: The design of study PLC-010 was similar to that of SULF-007, except that it evaluated the efficacy and safety of 2 doses of alogliptin versus placebo.

Main inclusion criteria which differed from study SULF-007:

- Subjects had inadequate glycemic control and were receiving no antidiabetic therapy. Subject had failed treatment with diet and exercise for at least 1 month prior to screening. Subjects had received < 7 days of antidiabetic therapy within 3 months prior to screening.

Exclusion criteria: There criteria were similar to study SULF-007.

Treatments and management which differed from study SULF-007: Subjects were randomized (1:2:2) to placebo, 12.5 mg alogliptin, or 25 mg alogliptin.

Rescue criteria were similar to that of study SULF-007. As in study SULF-007, subjects who met the criteria for rescue were considered to have completed the study and were eligible to enter open label, uncontrolled, extension study OLE-012.

Study sites including enrollment: There were 117 sites in 16 countries (United States, Argentina, Brazil, Chile, Dominican Republic, Guatemala, Mexico, Peru, Australia, Netherlands, New Zealand, United Kingdom, Hungary, India, Poland, and South Africa).

Efficacy (exposure/response) and safety assessments: These assessments were similar to those in study SULF-007.

6) SYR-322-INS-011: A multicenter, randomized, double blind, placebo controlled study to determine the efficacy and safety of SYR110322 (SYR-322) when used in combination with insulin in subjects with T2D

Study phase and dates conducted: Phase 3 study completed February 24, 2006-May 17, 2007

Objectives: The objectives were similar to those of study SULF-007, except that they compared treatment with alogliptin and insulin as compared to insulin alone.

Study design: The design of study PLC-010 was similar to that of SULF-007, except that it evaluated the efficacy and safety of 2 doses of alogliptin and insulin as compared to insulin alone (with or without metformin).

Main inclusion criteria which differed from study SULF-007:

- Subjects were inadequately controlled with insulin alone (with or without metformin, which must have been stable for at least 8 weeks prior to randomization).
- Insulin (short and long-acting) dose must have been ≥ 15 units and ≤ 100 units per day for at least 8 weeks prior to randomization. A daily dose of insulin that varied by up to 15% of the mean was considered stable.

Additional inclusion criteria prior to randomization:

- HbA1c \geq 8% at week -1 visit (Assessment may have been repeated weekly for a maximum of 4 additional weeks.)
- FPG < 300 mg/dl at week -1 (Assessment may have been repeated weekly for a maximum of 4 additional weeks.)

Exclusion criteria: The exclusion criteria did not differ from study SULF-007.

Treatments and management: At the conclusion of the run in/stabilization period, subjects were randomly assigned (1:1:1) to 1 of 3 groups as follows: alogliptin 12.5 add-on to insulin (with or without metformin), 25 mg alogliptin add-on to insulin (with or without metformin), or placebo add-on to insulin (with or without metformin).

During the run in/stabilization (weeks -4 to -1) and treatment period (weeks 1 - 26), subjects continued their established daily insulin dose as well as the same daily metformin dose, if applicable. Alterations were permitted only in subjects who needed insulin dose reduction due to hypoglycemia. The metformin dose, if applicable, remained unchanged throughout the study.

If randomized subjects met any of the following criteria relating to efficacy, there were removed from the study and completed an early termination visit:

- Weeks 1-4: a single fasting glucose \geq 300 mg/dl as determined by the central laboratory and confirmed by a second sample drawn within 5 days after the first sample and analyzed by the central laboratory
- Weeks 4-8: a single fasting glucose \geq 275 mg/dl as determined by the central laboratory and confirmed by a second sample drawn within 5 days after the first sample and analyzed by the central laboratory
- Weeks 8-12: a single fasting glucose \geq 250 mg/dl as determined by the central laboratory and confirmed by a second sample drawn within 5 days after the first sample and analyzed by the central laboratory
- Week 12 to end of treatment: HbA1c \geq 8.7% and \leq 0.5% reduction in HbA1c as compared with the baseline HbA1c, confirmed by a second sample drawn within 5 days after the first and analyzed by the central laboratory

As in study SULF-007, subjects who met the criteria for rescue were considered to have completed the study and were eligible to enter open label, uncontrolled extension study OLE-012.

Study sites including enrollment: The study was conducted at 110 sites in 13 countries (United States, Brazil, Chile, Guatemala, Mexico, Australia, Germany, Netherlands, New Zealand, Hungary, India, Poland, and South Africa).

Efficacy (exposure/response) and safety assessments which differed from study SULF-007: The only pancreatic function variable measured was C-peptide at weeks 4, 8, 12, 16, 20, and 26.

7) 01-06-TL-322OPI-002: A multicenter, double blind study to determine the efficacy and safety of SYR-322 plus pioglitazone HCl (Actos), SYR-322 alone, or pioglitazone HCl alone in subjects with T2D

Study phase and dates conducted: Phase 3 study conducted November 2, 2006 – February 13, 2008.

Objectives: The objectives were similar to those of study SULF-007, except that they compared treatment with alogliptin and pioglitazone to either alogliptin or pioglitazone alone in treatment-naïve patients. Specific secondary objectives also included the following:

- Homeostasis model assessments (HOMA) of insulin resistance and beta cell function
- Serum lipids, nuclear magnetic resonance (NMR) fractionation, and apoproteins A1, A2, B, and C-III.
- Plasminogen activator inhibitor-1 (PAI-1), adiponectin, and high-sensitivity C-reactive protein (hsCRP)

Study design: The design of study OPI-002 was similar to that of SULF-007, except that it evaluated the efficacy and safety of 2 doses of alogliptin and pioglitazone to both alogliptin and pioglitazone alone. (This was an active comparator trial; there was no placebo treatment group.) Consistent with the additional objectives, FFAs; NMR

lipid fractionation; apolipoprotein A1, A2, B, and C-III; PAI-I; and adiponectin were also measured at baseline (day 1) and weeks 12 and 26.

Main inclusion criteria which differed from study SULF-007:

- HbA1c concentration 7.5-11%
- Subject had failed treatment with diet and exercise for at least 2 months prior to screening
- Received less than 7 days of any antidiabetic therapy within 3 months prior to screening

Additional inclusion criteria prior to randomization:

- HbA1c concentration between 7.5-11% and a FPG < 310 mg/dl at week -1 visit (Assessment may have been repeated weekly for a maximum of 4 additional weeks.)

Exclusion criteria which differed from study SULF-007:

- ALT \geq 2.5x ULN

Treatments and management: Subjects were randomized (1:1:1:1) to the following treatments:

- Alogliptin 25 mg (A25)
- Pioglitazone 30 mg (P30)
- Alogliptin 12.5 mg and pioglitazone 30 mg (A12.5+P30)
- Alogliptin 25 mg and pioglitazone 30 mg (A25+P30)

Like in study SULF-007, subjects received dietary, exercise, and hypoglycemia education. If randomized subjects met any of the following criteria relating to efficacy, there were removed from the study and completed an early termination visit:

- Weeks 4-8: a single fasting glucose \geq 310 mg/dl as determined by the central laboratory and confirmed by a second sample drawn within 5 days after the first sample and analyzed by the central laboratory
- Weeks 8-12: a single fasting glucose \geq 275 mg/dl as determined by the central laboratory and confirmed by a second sample drawn within 5 days after the first sample and analyzed by the central laboratory
- Week 12 to end of treatment: HbA1c \geq 8.5% and \leq 0.5% reduction in HbA1c as compared with the baseline HbA1c, confirmed by a second sample drawn within 5 days after the first and analyzed by the central laboratory

Subjects who met the criteria for rescue were considered to have completed the study and were eligible to enter open label, uncontrolled extension study OLE-012.

Study sites including enrollment: Study OPI-002 was conducted at 268 sites in 23 countries (United States, Argentina, Brazil, Chile, Guatemala, Mexico, Australia, New Zealand, Bulgaria, Croatia, Estonia, Hungary, India, Israel, Latvia, Lithuania, Poland, Romania, Russia, Serbia, Slovak Republic, South Africa, and the Ukraine).

Secondary efficacy assessments which differed from study SULF-007:

- Change from baseline in total cholesterol, LDL, HDL, and triglycerides at weeks 4, 8, 12, 16, 20, and 26
- Change from baseline in NMR lipid fractionation at weeks 12 and 26
- Change from baseline in FFA; apolipoprotein A1, A2, b, and C-III; PAI-1; and hsCRP at weeks 12 and 26
- Change from baseline in adiponectin at weeks 12 and 26
- Change from baseline in body weight at weeks 8, 12, 20, and 26
- Change from baseline in HOMA insulin resistance and beta cell function at weeks 12 and 26

8) 01-05-TL-322OPI-001: A multicenter, randomized, double blind, placebo controlled study to determine the efficacy and safety of the combination of SYR-322 (SYR100322) and pioglitazone HCl (Actos) in subjects with T2D

Study phase and dates conducted: Phase 3 study conducted May 31, 2006 – March 17, 2008.

Objectives: The objectives were similar to those of study SULF-007, except that they compared treatment with alogliptin and pioglitazone to pioglitazone alone. Specific secondary objectives also included the following:

- HOMA of insulin resistance and beta cell function
- Serum lipids, NMR fractionation, and apoproteins A1, A2, B, and C-III.
- PAI-1, adiponectin, and hsCRP

Study design: The design of study OPI-001 was similar to that of SULF-007, except that it evaluated the efficacy and safety of 2 doses of alogliptin in combination with 3 doses of pioglitazone to pioglitazone alone, alogliptin alone, and to placebo in T2D subjects who were inadequately controlled with a stable dose of metformin for at least 2 months prior to screening. The subject must have been receiving at least 1500 mg/day metformin unless there was documentation that the subject's current dose was his or her MTD. As shown in study schedule A, these subjects entered a screening period of up to 2 weeks, a 4 week stabilization period, a 26 week treatment period, and a 2 week follow up period. Consistent with the additional objectives, FFAs; NMR lipid fractionation; apolipoprotein A1, A2, B, and C-III; PAI-I; and adiponectin were also measured at baseline (day 1) and weeks 12 and 26.

Subjects, who had inadequate glycemic control (i.e. HbA1c 7.5-12%) while receiving metformin 1000 mg alone, entered a 2 week prescreening period, as outlined in study schedule B. These subjects were titrated from 1000 to 1500 mg/day and then underwent an optional 12 week titration period and returned for a 2 week screening period to assess their glycemic control. If the subject had an HbA1c between 7.5-10% inclusive, they then entered a 4 week stabilization period. If the subject could not tolerate the increase in metformin to 1500 mg within the first 2 weeks, they could decrease the dose to 1000 mg and go directly into the screening period. This documented that the subject had reached their MTD; these subject followed study schedule A.

SYR-322-OPI-001. Study designs A and B (Reproduced from the sponsor)

A

Screening Weeks -6 through -5 Before Randomization	Run-in/Stabilization Weeks -4 through -1 Before Randomization					Treatment Period Weeks 1 through 26 After Randomization								End-of- treatment	Follow- up Period
Week															
-6 to -5	-4	-3	-2	-1	Baseline Visit (Day 1)	1	2	4	8	12	16	20	26	28	

B

Prescreening Period	Optional Titration Period	Screening Weeks -6 through -5 Prior to Randomization	Run-in/Stabilization Weeks -4 through -1 Prior to Randomization				Treatment Period Weeks 1-26 After Randomization								End- of- Treat- ment	Follow- up Period
			Week													
Up to 2 weeks	12 weeks	-6 to -5	-4	-3	-2	-1	Baseline Visit (Day 1)	1	2	4	8	12	16	20	26	28

Consistent with the additional objectives, FFAs; NMR lipid fractionation; apolipoprotein A1, A2, B, and C-III; PAI-I; and adiponectin were also measured at baseline (day 1) and weeks 12 and 26.

Main inclusion criteria which differed from study SULF-007:

- T2D subjects who were treated with metformin \geq 1500 mg alone but were experiencing inadequate glycemic control defined as HbA1c concentration 7.5-10%. These subjects entered stabilization according to study schedule A.
- In addition, T2D subjects who were treated with metformin \geq 1000 mg alone but were experiencing inadequate glycemic control defined as HbA1c concentration 7.5-12% were evaluated for entry into a stabilization following a titration of metformin. After completing the prescreening visit, these subjects were titrated to a stable dose of metformin \geq 1500 mg. The subjects underwent an optional 12 week titration period according to study schedule B. Following this 12 week period, the subject must have qualified for entry into the stabilization period by completing the screening visit. If the subject could not

tolerate the increase in metformin of 1500 mg within the first 2 weeks, then they could down titrate immediately back to the tolerated dose of 1000 mg and go directly into the screening period per study schedule A, as the patient had reached their MTD.

- A stable dose of metformin of ≥ 1500 mg or MTD for at least 2 months prior to screening for those subjects not going through a metformin titration period.

Additional inclusion criteria prior to randomization:

- HbA1c between 7.5-10% and FPG ≤ 300 mg/dl at the week -1 visit (Assessment may have been repeated weekly for a maximum of 4 additional weeks.)

Exclusion criteria: The exclusion criteria did not differ from study SULF-007:

Treatments and management: Subjects were randomized (1:1) to 1 of the following 12 treatment groups:

- Alogliptin placebo and pioglitazone placebo (placebo)
- Alogliptin placebo and pioglitazone 15 mg (P15)
- Alogliptin placebo and pioglitazone 30 mg (P30)
- Alogliptin placebo and pioglitazone 45 mg (P45)
- Alogliptin 12.5 mg and pioglitazone placebo (A12.5)
- Alogliptin 12.5 mg and pioglitazone 15 mg (A12.5+P15)
- Alogliptin 12.5 mg and pioglitazone 30 mg (A12.5+P30)
- Alogliptin 12.5 mg and pioglitazone 45 mg (A12.5+P45)
- Alogliptin 25 mg and pioglitazone placebo (A25)
- Alogliptin 25 mg and pioglitazone 15 mg (A25+P15)
- Alogliptin 25 mg and pioglitazone 30 mg (A25+P30)
- Alogliptin 25 mg and pioglitazone 45 mg (A25+P45)

Like in study SULF-007, subjects received dietary, exercise, and hypoglycemia education. If randomized subjects met any of the following criteria relating to efficacy, there were removed from the study and completed an early termination visit:

- Weeks 1-4: a single fasting glucose ≥ 300 mg/dl as determined by the central laboratory and confirmed by a second sample drawn within 5 days after the first sample and analyzed by the central laboratory
- Weeks 4-8: a single fasting glucose ≥ 275 mg/dl as determined by the central laboratory and confirmed by a second sample drawn within 5 days after the first sample and analyzed by the central laboratory
- Weeks 8-12: a single fasting glucose ≥ 250 mg/dl as determined by the central laboratory and confirmed by a second sample drawn within 5 days after the first sample and analyzed by the central laboratory
- Week 12 to end of treatment: HbA1c $\geq 8.5\%$ and $\leq 0.5\%$ reduction in HbA1c as compared with the baseline HbA1c, confirmed by a second sample drawn within 5 days after the first and analyzed by the central laboratory

Subjects who met criteria for rescue were considered to have completed the study at the time of rescue and were eligible to enter study OLE-012.

Study sites including enrollment: Study OPI-001 took place at 327 sites in 20 countries (United States, Argentina, Brazil, Chile, Guatemala, Mexico, Peru, Australia, New Zealand, Bulgaria, Croatia, Estonia, India, Israel, Latvia, Romania, Russia, Serbia, South Africa, and the Ukraine).

Efficacy (exposure/response) and safety assessments which differed from study SULF-007:

- Change from baseline in total cholesterol, LDL, HDL, and triglycerides at weeks 4, 8, 12, 16, 20, and 26
- Change from baseline in NMR lipid fractionation at weeks 12 and 26
- Change from baseline in FFA; apolipoprotein A1, A2, B, and C-III; PAI-1; and hsCRP at weeks 12 and 26
- Change from baseline in adiponectin at weeks 12 and 26
- Change from baseline in body weight at weeks 8, 12, 20, and 26
- Change from baseline in HOMA insulin resistance and beta cell function at weeks 12 and 26

9) SYR-322-OLE-012: A longterm, open label, extension study to investigate the long term safety of SYR110322 (SYR-322) in subjects with T2D

Study phase and dates conducted: Phase 3 study ongoing since March 13, 2006

Objectives:

Primary: To evaluate the safety of alogliptin administered alone or in combination with a SFU, metformin, a TZD, or insulin by evaluating AEs, clinical laboratory parameters, ECGs, vital sign measurements, oral temperature, physical examinations, and hypoglycemic events

Secondary: To investigate the durability of glycemic control of alogliptin administered alone or in combination with a SFU, metformin, a TZD, or insulin

Study design: This is an open label, uncontrolled extension of 7 controlled phase 3 studies. The phase 3 studies included 1 alogliptin monotherapy study (SYR-322-PLC-010); 4 placebo controlled add on studies of alogliptin in combination with a SULF, metformin, TZD, and insulin (SYR-322-SULF-007, SYR-322-MET-008, SYR-322-TZD-009, and SYR-322-INS-011, respectively); 1 coadministration study with pioglitazone and metformin (01-05-TL-322OPI-001), and 1 coadministration study with pioglitazone (01-06-TL-322OPI-002).

The end of treatment assessments from the controlled phase 3 studies served as the screening (day 1) for the open label extension. After entry, subjects from all treatment arms received alogliptin and were to continue their current add on therapy, although it was not provided by the sponsor. Subjects who were rescued from 1 of the 7 controlled phase 3 studies for hyperglycemia started a dose of 25 mg/day. Subjects who completed 1 of the 7 phase 3 studies were randomized (1:1) to either 12.5 or 25 mg/day alogliptin. Subjects visited the study center after 2, 4, 8, and 12 weeks of open treatment and then every 3 months.

Approximately 2,200 subjects were expected to enter the study. Subjects were allowed to receive study drug for up to 2 years.

Subjects were asked to return to the study center for an interim visit prior to 2 weeks before interim database lock on August 29, 2007, unless a scheduled visit was planned. During this visit, diaries and glucometer readings were reviewed. A complete physical examination, including skin and digits, was performed. Body weight, vital signs, and oral temperature were collected, and concomitant medications and AEs were reviewed. An ECG was performed. Samples for hematology serum chemistry and urinalysis were obtained fasting. A serum pregnancy test was administered to women of child bearing potential (WOCBP).

SYR-322-OLE-012. Study design (Reproduced from the sponsor)

Screening	Treatment				End-of-treatment (or Early Termination)	Follow-up	
Visit							
Day 1	Week				Every 3 Months	1 Day After Final Dose	2 Weeks After End- of-treatment
	2	4	8	12			

SYR-322-OLE-012. Study schedule (Reproduced from the sponsor)

Assessment	Screening	Treatment					End-of-treatment (or Early Termination)	Follow-up
		Visit						
	Day 1	Week				Every 3 Months	1 Day After Final Dose	2 Weeks After End-of- treatment
		2	4	8	12			
Informed consent	X							
Inclusion/exclusion	X							
Overnight fast	X	X	X	X	X	X	X	
Complete physical examination	X (a)						X	
Brief physical examination		X	X	X	X	X		X
Clinical examination of skin and digits	X	X	X	X	X	X	X	X
Vital signs	X (a)	X	X	X	X	X	X	X
Oral temperature	X (a)						X	
Body weight	X (a)	X	X	X	X	X	X	
12-lead ECG (b)	X (a)			X		X (b)	X	
Laboratory tests								
Hematology, serum chemistry (including lipid panel and plasma glucose) (c)	X (a)	X (d)	X	X	X	X	X	
Urinalysis (e)	X (a,e)					X (e)	X (e)	
Proinsulin	X (a,f)				X	X	X	
Insulin	X (a,f)				X	X	X	
Glucagon	X (g)							
C-peptide	X (a)				X	X	X	
HbA1c	X (a)				X	X	X	
CRP	X				X	X	X	
FFA (i)	X							
NMR lipid fractionation (i)	X							
Apolipoprotein A1, A2, B, and C-III (i)	X							
PAI-1 (i)	X							
Adiponectin (i)	X							
Serum pregnancy test (h)	X (a)						X	
Urine pregnancy test (h)					X	X		
Issue subject diary	X	X	X	X	X	X		
Review diaries and glucometer readings	X (a)	X	X	X	X	X	X	
Review concomitant medications and AEs	X (a)	X	X	X	X	X	X	X
Dispense study drug	X	X	X	X	X	X		
Document drug accountability	X (a)	X	X	X	X	X	X	

CRP=C-reactive protein; FFA=free fatty acid; NMR=nuclear magnetic resonance; PAI-1=plasminogen activator inhibitor 1.

(a) Done as end-of-treatment (or early termination) assessment for the controlled phase 3 studies.

(b) An ECG was obtained at Screening, at the Week 8 visit, after 6 months, after 18 months, and at the end-of-treatment (or early termination) visit.

(c) The samples were obtained under fasting conditions.

(d) No lipid panel was obtained at the Week 2 visit.

(e) Urinalysis was only to be done at Screening (Day 1), every 6 months thereafter, and at the end-of-treatment (or early termination) visit. In addition to the (qualitative) urinalysis, an albumin/creatinine ratio was determined at Screening and at the end-of-treatment (or early termination) visit.

(f) Except for the insulin add-on study (SYR-322-INS-011).

(g) Only done as end-of-treatment (or early termination) assessment of the controlled phase 3 monotherapy study (SYR-322-PLC-010).

(h) Women of childbearing potential only.

(i) Done at screening only as end-of-treatment (or early termination) assessment for subjects from Protocol

Main inclusion criteria which differed from study SULF-007:

- Subjects were enrolled in 1 of 7 controlled phase 3 studies. The study was open to all subjects who either completed 1 of these studies or was rescued.

Exclusion criteria which differed from study SULF-007:

- The occurrence of an AE or condition during the controlled phase 3 study, which in the opinion of the investigator, should have excluded the subject from participating in the open label extension

Treatments and management: After entry, subjects from all treatment arms received alogliptin and were to continue their current add on therapy, although it was not provided by the sponsor. Subjects who were rescued from 1 of the 7 controlled phase 3 studies for hyperglycemia started an alogliptin dose of 25 mg/day. Subjects who completed 1 of the 7 phase 3 studies were randomized (1:1) to either 12.5 or 25 mg/day alogliptin.

During the study, 25 mg alogliptin could be lowered to 12.5 mg if the subject could not tolerate the higher dose. However, if a subject who was using additional antidiabetic medications experienced hypoglycemia, the doses of the other medications, rather than alogliptin, were lowered.

As in previous studies, subjects were to take alogliptin prior to the first meal of the day with 8 ounces of water.

Study sites including enrollment: Study OLE-012 is currently ongoing at 246 sites in 22 countries.

Efficacy (exposure/response) assessments: HbA1c, FPG, proinsulin, insulin, C-peptide, body weight, and incidence of marked hyperglycemia (FPG \geq 200 mg/dl)

Safety assessments: The planned safety assessments for study OLE-012 are similar to SULF-007.

Discussion of findings/conclusions: A minimum of 300 subjects who were on alogliptin for \geq 1 year were required for the interim analysis. The 1 year included not only the time that the subjects were on alogliptin during the open label study but also during the double blind studies. The submitted report included data up to the interim database lock on August 29, 2007.

Subjects who completed a double blind study ("completers") were randomized in a 1:1 manner to either 12.5 or 25 mg alogliptin, while subjects who were rescued from a double blind study ("rescued group") due to hyperglycemia were assigned to 25 mg alogliptin. Thus, it was expected that there would be a difference between the 12.5 and 25 mg alogliptin groups. Therefore, the 12.5 and 25 mg alogliptin completers were compared for efficacy versus the 25 mg alogliptin rescued group. Analysis was also conducted based on prior treatment in the double blind studies to examine the potential impact on the glycemic parameters in this study.

6 Review of Efficacy

Efficacy Summary

The sponsor proposes that alogliptin be indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with T2D (b) (4)

This review focused on the controlled phase 2 and 3 clinical studies pertinent to the claimed indication that were originally submitted to NDA 22-271 (i.e. SYR-322 studies 003, SULF-007, MED-008, TZD-009, PLC-010, INS-011). The uncontrolled extension study OLE-012 was used to support durability of effect and long-term safety. Efficacy analyses were conducted by the sponsor using the last observation carried forward (LOCF) and full analysis set (FAS), consisting of all randomized and treated subjects who had a baseline value and at least one post-treatment

measurement for the parameter of interest. For each study, the HbA1c lowering effect of 25 mg daily dose was compared with placebo using ANCOVA at the 2-sided 0.05 significance level. If this test was statistically significant, the 12.5 mg daily dose was evaluated in a similar fashion.

The majority of all randomized subjects were Caucasian. Approximately half of the subjects were male. The median age across studies ranged from 53–57 years, with approximately 15–20% subjects ≥ 65 years. The duration of diabetes differed among studies, with subjects in INS-011 having a longer mean duration of diabetes compared to other studies. The duration of diabetes ranged from 2.8 years in the treatment naïve trial (PLC-010) to 13.4 years in the add-on to insulin trial (INS-011).

The use of HbA1c for hyperglycemic rescue from weeks 12 – 26 resulted in an unusually high level of rescue after week 12. Subjects who entered a study in the higher baseline HbA1c stratification level were more likely to receive hyperglycemic rescue, compared to subjects in the lower HbA1c stratification level. The high rate of discontinuation limits our confidence in the HbA1c results, due to the imputation of missing value. Estimates of the placebo-adjusted effect of alogliptin from the 2 subsets of completers and noncompleters were influenced by the differential rescue rate in the alogliptin and placebo arms, thus complicating data interpretation. Subjects with higher baseline HbA1c also generally had greater HbA1c reductions compared to subjects with lower baseline HbA1c values when the alogliptin arms were compared to placebo.

Furthermore, the insulin add-on study INS-011 was different from the 4 other studies in the larger percentage of subjects in each arm who were rescued or discontinued (58% placebo, 37% alogliptin 12.5 mg, 40% alogliptin 25 mg). The large percentage of subjects who were rescued or discontinued makes it difficult to ascertain the quantity of change in HbA1c when alogliptin was added-on to insulin, although statistical analysis supported an improvement in HbA1c.

The primary efficacy variable for all 5 controlled, pivotal, phase 3 studies was the difference in HbA1c at study endpoint (after 26 weeks of treatment) compared to baseline. Both the 12.5 and 25 mg doses achieved statistically significant LS mean reductions in HbA1c reductions from baseline to week 26 compared to placebo, regardless of the add-on therapy. The net LS mean reduction in HbA1c with alogliptin 25 mg relative to placebo was 0.4 - 0.5% across the 5 studies. In all but the MET-008 trial, the LS mean difference was slightly greater in the 25 mg group compared to the 12.5 mg group. The net effect of the alogliptin 12.5 and 25 mg doses were very similar and not statistically separable, although this was not an objective of the studies.

Estimates of the placebo-adjusted effect of alogliptin from the 2 subsets of completers and noncompleters were influenced by the differential rescue rate in the alogliptin and placebo arms, thus complicating data interpretation.

Subjects treated with both alogliptin 12.5 and 25 mg achieved consistent mean reductions in HbA1c levels from baseline to week 26 in all subpopulations (gender, age, race, ethnicity, and baseline BMI).

The change from baseline in HbA1c was also analyzed by baseline HbA1c. Subjects who entered a study in the higher baseline HbA1c stratification level were more likely to receive hyperglycemic rescue, compared to subjects in the lower HbA1c stratification level. Subjects with higher baseline HbA1c generally had greater HbA1c reductions compared to subjects with lower baseline HbA1c values when the alogliptin arms were compared to placebo. This relationship, which was seen in both the alogliptin and placebo groups, has been seen in other diabetic drug clinical trials.

Without a controlled extension study, it is difficult to determine the durability of alogliptin's glycemic control. However, as discussed in section 6.1.4 Analysis of Primary Endpoint, in the 5 controlled, pivotal phase 3 trials of alogliptin, both the 12.5 and 25 mg doses achieved statistically significant LS mean reductions in HbA1c reductions from baseline to week 26 compared to placebo, regardless of the add-on therapy. The effect of alogliptin in the controlled phase 3 trials was established by week 12, after which the placebo-adjusted effect of alogliptin remained relatively constant, even though the average change from baseline decreased from week 12 – 26 in the alogliptin and placebo arms. This decrease may have resulted from the progression of diabetes over time. However, the apparent stabilization at week 12 may have also resulted from changes in disposition.

The major secondary efficacy parameters were the percentage of alogliptin-treated subjects achieving HbA1c < 6.5% and < 7%, FPG, and body weight.

- All alogliptin study groups, except the SULF-007 alogliptin 12.5 mg and INS-011 25 mg groups, had a statistically significantly greater number of alogliptin subjects who achieved HbA1c $\leq 7.0\%$ ($p < 0.05$) compared to placebo. Only the MET-008 and TZD-009 studies had a statistically significantly greater number of alogliptin subjects who achieved HbA1c levels $\leq 6.5\%$ ($p < 0.05$) compared to placebo. These statistical comparisons should be considered exploratory because there is no control of the type 1 error rate and several of the p-values are nominally significant.
- The LS mean decreases in fasting plasma glucose (FPG) observed in the alogliptin groups were statistically significant compared with the placebo group in studies MET-008, TZD-009, PLC-010, and INS-011 (alogliptin 25 mg dose group only in INS-011). In SULF-007, both alogliptin 12.5 and 25 mg groups had LS mean decreases from baseline in FPG values compared with placebo. However, the differences between alogliptin and placebo-treated subjects were not statistically significant. No difference in changes in FPG was observed between the alogliptin 12.5 mg dose group and placebo in study INS-011.
- No consistent effect on the change from baseline in weight at week 26 was seen in the 5 pivotal studies.

No titration of 12.5 to 25 mg or vice versa was performed during phase 3 clinical studies. Thus, no data exists to provide clinical recommendations for dosage adjustment beyond the general comment that alogliptin should be titrated in individual patients based on glycemic response.

6.1 Indication

The sponsor proposes that alogliptin be indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with T2D (b) (4)

The Division recently simplified the indication for products developed for the treatment of type 2 diabetes. Therefore, if/when alogliptin can be approved, the indication will be streamlined to "...indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."

6.1.1 Methods

Alogliptin has been studied in 29 completed clinical trials. Administration of alogliptin has been tolerated by healthy subjects at doses up to 800 mg and in T2D subjects at doses up to 400 mg. This review focused on the controlled phase 2 and 3 clinical studies pertinent to the claimed indication that were originally submitted to NDA 22-271 (i.e. SYR-322 studies 003, SULF-007, MED-008, TZD-009, PLC-010, INS-011). The uncontrolled extension study OLE-012 was used to support durability of effect and long-term safety.

Efficacy analyses were conducted by the sponsor using the last observation carried forward (LOCF) and full analysis set (FAS), consisting of all randomized and treated subjects. The FAS consisted of all randomized and treated subjects with a baseline value and at least 1 post-baseline on-treatment value for the variable. For each study, the HbA1c efficacy with the 25 mg daily dose was compared with that of placebo using ANCOVA at the 2-sided 0.05 significance level. If this test was statistically significant, the 12.5 mg daily dose was evaluated in a similar fashion. Please refer to Dr. Janice Derr's statistical review for full details.

As discussed in section 5.3 Discussion of Individual Studies, phase 2 dose ranging study 003 investigated alogliptin doses 6.25, 12.5, 25, 50, and 100 mg daily for 12 weeks in T2D subjects. Alogliptin doses 12.5 and 25 mg daily for 26 weeks were evaluated in T2D subjects without (010) and with (SULF-007, MET-008, TZD-009, and INS-011) add-on therapy. More phase 3 study subjects received alogliptin than placebo due to the 1:2:2 (placebo: alogliptin 12.5 mg: alogliptin 25 mg) randomization used in studies SULF-007, MET-008, TZD-09, and PLC-010. Please also refer to section 5.1 Tables of Clinical Studies for more information.

6.1.2 Demographics

Across the phase 2/3 program, the mean age of subjects was 55 years. The proportion of males in the placebo and alogliptin treatment groups ranged from 42.5-53.3%. Nearly all subjects had normal baseline serum creatinine. The majority of subjects were Caucasian (72.0-85.1%) and obese (57.3-73.8%). The mean duration of T2D ranged from 4.0-6.6 years.

1) SYR-322-003: The majority of subjects in each treatment group were Caucasian (84.1-90.9%). Roughly half of the subjects were male. The mean BMI was similar between each treatment groups (31.4-33.0 kg/m²). The mean duration of diabetes ranged between 3.3-6.8 years across treatment groups. However, the mean HbA1c at baseline

was approximately 8% in each treatment group and less than one-half of the patients in each group were treatment-naïve.

SYR-322-003. Demographic and baseline characteristics (Randomized subjects)							
Characteristic	No. of subjects (%)						
	Placebo (n=43)	SYR-322 dose (mg)					
		6.25 (n=44)	12.5 (n=44)	25 mg (n=45)	50 mg (n=44)	100 mg (n=45)	Total (n=265)
Age, mean (SD)	56.0 (10.9)	53.4 (10.1)	57.1 (9.1)	54.8 (11.1)	56.3 (11.3)	57.3 (9.2)	55.8 (10.3)
Male (%)	19 (44.2)	19 (43.2)	22 (50.0)	28 (62.2)	18 (40.9)	20 (44.4)	126 (47.5)
Race							
White	38 (88.4)	38 (86.4)	40 (90.9)	39 (86.7)	37 (84.1)	39 (86.7)	231 (87.2)
Other	2 (4.7)	1 (2.3)	1 (2.3)	2 (4.4)	2 (4.5)	0	8 (3.0)
BMI, mean (SD)	31.9 (5.2)	32.8 (4.5)	31.4 (4.4)	32.3 (4.8)	33.0 (4.6)	31.2 (5.3)	32.1 (4.8)
Diabetes duration, mean (SD)	6.8 (5.4)	4.9 (4.0)	5.2 (5.6)	5.8 (5.4)	3.3 (2.6)	6.4 (6.1)	5.4 (5.1)
Prior antidiabetic treatment	25 (58.1)	25 (56.8)	24 (54.5)	27 (60.0)	26 (59.1)	25 (55.6)	152 (57.4)
HbA1c, mean (SD)	8.2 (1.0)	8.0 (1.0)	7.9 (0.9)	8.0 (1.0)	8.1 (1.0)	8.0 (1.0)	

In addition to T2D, other common medical conditions reported by the randomized subjects who received at least 1 dose of study drug (safety sample) included cardiovascular (170/259, 65.6%); musculoskeletal (149/259, 57.5%); genitourinary (142/259, 54.8%); gastrointestinal (98/259, 37.8%); allergic (90/259, 34.7%); head, eyes, ears, nose, and throat (87/259, 33.6%), and other (81/259, 31.3%).

Of the 259 safety subjects, 241 (93.1%) were taking at least 1 concomitant medication. The percentage of subjects taking at least 1 concomitant medication was highest in the 100 mg group (44/44, 100%) and lowest in the 25 mg group (38/45, 84.4%). The most common concomitant medications, excluding antidiabetic medication for hyperglycemic rescue, are shown in the table below.

SYR-322-003. Most common concomitant medications, excluding antidiabetic medication for hyperglycemic rescue (%)							
Medication	Placebo	Alogliptin (mg)					Total (n, %)
		6.25	12.5	25	50	100	
HMG CoA reductase inhibitors	34.1	45.2	38.6	31.1	30.2	27.3	89/259 (34.4%)
Platelet aggregation inhibitors, excluding heparin	29.3	28.6	36.4	40.0	20.9	25.0	78/259 (30.1%)
Angiotensin converting enzyme inhibitors	34.1	23.8	34.1	24.4	23.3	27.3	72/259 (27.8%)
Propionic acid derivatives	14.6	16.7	13.6	13.3	16.3	22.7	42/259 (16.2%)
Multivitamins, other combinations	24.4	16.7	13.6	17.8	11.6	4.5	38/259 (14.7%)
Beta-blocking agents, selective	14.6	4.8	13.6	20.0	14.0	15.9	36/259 (13.9%)
Thyroid hormones	14.6	9.5	9.1	8.9	11.6	13.6	29/259 (11.2%)
Proton pump inhibitors	2.4	7.1	16.9	6.7	7.0	20.5	26/259 (10.0%)

2) SULF-007: Demographic and baseline characteristics were similar between treatment groups. Approximately 50% of subjects were male. The mean age was 56.6 years. Most subjects were Caucasian (71%). Asians, Blacks, and other ethnic groups composed 12%, 4%, and 13% of subjects, respectively. The mean duration of diabetes was 7.7 years. The mean glyburide dose was 12.2 mg.

Clinical Review
Valerie S. W. Pratt, M.D.
NDA 21-271/S-000
Alogliptin (Nesina) 6.25, 12.5 or 25 mg daily

NDA 22-271. Demographics of controlled phase 3 studies (Randomized set) (n, %)															
Demographic	SULF-007			MET-008			TZD-009			PLC-010			INS-011		
	Glyburide with			Metformin with			Pioglitazone with/without metformin or SULF						Insulin with/without metformin		
	Plb N=99	Alogliptin		Plb N=99	Alogliptin		Plb N=97	Alogliptin		Plb N=97	Alogliptin		Plb N=130	Alogliptin	
		12.5 N=203	25 N=198		12.5 N=203	25 N=198		12.5 N=197	25 N=199		12.5 N=197	25 N=199		12.5 N=131	25 N=129
Male	51 (52)	11 (55)	99 (50)	50 (48)	101 (47)	114 (54)	53 (55)	109 (55)	125 (63)	33 (51)	65 (49)	77 (59)	62 (48)	55 (42)	44 (34)
Age, mean years (SD)	57.1 (10.1)	56.5 (11.1)	56.5 (11.7)	56.0 (10.6)	55.2 (10.6)	53.6 (10.5)	55.2 (10.8)	55.5 (9.4)	55.4 (10.2)	53.8 (11.0)	52.6 (12.0)	54.2 (10.2)	55.0 (10.6)	55.4 (9.8)	55.9 (10.2)
Caucasian	72 (73)	141 (70)	141 (71)	79 (76)	170 (80)	159 (76)	71 (73)	143 (73)	152 (76)	44 (68)	88 (66)	88 (67)	89 (69)	81 (62)	85 (66)
BMI, mean (SD)	30.0 (5.3)	30.2 (4.8)	30.1 (4.8)	32.4 (5.8)	31.6 (5.2)	31.8 (5.3)	33.2 (6.2)	32.3 (5.7)	33.1 (5.4)	32.2 (5.7)	31.8 (5.2)	32.2 (5.9)	32.4 (5.6)	32.7 (5.5)	32.3 (5.6)
Diabetes duration, mean years (SD)	7.7 (5.3)	7.8 (6.1)	7.6 (6.0)	6.3 (5.4)	6.2 (5.1)	5.9 (4.3)	7.8 (6.7)	7.7 (5.6)	7.4 (5.4)	4.3 (5.3)	3.1 (3.8)	2.8 (3.0)	12.2 (7.1)	12.1 (7.2)	13.4 (6.3)

SYR-322-SULF-007. Subject demographics and baseline characteristics (Randomized set) (n, %)				
Disposition	Glyburide with			Overall (n=500)
	Placebo (n=99)	Alogliptin		
		12.5 mg (n=203)	25 mg (n=198)	
Add on therapy, mean glyburide dose (mg) (SD)	11.2 (4.1)	12.3 (4.5)	12.4 (4.5)	12.2 (4.4)

Greater than 99% of subjects in each treatment group took concomitant medications. The most common ($\geq 15\%$ subjects) nondiabetes concomitant medications used in study SYR-322-SULF-007 are listed below by drug class. The most common ($\geq 10\%$ subjects) nondiabetic medications were acetylsalicylic acid (31%), paracetamol (15%), enalapril (15%), and simvastatin (11%).

SYR-322-SULF-007. Most common ($\geq 15\%$ subjects) nondiabetes concomitant medications by drug class (%)				
Medication	Placebo (n=99)	Alogliptin (mg)		Total (n=500)
		12.5 (n=203)	25 (n=198)	
Agents acting on the rennin-angiotensin system	48.5	47.3	44.9	46.6
Lipid modifying agents	34.3	34.0	37.4	35.4
Analgesics	21.2	23.2	22.2	22.4
Stomatological preparations	41.1	32.5	35.4	35.4
Antibacterials	26.3	25.1	21.2	23.8
Diuretics	15.2	18.7	17.2	17.4
Beta-blocking agents	19.2	16.3	14.6	16.2
Cardiac therapy	15.2	15.3	16.2	15.6

3) MET-008: Demographic characteristics were similar between treatment groups. Half of the subjects were male. The majority (77%) were Caucasian. The percentage of Black, Asian, Pacific Islander, Native American, or other ethnic groups were 5%, 8%, 0.2%, 0.6%, and 9% respectively. The mean duration of diabetes was 6.1 years. The mean metformin dose was 1847 mg.

SYR-322-MET-008. Subject demographics and baseline characteristics (Randomized set) (n, %)				
Demographic	Metformin with			Overall (n=500)
	Placebo (n=99)	Alogliptin		
		12.5 mg (n=203)	25 mg (n=198)	
Add on therapy, mean metformin dose (mg) (SD)	1868 (445)	1837 (479)	1846 (470)	1847 (468)

The most common ($\geq 10\%$ subjects) concurrent medical conditions were as follows hypertension (54%), hyperlipidemia (22%), obesity (17%), dyslipidemia (16%), hypercholesterolemia (16%), postmenopause (15%), osteoarthritis (11%), and depression (11%). The percentage of subjects with concurrent medical conditions was similar between treatment groups for most system organ classes (SOCs).

The most common nondiabetic concomitant medications are listed by drug class below. The most common nondiabetic concomitant medications ($\geq 10\%$ subjects) included acetylsalicylic acid (30%), simvastatin (13%), atorvastatin (11%), ibuprofen (10%), and paracetamol (10%). In general, the percentage of subjects receiving a particular concomitant medication was similar between treatment groups.

SYR-322-MET-008. Most common ($\geq 15\%$ subjects) nondiabetes concomitant medications by drug class

Medication	Frequency of use (%)
Renin-angiotensin agents	50%
Lipid modifying agents	47%
Analgesics	20%
Acid-related agents	19%
Beta-blocking agents	17%
Cardiac therapy	16%
Diuretics	16%
Psychoanaleptics	12%
Calcium channel blockers	10%

4) TZD-009: Study TZD-009 randomized slightly more men than women (58%). The gender difference was greatest in the 25 mg alogliptin group (63% male). The majority of subjects were Caucasian (74%) and the average age was 55 years. The mean BMI (32.8 kg/m²) and duration of diabetes (7.6 years) were similar between groups, as were the percentages of subjects using additional antidiabetic therapy and the doses used. More than one-half of the randomized patients were taking pioglitazone+metformin background therapy.

SYR-322-TZD-009. Subject demographics and baseline characteristics (Randomized set) (n, %)				
Demographic	Pioglitazone with/without metformin or SULF with			Overall (n=493)
	Placebo (n=97)	Alogliptin		
		12.5 mg (n=197)	25 mg (n=199)	
Add on therapy (n, %)				
Pioglitazone	23 (24)	48 (24)	41 (21)	112 (23)
Pioglitazone + SULF	18 (19)	42 (21)	44 (22)	104 (21)
Pioglitazone + metformin	56 (58)	107 (54)	114 (57)	277 (56)
Pioglitazone mean dose (mg) (SD)	36.2 (8.5)	34.0 (9.3)	35.4 (9.0)	35.0 (9.1)
SULF mean dose (mg) (SD)	30.4 (72.7)	49.3 (96.5)	28.7 (67.7)	37.3 (81.2)
Metformin mean dose (mg) (SD)	1717.4 (632.5)	1689.3 (604.0)	1672.4 (576.31)	1688.0 (596.7)

The most common ($\geq 10\%$ subjects) concurrent medical conditions included hypertension (61%), hyperlipidemia (27%), hypercholesterolemia (22%), dyslipidemia (19%), osteoarthritis (15%), obesity (15%), gastroesophageal reflux disease (14%), drug hypersensitivity (14%), depression (12%), and postmenopause (11%). The percentage of subjects with concurrent medical conditions was similar among treatment groups for most SOC.

All subjects in each treatment group took concomitant medications. The most common ($\geq 10\%$ subjects) included acetylsalicylic acid (38%), atorvastatin (17%), simvastatin (16%), paracetamol (15%), ibuprofen (13%), lisinopril (13%), and multivitamins (11%). In general, the percentage of subjects receiving a particular concomitant medication was similar among the treatment groups.

5) PLC-010: Baseline demographic characteristics were similar between treatment groups. Approximately half of subjects were male (53%). The majority of subjects were Caucasian (67%). The mean age of subjects and duration of diabetes were 53.4 and 3.2 years, respectively.

The most common ($\geq 10\%$ subjects) concurrent medical conditions included hypertension (43%), hyperlipidemia (23%), obesity (13%), hypercholesterolemia (12%), osteoarthritis (12%), dyslipidemia (12%), postmenopause (12%), and drug hypersensitivity (11%). The percentage of subjects with concurrent medical conditions in a SOC was similar between treatment groups.

The most common ($\geq 10\%$ subjects) nondiabetic medications taken by subjects were acetylsalicylic acid (24%), ibuprofen (16%), and multivitamins (11%). The use of concomitant medications was generally similar between treatment groups.

6) INS-011: The baseline demographics were distributed similarly between treatment groups. The majority of subjects were female (59%) and Caucasian (65%). The mean age and duration of diabetes were 55.4 years and 12.6 years, respectively. The majority of subjects (59%) took insulin and metformin with their placebo or alogliptin tablets.

SYR-322-INS-011. Subject demographics and baseline characteristics (Randomized set) (n, %)				
Demographic	Insulin with/without metformin with			Overall (n=390)
	Placebo (n=130)	Alogliptin		
		12.5 mg (n=131)	25 mg (n=129)	
Add on therapy				
Insulin	51 (39)	54 (41)	57 (44)	162 (42)
Insulin + metformin	79 (61)	77 (59)	72 (56)	228 (59)
Insulin mean dose (IU) (SD)	56.7 (22.9)	57.5 (23.3)	55.2 (22.6)	56.5 (22.6)
Metformin mean dose (mg) (SD)	1849.1 (642.7)	1631.8 (645.6)	1712.8 (573.6)	1732.7 (626.6)

The most common ($\geq 10\%$ subjects) concurrent medical conditions included hypertension (70%), dyslipidemia (21%), hyperlipidemia (20%), hypercholesterolemia (17%), menopause (14%), postmenopause (13%), obesity (13%), diabetic retinopathy (12%), diabetic neuropathy (12%), osteoarthritis (11%), and headache (10%). The percentage of subjects with a concurrent medical condition was similar among treatment groups for most SOC.

The most common ($\geq 10\%$ subjects) nondiabetic concomitant medications included acetylsalicylic acid (44%), simvastatin (20%), paracetamol (15%), hydrochlorothiazide (12%), atorvastatin (11%), ibuprofen (11%), lisinopril (10%), and atenolol (10%). In general, the percentage of subjects receiving a particular concomitant medication was similar among the treatment groups.

7) OPI-002: Baseline demographics were similar between treatment groups. Slightly over half of all subjects were female (51%). The majority of subjects were white (80%). The mean age and duration of diabetes were 52.6 and 3.2 years, respectively. The mean BMI was 31.1 kg/m².

01-06-TL-322OPI-002. Subject demographics and baseline characteristics (Randomized set) (n, %)					
Demographics	A25 (n=164)	P30 (n=163)	A12.5+P30 (n=164)	A25+P30 (n=164)	Overall (n=655)
Male	76 (46)	90 (55)	81 (49)	73 (45)	320 (49)
Age, mean years (SD)	52.6 (10.4)	51.5 (10.8)	53.5 (11.4)	52.8 (11.0)	52.6 (10.9)
White	135 (82)	130 (80)	132 (81)	129 (79)	526 (80)
BMI, mean (SD)	31.6 (5.6)	30.9 (4.9)	30.7 (5.6)	31.3 (5.4)	31.1 (5.4)
Diabetes duration, mean years (SD)	3.2 (3.6)	3.2 (3.7)	3.4 (4.2)	3.05 (3.3)	3.2 (3.7)

The most common ($\geq 10\%$ subjects) concurrent medical conditions included hypertension (44%), lipid disorders (29%), postmenopause (13%), and obesity 12%. The percentage of subjects with concurrent medical conditions was similar among treatment groups for most SOC.

Most subjects (78-89% subjects) in each treatment group took concomitant medications. The medications used were similar to those described in the studies above and did not differ significantly between treatment groups.

8) OPI-001: (Please refer to the table in section 6.1.3.) The majority of subjects were female and Caucasian. The mean age was 54 years, BMI 31 kg/m², duration of diabetes 6 years, and metformin dose 1887 mg. The distribution of these characteristics was similar between treatment groups.

The most common concurrent medical conditions included hypertension (55%), dyslipidemia (20%), menopause (19%), obesity (18%), hyperlipidemia 913%, and postmenopause (11%). The percentage of subjects with concurrent medical conditions was similar among treatment groups for most SOC.

Most subjects (99-100%) in each treatment group took concomitant medications. The medications used were similar to those described in the studies above and did not differ significantly between treatment groups.

9) OLE-012: Approximately half of the subjects were male. The majority (72%) were white. The mean age was 55.6 years, BMI 32 kg/m², and duration of diabetes 8 years.

SYR-322-OLE-012. Demographic and baseline characteristics (Randomized set) (n, %)					
	Open label treatment group				
	Completed P3		Rescued from P3	Total	Overall
	Alogliptin 12.5 (n=680)	Alogliptin 25 (n=682)	Alogliptin 25 (n=387)	Alogliptin 25 (n=1069)	(n=1749)
Male	376 (55)	345 (51)	177 (46)	522 (49)	898 (51)
Mean age (y)	56.9 (10.0)	55.7 (10.3)	52.9 (10.3)	54.7 (10.4)	55.6 (10.3)
White	494 (73)	487 (71)	283 (73)	770 (72)	1264 (72)
BMI (kg/m ²)	31.7 (5.5)	31.9 (5.3)	32.9 (5.7)	32.3 (5.5)	32.0 (5.5)
Diabetes duration (y)	7.6 (5.9)	7.9 (6.1)	8.8 (6.6)	8.2 (6.3)	8.0 (6.2)
Previous double blind study treatment					
Placebo	118 (17)	110 (16)	135 (35)	245 (23)	363 (21)
12.5 alogliptin	274 (40)	261 (38)	105 (27)	366 (34)	640 (37)
25 alogliptin	241 (35)	261 (38)	99 (26)	360 (34)	601 (34)
Unknown*	241 (35)	261 (38)	99 (26)	360 (34)	601 (34)
*Blinded studies still ongoing; randomized treatment unknown for studies 01-05-TL322OPI-001 and 01-06-TL-322OPI-002					

Because patients in OLE-012 come from the core phase 3 studies, the most common concurrent medical conditions and concurrent medications were similar to those described in the studies above and did not differ significantly between treatment groups. The medication history was not collected in this extension study, as it was collected in each of the double blind studies. Six of the 9 controlled studies required subjects to be on a background antidiabetic agent prior to enrollment.

NDA22-271. Alogliptin studies and required background antidiabetic agent	
Study	Required background antidiabetic agent
SYR-322-003	N/A
SYR-322-SULF-007	Glyburide
SYR-322-MET-008	Metformin
SYR-322-TZD-009	Pioglitazone alone or in combination with metformin or sulfonylurea
SYR-322-PLC-010	N/A
SYR-322-INS-011	Insulin alone or in combination with metformin
01-06-TL-322OPI-002	Pioglitazone
01-05-TL-322OPI-001	Pioglitazone and metformin
SYR-322-OLE-012	N/A

6.1.3 Patient Disposition

Across controlled phase 2/3 studies, the percentage of subjects who completed the study was higher in the all alogliptin group (75.3%) than the placebo group (59.6%). This difference was mainly due to the higher percentage of placebo subjects who withdrew due to hyperglycemic rescue (29.4% placebo; 12.4% alogliptin). The percentage of subjects who completed a study or withdrew due to hyperglycemic rescue was similar in the alogliptin 12.5 and 25 mg groups.

The percentage of subjects who withdrew from a study for reasons other than hyperglycemic rescue was similar in the alogliptin and placebo groups (12.1% and 11.0%, respectively). However, the percentage of subjects who voluntarily withdrew was higher in the all alogliptin than placebo group (4.4% vs. 1.9%), and the percentage of subjects who withdrew due to investigator discretion was higher in the placebo group than the all alogliptin group (4.1% vs. 1.6%). The percentage of subjects who withdrew due to AEs was similar in the placebo, all alogliptin, and alogliptin 12.5 and 25 mg groups (2.1-2.8%).

1) SYR-322-003: Hyperglycemic rescue was approximately 3x more common in the placebo group (49%) as opposed to the SYR-322 groups (11-18%). The high rate of rescue limits our confidence in the HbA1c results due to the frequency of imputation for missing values.

At least 95% of the randomized patients were included in the FAS and safety populations, but only 42-73% of patients completed the trial. The frequency of discontinuation (excluding patients requiring glycemic rescue therapy) ranged from 9-23% in the various treatment groups. Withdrawal due to an adverse event occurred in only 2% of patients, all of whom were receiving ≥ 25 mg without convincing evidence of a dose-response relationship. However, subjects were more likely to voluntarily withdraw in the lower dose groups (i.e. placebo, and SYR-322 6.25, 12.5, and 25 mg). Withdrawal due to a protocol violation occurred equally in all treatment groups (n=1).

Subject 226/2004 was advised to stop 50 mg SYR-322 and resume antidiabetic medication when she telephoned to say that her blood glucose was elevated. When she came in for the final visit procedures, it was determined that she had not met rescue criteria. However, because she had already discontinued SYR-322, early discontinuation procedures were continued and the reason listed as “other” and she was not included in the per protocol (PP) dataset.

SYR-322-003. Disposition of randomized subjects (N, %)							
	Placebo (n=43)	SYR-322 Dose (mg)					
		6.25 (n=44)	12.5 (n=44)	25 (n=45)	50 (n=44)	100 (n=45)	Total (n=265)
Subject sample							
All randomized	43 (100)	44 (100)	45 (100)	44 (100)	44 (100)	45 (100)	265 (100)
Safety sample	41 (95)	42 (95)	44 (100)	45 (100)	43 (98)	44 (98)	259 (98)
ITT Sample	41 (95)	42 (96)	42 (96)	45 (100)	43 (98)	44 (98)	257 (97)
Per Protocol Sample	39 (91)	32 (73)	36 (82)	37 (82)	35 (80)	37 (82)	216 (82)
Completed	18 (42)	27 (61)	32 (73)	32 (71)	27 (61)	31 (69)	167 (63)
Hyperglycemic rescue	21 (49)	7 (16)	5 (11)	8 (18)	8 (18)	7 (16)	56 (21)
Discontinued	4 (9)	10 (23)	7 (16)	5 (11)	9 (21)	7 (16)	42 (16)
Primary reason for discontinuation							
Adverse event	0	0	0	1 (2)	3 (7)	2 (4)	6 (2)
Protocol violation	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	6 (2)
Lost to follow up	0	2 (5)	1 (2)	0	4 (9)	2 (4)	9 (3)
Voluntarily withdrew	2 (5)	3 (7)	5 (11)	2 (4)	0	1 (2)	13 (5)
Physician decision	1 (2)	3 (7)	0	1 (2)	0	1 (2)	6 (2)
Other	0	1 (2)	0	0	1 (2)	0	2 (0.8)

2) SULF-007: The geographic distribution of subjects was similar between treatment groups (Mexico, Central/South America 43%; Western Europe, Australia, New Zealand 6%; United States 27%; Rest of the world 24%). A higher percentage of alogliptin than placebo subjects completed the trial (75% vs. 63%). A significant percentage of patients required hyperglycemic rescue (28% placebo vs. 15% alogliptin). A similar percentage of placebo and alogliptin subjects discontinued from the trial, excluding those patients requiring glycemic rescue (9%).

The reasons for discontinuation were similarly distributed between the 3 treatment groups. The most common reason for discontinuation was voluntary withdrawal. The reasons for voluntary withdrawal were as follows:

- Placebo: transportation issues and not in his/her best interest (1), personal reasons (1), inadequate glycemic control (1)
- 12.5 mg alogliptin: moving (2), withdrawal of consent (2), inadequate glycemic control (1), personal reasons (1), travel (1), job commitments (1)
- 25 mg alogliptin: moving (3), withdrawal of consent (2), work schedule prohibited attendance (1), not in his/her best interest (1), withdrawal of consent (1), personal reasons (1), travel (1), glycemic control (1)

Clinical Review
Valerie S. W. Pratt, M.D.
NDA 21-271/S-000
Alogliptin (Nesina) 6.25, 12.5 or 25 mg daily

COMMENT: The use of HbA1c for hyperglycemic rescue from weeks 12 – 26 resulted in an unusually high level of rescue after week 12. The high rate of discontinuation limits our confidence in the HbA1c results, due to the imputation of missing value.

Furthermore, the insulin add-on study INS-011 was different from the 4 other studies in the larger percentage of subjects in each arm who were rescued or discontinued (58% placebo, 37% alogliptin 12.5 mg, 40% alogliptin 25 mg). The large percentage of subjects who were rescued or discontinued makes it difficult to ascertain the effect of alogliptin as an add-on to insulin.

Protocol deviations included 4 alogliptin subjects (12.5 mg group 3; 25 mg group 1). The deviations included 1 subject each who took excluded metformin, had inadequate study drug consumption, received concomitant systemic steroids, and was provided with an incorrect bottle of medication at week 16.

Treatment compliance was defined as the total number of tablets taken, divided by the total number of days in the treatment period, expressed as a percentage. Mean compliance during the treatment period for the prescribed study drug was 98.8%. One subject was misallocated drug. Subject 319/7008 was randomized to the 12.5 mg group but received placebo for 8 days beginning at week 16. According to the sponsor, this subject was not listed as having experienced a major protocol violation as the error was brief and the correct study drug was received for the majority of the treatment period.

NOTE: The subject described above met criteria for a category 2 major protocol violation (medication violation during the study; subject who received treatment different from randomized treatment) and should have been classified as such. This finding in an isolated patient is not expected to affect study conclusions.

3) MET-008: Only 3 randomized subjects (306/8001, 320/8001, and 427/8004 in the alogliptin 25 mg group) did not receive study drug. The treatment group with the highest percentage of completers was the alogliptin 12.5 mg group (83%), followed by the alogliptin 25 mg (79%) and placebo (69%) groups. Significantly more subjects in the placebo group required hyperglycemic rescue when compared to the alogliptin groups (24% vs. 8.5%).

Alogliptin subjects were slightly more likely to withdraw due to AEs than placebo subjects (3% vs. 1%). The most common reason for discontinuation was voluntary withdrawal, which occurred most often in the alogliptin 25 mg group. Reasons for voluntary withdrawal were as follows:

- Placebo: high blood sugar (1) and no longer willing to participate (1)
- 12.5 mg alogliptin: no longer willing to participate (2)
- 25 mg alogliptin: personal (2), no longer willing to participate (6), work related (3), relocation (1), not willing to wait for control (1), and unknown (1)

Protocol deviations included 2 subjects each who took excluded medications or did not have retests of their laboratory values, and 1 subject each who was given the wrong study drug bottle, went more than 7 days without study drug, did not meet the BMI criterion, or violated another inclusion/exclusion criterion.

Mean compliance during the treatment period was 99%. Three subjects briefly received incorrect study drug. Subject 329/8001 took placebo, instead of 12.5 mg alogliptin, for 10 days at week 20. Subject 429/8012 took placebo for 10 days, instead of 12.5 mg alogliptin, at the start of the study. Subject 395/8026 took 12.5 mg, instead of 25 mg, for 7 days at week 4. According to the sponsor, these events were not considered major protocol violations due to the brief duration of misdosing.

NOTE: The 3 subjects described above met criteria for a category 2 major protocol violation (medication violation during the study; subject who received treatment different from randomized treatment) and should have been classified as such. This finding in 3 isolated patients is not expected to affect study conclusions.

4) TZD-009: Patient disposition: Six hundred subjects were enrolled. A total of 493 subjects were randomized. Reasons for randomization failure of 107 subjects included inclusion criteria not met (43), voluntary withdrawal (28), major protocol deviations (16), lost to follow up (6), investigator discretion (4), adverse event (2), and other reasons (8). The other reasons included 6 subjects who did not meet inclusion criteria and 2 subjects for which there were errors with the interactive voice response system (IVRS).

The majority of subjects were randomized in the United States (67%). The majority of randomized subjects completed the study (78%), although the most common reasons for discontinuation were voluntary withdrawal (4%) and AE (3%). Hyperglycemic rescue was slightly more common in the placebo group when compared to alogliptin (12% vs. 9.5%). A similar percentage of subjects in each group were discontinued for reasons other than hyperglycemia (~12%).

Reasons for voluntary withdrawal included the following:

- Placebo: high blood glucose (2)
- 12.5 mg alogliptin: personal (2), high blood glucose (1), scheduling conflict (1), began insulin therapy (1), out of town for an extended period (4), perceived lack of efficacy (1)
- 25 mg alogliptin: personal (2), high blood glucose (1), out of town for an extended period (2), perceived lack of efficacy (1), no longer willing to participate (2), relocation (1)

Four of 493 (0.8%) subjects were discontinued due to a protocol deviation (placebo group 1; 12.5 mg group 1; 25 mg group 2). Deviations included 2 subjects with changes in their metformin dose during the stabilization period, 1 subject who received a prohibited medication, and 1 subject who stopped her add-on SFU. These findings in 4 isolated patients are not expected to affect study conclusions.

5) PLC-010: A total of 420 subjects enrolled in study PLC-010. A total of 91 subjects were not randomized. More than half of those not randomized (49/91) failed at least 1 of the following inclusion criteria: HbA1c or FPG at specified values at week -1, appropriate compliance with single blind placebo, or in appropriate use of glucocorticoids or weight loss drugs.

Of the subjects that were randomized, 52% were from the United States. A greater percentage of the alogliptin subjects (80.5%) completed study PLC-010 than on placebo (62%). This was in part due to the difference in hyperglycemic rescue between treatment groups (placebo 29% vs. alogliptin 9%). Among those subjects who were discontinued for reasons other than hyperglycemia, voluntary withdrawal was the most common reason; it occurred more frequently in the alogliptin groups (6% vs. 0%) when compared to placebo. Reasons for voluntary withdrawal included the following:

- 12.5 mg alogliptin: personal problems (3), travel/work schedule issues (2), left the country (1), diabetes not controlled and could not attend study visits due to job commitments (1), and subject not satisfied with blood glucose results (1)
- 25 mg alogliptin: withdrawal of consent (3), conflict with work (1), could not attend clinic visits (1), subject was not satisfied with blood glucose and HbA1c values (1), and personal reasons (1)

Withdrawal due to investigator discretion occurred more commonly in the placebo group (5% vs. 1%). AEs, loss to follow up, major protocol deviations, and other reasons for discontinuation occurred in a similar percentage of subjects in each treatment group. Protocol deviations included 1 subject randomized to placebo who did not meet inclusion criteria and one 12.5 mg alogliptin subject who began an oral hypoglycemic drug during the study.

6) INS-011: Patient disposition: A total of 477 subjects were enrolled in INS-011. Of these, 390 subjects were randomized. The most common reasons for randomization failure included additional inclusion criteria not met (30/87, 34%), voluntary withdrawal (17/87, 20%), loss to follow up (14/87, 16%), and major protocol deviations (11/87, 13%).

The 390 randomized subjects were distributed amongst the geographic regions as follows: United States (37%); Mexico and Central/South America (27%); Western Europe, Australia, and New Zealand (9%); and the rest of the world (26%). Only 55% of subjects completed the study. Although the percentage of subjects who discontinued

from the study was similar between groups (~18%), placebo subjects were more likely than alogliptin subjects to receive hyperglycemic rescue (40% vs. 20%). The primary reasons for study discontinuation were similar between treatment groups and are listed below.

The reasons for voluntary withdrawal included the following:

- Placebo: no longer willing to participate (2), out of town for extended period (1)
- 12.5 mg alogliptin: cannot attend appointment (1), work related (1)
- 25 mg alogliptin: personal (1), no longer willing to participate (2), lack of efficacy (1), wishes to participate in another study (1), withdrew consent (1)

Drug misallocation occurred with 1 subject. Subject 395/5017 was randomized to 12.5 mg alogliptin but received placebo at day 1; it was taken for 5 days. This event was not considered a major protocol deviation. Overall, 12 subjects were discontinued due to protocol deviations. Deviations included 8 subjects with substantial insulin dose changes and 1 subject each who was unable to come in for study visits, given the wrong study drug, received another antidiabetic drug, or went 15 days without study drug.

7) OPI-002: A total of 887 subjects were enrolled. Of these, 655 were randomized, and 232 were not. The most common reasons for randomization failure included inclusion criteria not met (82, 35%), other (63, 27%), voluntary withdrawal (41, 18%), major protocol deviation (9%), and lost to follow up (12, 5%). The majority of subjects not randomized for “other” reasons were due to closure of enrollment.

The majority of randomized subjects completed the study (79%). More subjects on A25 required hyperglycemic rescue than those on P30, A12.5+P30, or A25+P30 (11% vs. 6%, 4%, and 2%, respectively). The reasons for discontinuation other than hyperglycemia were similar between treatment groups and are listed below. The primary explanation for the 28 subjects who discontinued for voluntary withdrawal was “personal reasons”. Most of the subjects removed due to investigator discretion were due to meeting some but not all of the rescue criteria.

01-06-TL-322OPI-002. Subject disposition (Randomized set) (n, %)					
Disposition	A25 (n=164)	P30 (n=163)	A12.5+P30 (n=164)	A25+P30 (n=164)	Overall (n=655)
Randomized set	164	163	164	164	655
Safety set	164 (100)	163 (100)	163 (99)	164 (100)	654 (100)
Full analysis set	164 (100)	163 (100)	163 (99)	164 (100)	654 (100)
Per Protocol set	154 (94)	143 (88)	142 (87)	149 (91)	588 (90)
Completed	126 (77)	126 (77)	126 (77)	136 (83)	514 (79)
Hyperglycemic rescue	18 (11)	10 (6)	6 (3.7)	4 (2.4)	38 (5.8)
Discontinued	20 (12)	27 (17)	32 (20)	24 (15)	103 (16)
Primary reasons for discontinuation					
Voluntary withdrawal	6 (4)	5 (3)	12 (7)	5 (3)	28 (4.3)
Adverse event	3 (2)	8 (5)	6 (4)	6 (4)	23 (4)
Major protocol deviation	2 (1)	3 (2)	7 (4)	6 (4)	18 (3)
Lost to follow up	2 (1)	6 (4)	5 (3)	5 (3)	18 (3)
Investigator discretion	6 (4)	4 (3)	2 (1)	2 (1)	14 (2)
Other	1 (1)	1 (1)	0	0	2 (0.3)

Drug misallocations occurred with 3 subjects. Subjects 625/2509 and 625/2513 were randomized to receive A25+P30 and A12.5+P30, respectively. However, their assigned study drugs were switched leading them to receive the incorrect medication for 27 days. Subject 920/2502 was randomized to A12.5+P30 but received A25+P30 at week 12. These events were not considered major protocol deviations. However, according to appendix 16.2.2.3 which defines the deviations, they should have been classified as “subject who received treatment different from randomized treatment.”

Overall, 18 subjects were discontinued due to protocol deviations. Deviations included 3 subjects who received misallocations of study drug, 2 subjects who received a misallocated bottle but correct drug, 5 subjects who violated inclusion/exclusion criteria, 4 subjects who were noncompliant, 2 subjects who took excluded medications, 1 subject who was incorrectly randomized, and 1 subject who did not fully disclose medical history.

8) OPI-001: A total of 1948 subjects were enrolled at 327 sites in 20 countries, including 7 subjects who were first titrated according to schedule B. Of these, 1554 were randomized. The majority (63%) of subjects who failed randomization did so as a result of not meeting additional inclusion criteria. Additional reasons for failure to randomize subjects were voluntary withdrawal, major protocol deviation, loss to follow up, investigator discretion, or AE. Thirty subjects were not randomized due to other reasons; the majority of these were not randomized due to laboratory values out of range at screening. Of the 1554 randomized subjects, 1232 completed the study.

The 3 subjects enrolled and randomized at site 144 were excluded from all analyses due to significant GCP issues and are not included in the tallies of enrolled and randomized subjects.

Only 54% of placebo-treated patients completed the trial, compared to 72-78% of patients treated with alogliptin or pioglitazone, and 85-89% of patients treated with alogliptin in combination with pioglitazone. These differences in completion rates were predominantly driven by differences in the rates of discontinuation due to hyperglycemia, which was most common in the placebo group (32%). Subjects receiving A+P combination therapy were less likely to require hyperglycemic rescue than subjects taking either alogliptin or pioglitazone alone.

The percentage of subjects who discontinued from the study for reasons other than hyperglycemia ranged from 7-19%. The pioglitazone groups (12, 30, and 45 mg) experienced higher rates of discontinuation (12-19%) than the alogliptin groups (9-10%). The 12.5 mg alogliptin with pioglitazone groups experienced the lowest rates of discontinuation (6-12%). Reasons for discontinuation were similar between treatment groups and included voluntary withdrawal, major protocol deviation, AE, lost to follow up, investigator discretion, and pregnancy. Of the 53 subjects who voluntarily withdrew, most did so for personal reasons.

A total of 46 (3%) subjects were discontinued due to protocol deviations. These included 10 subjects who received misallocated study drug, 10 subjects who violated inclusion/exclusion criteria, 18 subjects who were noncompliant with study drug, 1 subject who was noncompliant with study visits, 2 subjects who took excluded medications, and 5 subjects with visits outside the specified window.

01-05-TL-322OPI-001. Subject disposition (Randomized set) (%)													
	Placebo (n=129)	Alo		Pio			A12.5+P			A25+P			Total (n=1554)
		A12.5 (n=128)	A25 (n=129)	P15 (n=130)	P30 (n=129)	P45 (n=129)	A12.5+P15 (n=130)	A12.5+P30 (n=130)	A12.5+P45 (n=130)	A25+P15 (n=130)	A25+P30 (n=130)	A25+P45 (n=130)	
Safety	100	100	100	99	100	100	100	100	100	100	100	100	100
Full analysis	100	100	100	99	100	100	100	100	100	100	100	100	100
Per protocol	93	88	91	90	89	88	95	95	90	92	92	92	91
Completed	54	76	78	72	73	75	89	89	86	85	87	88	79
Hyperglycemic	32	14	12	10	15	9	5	5	2	4	5	2	9
Discontinued	14	10	9	19	12	16	7	6	12	12	9	11	11
Primary reason for discontinuation													
Voluntary withdrawal	4	3	4	5	3	4	2	3	2	4	3	5	3
Major protocol deviation	2	2	2	6	5	3	4	2	5	4	1	2	3
Adverse event	2	1	2	2	1	5	1	2	4	2	0	3	2
Lost to follow up	3	2	2	3	2	2	0	0	0	2	2	1	2
Investigator discretion	3	2	1	2	1	2	1	0	1	1	2	0	1
Pregnancy	0	1	0	0	0	0	0	0	0	0	0	0	0.1
Other	0	0	0	1	1	1	0	0	1	0	0	0	0.3

01-05-TL-322OPI-001. Demographic and baseline characteristics (Randomized set) (%)													
	Placebo (n=129)	Alo		Pio			A12.5+P			A25+P			Total (n=1554)
		A12.5 (n=128)	A25 (n=129)	P15 (n=130)	P30 (n=129)	P45 (n=129)	A12.5+P15 (n=130)	A12.5+P30 (n=130)	A12.5+P45 (n=130)	A25+P15 (n=130)	A25+P30 (n=130)	A25+P45 (n=130)	
Male	47	52	39	47	49	41	46	42	46	47	42	40	45
Mean age (y)	55	53	54	54	56	55	54	55	54	55	54	54	54
White	72	70	62	65	74	66	73	82	71	74	65	72	71
BMI (kg/m ²)	31	31	31	31	31	31	32	31	32	31	32	31	31
Diabetes	6	6	6	6	8	6	6	6	7	7	7	6	6
Duration (y)													
Metformin(mg)	1937	1902	1851	1893	1854	1919	1910	1822	1920	1880	1867	1885	1887

9) OLE-012: A total of 1749 subjects were enrolled in the open label extension study at the time of interim analysis. Data for all but 27 (total 1722) were included in the safety set. These 27 subjects were not included because their study drug dosing page was missing from the interim database due to the timing of the lock (August 29, 2007). Two additional subjects (504/5008 and 558/9002) had limited data included in the interim analysis database but were not included in the tables or listings. The sponsor intends to correct this issue in the final database and report. Two additional subjects (392/5019 and 395/5012) were randomized to 25 mg alogliptin, but as those tablets were unavailable at the site, the subjects took 2 12.5 mg tablets for their 25 mg dose. As a result, these subjects were included in the 12.5 mg alogliptin completed group for the interim analysis, although this will be corrected in the final report.

Approximately 8% of subjects discontinued from the study. The percentage of discontinued subjects was greatest in the alogliptin 25 mg rescued group. The most common reason for discontinuation was voluntary withdrawal. Of the 49 subjects who voluntarily withdrew, the reasons were as follows (n=1 except where indicated):

- 12.5 mg alogliptin completed: AE, personal (3), surgery, high blood glucose, perceived lack of efficacy (2), unable to make it to scheduled appointments (5)
- 25 mg alogliptin completed; AE, personal (2), physician recommended (3), moved (4), wanted a prohibited/new medication (2), scheduling conflict, no reason given, withdrew consent
- 25 mg alogliptin rescued: personal (2), moved (3), perceived lack of efficacy (7), no reason given, never showed up for appointment, unable to make it to schedule appointments (3), financial reasons, has health insurance now, became angry and stopped taking drug, wanted new mediation

COMMENT: Subject 452-5001 was discontinued for “lack of efficacy.” However, the narrative (see section 7.3.2 Nonfatal SAEs) does not describe hyperglycemia and the discontinuation occurred 3 days after coronary artery stenosis, which is the more likely cause of subject discontinuation.

Although subject 440/9005 was discharged from the study due to the “length of time off study medication”, it must be noted that a myocardial infarction led to his discontinuing study medication.

SYR-322-OLE-012. Subject disposition (Randomized set) (n, %)					
	Open label treatment group				
	Completed P3		Rescued from P3	Total	Overall
	Alogliptin 12.5 (n=680)	Alogliptin 25 (n=682)	Alogliptin 25 (n=387)	Alogliptin 25 (n=1069)	(n=1749)
Enrolled set	680 (100)	682 (100)	387 (100)	1069 (100)	1749 (100)
Safety set	669 (98)	668 (98)	385 (99.5)	1053 (99)	1722 (99)
Completed	0	0	0	0	0
Discontinued	32 (5)	34 (5)	71 (18)	105 (10)	137 (8)
Primary reason for discontinuation					
AE	6 (1)	8 (1)	11 (3)	19 (2)	25 (1)
Major protocol deviation	0	1 (0.1)	1 (0.3)	2 (0.2)	2 (0.1)
Lost to follow up	1 (0.1)	1 (0.1)	9 (2)	10 (1)	11 (1)
Voluntary withdrawal	13 (2)	15 (2)	21 (5)	36 (3)	49 (3)
Pregnancy	1 (0.1)	0	1 (0.3)	1 (0.1)	2 (0.1)
Lack of Efficacy	5 (1)	5 (1)	20 (5)	25 (2)	30 (2)
Investigator discretion	1 (0.1)	1 (0.1)	6 (2)	7 (1)	8 (1)
Other	5 (1)	3 (0.4)	2 (1)	5 (1)	10 (1)

Two subjects were discontinued from the study due to protocol deviations; 1 each from the 25 mg alogliptin completed and rescued groups. The deviations were inclusion creatinine level exceeded and noncompliance, respectively.

6.1.4 Analysis of Primary Endpoint

The primary efficacy variable for all key studies was the change in HbA_{1c} at study endpoint (after 26 weeks of treatment) compared to baseline. HbA_{1c} is an appropriate endpoint for the following reasons:

- HbA_{1c} is a widely-accepted, objective, surrogate measure of glycemic control that correlates well with mean blood glucose over the preceding 1-3 months (Nathan DM 1984).
- The National Glycohemoglobin Standardization Program (NGSP) has established and promulgated standardized assays for HbA_{1c} based on data from the Diabetes Control and Complications Trial (DCCT). Use of standardized methodology has reduced inter-laboratory coefficients of variation to <5% (College of American Pathologists 1999; Goldstein 1982).
- HbA_{1c} has excellent reliability, predicts several diabetes-specific complications, and provides the current basis for treatment decisions (American Diabetes Association 2006).
- Lowering HbA_{1c} reduces microvascular complications in patients with type 1 and type 2 diabetes (Diabetes Control and Complications Trial Research Group 1993, UK Prospective Diabetes Study (UKPDS) Group 1998). There is weaker evidence showing that lowering HbA_{1c} reduces macrovascular complications in patients with type 1 diabetes (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group 2005).

The mean baseline HbA_{1c} ranged from 7.9-8.2% in all phase 3 trials except for the insulin trial which had a mean baseline HbA_{1c} of 9.3%. In the 5 controlled, pivotal phase 3 trials of alogliptin, both the 12.5 and 25 mg doses achieved statistically significant LS mean reductions in HbA_{1c} reductions from baseline to week 26 compared to placebo, regardless of the add-on therapy. The net effect of alogliptin 25 mg ranged from an average improvement of 0.4 - 0.6% across the 5 studies. In all but the MET-008 trial, the LS mean difference was slightly greater in the 25 mg group compared to the 12.5 mg group. However, according to Dr. Janice Derr's statistics review, the net effect of the alogliptin 12.5 and 25 mg doses were very similar and not statistically separable, although this was not an objective of the studies.

NDA 22-271. Summary of change from baseline in HbA_{1c} (FAS set)						
Study	N	Baseline HbA_{1c} (%) mean (SD)	Change in HbA_{1c} (%) LS mean (SE)	LS mean difference (SE)	95% CI for the LS mean difference	p-value
SULF-007						
Alo 25	197	8.09 (0.90)	-0.52 (0.06)	-0.53	-0.73, -0.33	< 0.001
Alo 12.5	201	8.08 (0.83)	-0.38 (0.06)	-0.39	-0.59, -0.19	< 0.001
Placebo	97	8.15 (0.85)	0.01 (0.08)			
MET-008						
Alo 25	203	7.93 (0.80)	-0.59 (0.05)	-0.48	-0.67, -0.30	< 0.001
Alo 12.5	210	7.89 (0.74)	-0.61 (0.05)	-0.50	-0.68, -0.32	< 0.001
Placebo	103	8.01 (0.87)	-0.10 (0.08)			

TZD-009						
Alo 25	195	8.01 (0.84)	-0.80 (0.06)	-0.61	-0.80, -0.41	< 0.001
Alo 12.5	196	8.08 (0.91)	-0.66 (0.06)	-0.47	-0.67, -0.28	< 0.001
Placebo	95	7.97 (0.82)	-0.19 (0.08)			
PLC-010						
Alo 25	128	7.91 (0.79)	-0.59 (0.07)	-0.57	-0.80, -0.35	< 0.001
Alo 12.5	131	7.91 (0.81)	-0.56 (0.07)	-0.54	-0.76, -0.31	< 0.001
Placebo	63	8.03 (0.91)	-0.02 (0.09)			
INS-011						
Alo 25	126	9.27 (1.13)	-0.71 (0.08)	-0.59	-0.80, -0.37	< 0.001
Alo 12.5	130	9.29 (1.06)	-0.63 (0.08)	-0.51	-0.72, -0.30	< 0.001
Placebo	126	9.28 (1.13)	-0.13 (0.08)			

According to the statistics reviewer, the per protocol population results were very similar to the FAS population results. The results from analyzing subjects who did not complete the study because they were discontinued or rescued were generally supportive, although the small number of subjects in this subgroup meant that the 95% CI of the placebo-adjusted effect of alogliptin included 0 in several comparisons. Estimates of the placebo-adjusted effect of alogliptin from the 2 subsets of completers and noncompleters are influenced by the differential rescue rate in the alogliptin and placebo arms, complicating data interpretation.

Compared to the placebo group, both the 12.5 and 25 mg alogliptin groups achieved statistically significant mean LS mean decreases from baseline HbA1c at every time point ($p < 0.001$). This effect occurred as early as week 4 and continued through the 26 week treatment period. The effect of alogliptin is established by week 12, after which the placebo-adjusted effect of alogliptin remained relatively constant, even though the average change from baseline decreased from week 12 – 26 in the alogliptin and placebo arms. This decrease may result from the progression of diabetes over time. However, the apparent stabilization at week 12 may also result from changes in disposition. In 4 of 5 studies, a substantial proportion of rescues/discontinuations took place from weeks 12 – 16 due to a change in the rescue criteria from FPG to HbA1c.

Please also refer to Dr. Janice Derr's statistical review.

6.1.5 Analysis of Secondary Endpoints

The major secondary efficacy parameters were the percentage of alogliptin-treated subjects achieving HbA1c < 6.5% and < 7%, FPG, and body weight.

The percentage of subjects who achieved HbA1c levels $\leq 6.5\%$ and $\leq 7.0\%$ were also assessed. In all 5 pivotal phase 3 studies, a numerically higher percentage of subjects in both alogliptin groups achieved HbA1c levels $\leq 6.5\%$ and $\leq 7.0\%$ at week 26 compared to placebo. All study groups, except the SULF-007 alogliptin 12.5 mg and INS-011 25 mg groups, had a statistically significant number of alogliptin subjects who achieved HbA1c $\leq 7.0\%$ ($p < 0.05$) compared to placebo. Only the MET-008 and TZD-009 studies had a statistically significant number of alogliptin subjects who achieved HbA1c levels $\leq 6.5\%$ ($p < 0.05$). Of note, these statistical

comparisons should be considered exploratory because there is no control of the type 1 error rate and several of the p-values are nominally significant.

NDA 22-271. Number (%) of subjects who achieved HbA1c levels $\leq 6.5\%$ and $\leq 7.0\%$ at week 26 in the pivotal phase 3 studies					
Study	N	HbA1c $\leq 6.5\%$		HbA1c $\leq 7.0\%$	
		# subjects (%)	p-value	# subjects (%)	p-value
SULF-007					
Alo 25	198	28 (14.1)	0.174	69 (34.8)	0.002
Alo 12.5	203	19 (9.4)	0.762	60 (29.6)	0.057
Placebo	99	7 (7.1)	-	18 (18.2)	-
MET-008					
Alo 25	207	36 (17.4)	0.013	92 (44.4)	< 0.001
Alo 12.5	213	42 (19.7)	0.037	110 (51.6)	< 0.001
Placebo	104	4 (3.8)	-	19 (18.3)	-
TZD-009					
Alo 25	199	41 (20.6)	0.005	98 (49.2)	0.004
Alo 12.5	197	34 (17.3)	0.002	87 (44.2)	0.016
Placebo	97	5 (5.2)	-	33 (34.0)	-
PLC-010					
Alo 25	131	27 (20.6)	0.294	58 (44.3)	0.008
Alo 12.5	133	23 (17.3)	0.818	63 (47.4)	0.001
Placebo	64	7 (10.9)	-	15 (23.4)	-
INS-011					
Alo 25	129	3 (2.3)	0.637	10 (7.8)	0.227
Alo 12.5	131	3 (2.3)	0.448	11 (8.4)	0.048
Placebo	129	0	-	1 (0.8)	-

The change from baseline in FPG also supports the efficacy of alogliptin. The LS mean decreases observed in alogliptin-treated subjects were statistically significant compared with the placebo group in studies MET-008, TZD-009, PLC-010, and INS-011 (alogliptin 25 mg dose group only in INS-011). In SULF-007, both alogliptin 12.5 and 25 mg groups had LS mean decreases from baseline in FPG values compared with placebo. However, the differences between alogliptin and placebo-treated subjects were not statistically significant. No difference was observed between the alogliptin 12.5 mg dose group and placebo in study INS-011.

NDA 22-271. Summary of change from baseline in FPG (FAS set)					
Study	N	Baseline FPG mean (SD)	Change in FPG LS mean (SE)	LS mean difference	p-value
SULF-007					
Alo 25	198	173.9 (48.8)	-8.4 (3.4)	-10.5	0.072
Alo 12.5	203	171.9 (50.6)	-4.7 (3.3)	-6.8	0.241
Placebo	99	177.3 (52.2)	2.2 (4.8)	-	-
MET-008					
Alo 25	207	171.9 (45.7)	-17.4 (2.5)	-17.4	<0.001
Alo 12.5	213	168.3 (44.0)	-18.7 (2.5)	-18.7	<0.001
Placebo	104	179.5 (50.3)	0.0 (3.6)	-	-
TZD-009					

Alo 25	199	169.5 (46.0)	-19.1 (2.7)	-14.1	0.003
Alo 12.5	197	173.4 (46.9)	-19.7 (2.7)	-13.9	0.003
Placebo	97	171.7 (51.6)	-5.7 (3.8)	-	-
PLC-010					
Alo 25	129	172.0 (42.1)	-16.4 (3.7)	-27.8	<0.001
Alo 12.5	132	173.5 (50.1)	-10.3 (3.6)	-21.6	<0.001
Placebo	64	173.4 (51.9)	11.3 (5.2)	-	-
INS-011					
Alo 25	128	186.3 (70.5)	-11.7 (5.7)	-17.6	0.030
Alo 12.5	131	189.8 (61.9)	2.3 (5.6)	-3.5	0.662
Placebo	127	196.0 (77.5)	5.8 (5.7)	-	-

No consistent effect on the change from baseline in weight at week 26 was seen in the 5 pivotal studies. Only 1 of the 5 studies, SULF-007, showed a statistically significant effect on the change in weight with alogliptin relative to placebo. In SULF-007, subjects in both the alogliptin 12.5 and 25 mg groups gained approximately 0.8 kg (1.76 pounds) when compared to placebo. The nonstatistically significant mean findings in the other 4 studies were as follows:

- MET-008: Alogliptin 12.5 mg subjects lost approximately 0.4 kg, which was the same as the placebo group; whereas alogliptin 25 mg subjects lost an additional 0.3 kg relative to placebo.
- TZD-009: Alogliptin 25 mg was weight neutral when compared to placebo; whereas alogliptin 12.5 mg resulted in a 0.4 kg gain compared to placebo.
- PLC-010: Both the alogliptin 12.5 and 25 mg groups lost weight when compared to placebo (-0.3 and -0.4 kg, respectively).
- INS-011: Both alogliptin 12.5 and 25 mg groups were relatively weight neutral when compared to placebo.

NDA 22-271. Change from baseline in weight (kg) at week 26 for pivotal phase 3 studies (LOCF)					
Study	N	Baseline weight mean (SD)	Change in weight LS mean (SE)	LS mean difference	p-value
SULF-007					
Alo 25	198	80.44 (18.87)	0.68 (0.19)	0.88	0.010
Alo 12.5	203	82.00 (17.47)	0.60 (0.19)	0.80	0.018
Placebo	99	80.77 (20.43)	-0.20 (0.28)	-	-
MET-008					
Alo 25	207	88.14 (19.55)	-0.67 (0.20)	-0.28	0.407
Alo 12.5	213	87.70 (18.44)	-0.39 (0.19)	0.00	0.996
Placebo	104	89.25 (20.44)	-0.39 (0.27)	-	-
TZD-009					
Alo 25	199	94.78 (20.02)	1.09 (0.23)	0.05	0.900
Alo 12.5	197	92.68 (20.61)	1.46 (0.23)	0.42	0.294
Placebo	97	95.65 (22.37)	1.04 (0.33)	-	-
PLC-010					
Alo 25	131	88.76 (20.02)	-0.22 (0.26)	-0.40	0.379
Alo 12.5	133	88.19 (20.42)	-0.09 (0.26)	-0.28	0.539
Placebo	64	90.15 (22.07)	0.18 (0.37)	-	-
INS-011					
Alo 25	129	85.75 (18.58)	0.60 (0.24)	-0.02	0.948

Alo 12.5	131	88.23 (19.75)	0.68 (0.24)	0.05	0.874
Placebo	129	91.19 (20.88)	0.63 (0.24)	-	-

6.1.6 Subpopulations

Evaluations of change from baseline in HbA1c were conducted for subgroups defined by gender (male, female), age (< 65 years, ≥ 65 years), race, ethnicity (Hispanic, non-Hispanic), and baseline BMI (< 30 kg/m², ≥ 30 kg/m²). Most subjects were Caucasian in the 5 key studies. Studies MET-008 and INS-011 had a sufficient number of Hispanic subjects to support evaluation. Subjects treated with both alogliptin 12.5 and 25 mg achieved generally consistent mean reductions in HbA1c levels from baseline to week 26 in all subpopulations, although some subgroups have small sample sizes that limit conclusions.

Clinical Review
Valerie S. W. Pratt, M.D.
NDA 21-271/S-000
Alogliptin (Nesina) 6.25, 12.5 or 25 mg daily

NDA 22-271. Mean change from baseline to week 26 in HbA1c (%) by subgroup (LOCF)															
	PLC-010			SULF-007			MET-008			TZD-009			INS-011		
	Plb	12.5	25	Plb	12.5	25	Plb	12.5	25	Plb	12.5	25	Plb	12.5	25
Age (y)															
< 65	-0.03	-0.52	-0.55	-0.03	-0.29	-0.42	-0.10	-0.62	-0.60	-0.22	-0.66	-0.80	-0.08	-0.62	-0.73
≥ 65	-0.11	-0.69	-0.78	-0.01	-0.64	-0.78	-0.22	-0.51	-0.52	0.11	-0.71	-0.78	-0.36	-0.71	-0.68
Gender															
Male	-0.04	-0.65	-0.61	0.01	-0.44	-0.64	-0.15	-0.68	-0.58	-0.09	-0.64	-0.78	-0.13	-0.71	-0.66
Female	-0.05	-0.45	-0.55	-0.05	-0.30	-0.38	-0.09	-0.52	-0.60	-0.28	-0.71	-0.83	-0.12	-0.58	-0.75
Race															
Am native	-	-0.20	-	-	-	-	-0.10	-0.90	-0.30	-2.30	-0.40	-0.40	-	-	-0.90
Asian	-0.18	-0.61	-0.75	0.35	-0.44	-0.25	0.15	-0.76	-1.01	-0.52	-0.98	-0.83	-0.38	-0.41	-1.04
Black	-0.16	-0.34	-0.26	-0.03	-0.48	-0.70	-0.61	-0.60	-0.80	-0.07	-1.00	-1.11	0.11	-0.53	-0.78
Pacific isl	-0.70	-	-	-	-	-	-	-1.20	-	-	-0.80	-	-1.70	-0.70	-
White	0.06	-0.54	-0.57	-0.09	-0.04	-0.47	-0.12	-0.57	-0.48	-0.10	-0.8-	0.77	-0.12	-0.72	-0.63
Other	-0.40	-0.68	-0.72	-0.04	-0.36	-0.96	0.01	-0.68	-0.90	-0.28	-0.69	-0.82	-0.01	-0.50	-0.91
Ethnicity															
Hispanic	-0.53	-0.82	-0.68	-0.24	-0.27	-0.60	-0.17	-0.68	-0.64	-0.13	-0.65	-0.88	-0.22	-0.88	-0.73
Non-Hispanic	0.13	-0.45	-0.55	-0.19	-0.47	-0.42	-0.11	-0.56	-0.56	-0.18	-0.68	-0.78	-0.08	-0.50	-0.72

The change from baseline in HbA1c was also analyzed by baseline HbA1c. Subjects who entered a study in the higher baseline HbA1c stratification level were more likely to receive hyperglycemic rescue, compared to subjects in the lower HbA1c stratification level. Subjects with higher baseline HbA1c generally had greater HbA1c reductions compared to subjects with lower baseline HbA1c values when the alogliptin arms were compared to placebo. This relationship, which was seen in both the alogliptin and placebo groups, has been seen in other diabetic drug clinical trials. Due to the differential rescue rate in the alogliptin and placebo arms and the differential rescue rate in the higher baseline HbA1c stratification level, the statistical reviewer does not recommend reporting estimates from the HbA1c subgroups.

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

DPP-4 inhibition is targeted to > 80% for 24 hours to achieve desirable chronic glucose lowering in T2D. Clinical pharmacology studies 001, 002, and CPH-001, demonstrated that 25 mg alogliptin was the minimum dose required to achieve this goal. (Please also refer to Drs. Sang Chung and Luke Bi's clinical pharmacology review.)

Phase 2 dose ranging study 003 evaluated the HbA1c lowering effects of 6.25, 12.5, 25, 50, and 100 mg alogliptin. All doses, except 6.25 mg, significantly lowered HbA1c. The results of study 003 indicate that 12.5 mg is the minimally effective dose as well as the dose with maximum effect. Based on these results, the 12.5 and 25 mg doses were selected for phase 3 studies.

As described above, in all phase 3 clinical studies, except the MET-008 trial, the LS mean difference was slightly greater in the 25 mg group compared to the 12.5 mg group. However, no dose-effect relationship was observed, suggesting a lack of benefit in starting with 25 mg over 12.5 mg alogliptin for serum HbA1c reduction.

In the phase 3 clinical studies, no titration of alogliptin doses (either 12.5 to 25 mg or 25 mg to 12.5 mg) was done. Subjects experiencing hyperglycemia were rescued from the pivotal phase 3 trials and offered entry into uncontrolled OLE-012. Thus, no data exists to provide clinical recommendations for dosage adjustment beyond the general comment that alogliptin should be titrated in individual patients based on glycemic response.

Please also refer to section 7.4.5 Special Safety Studies for a discussion of the dosing recommendations as they pertain to renally impaired subjects.

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

The secondary objective of uncontrolled study OLE-012 was to evaluate the durability of glycemic control of alogliptin administered alone or in combination with a SULF, metformin, a TZD, or insulin. End of treatment or early termination assessments from controlled phase 3 studies SULF-007, MET-008, TZD-009, PLC-010, INS-011, OPI-001, and OPI-002 served as the screening for OLE-012. Following entry into OLE-012, subjects from all treatment arms

received alogliptin. It was recommended that subjects continue their current add-on therapy, although it was not provided by the sponsor.

Subjects who were rescued from 1 of the 7 controlled phase 3 studies started alogliptin 25 mg daily; whereas subjects who completed 1 of the 7 controlled phase 3 studies were randomized (1:1) to either 12.5 or 25 mg daily. At the time of the interim analysis (November 14, 2007), 1,749 subjects had enrolled into OLE-012. Exposure was as follows:

SYR-322-OLE-012. Total duration of treatment with study drug in the open label treatment group – Safety analysis set of interim report (November 14, 2007)					
	Completed phase 3		Rescued from phase 3	Total	Overall (n=1722)
	Alo 12.5 (n=671)	Alo 25 (n=666)	Alo 25 (n=385)	Alo 25 (n=1051)	
< 4 weeks	671	666	385	1051	1722
≥ 6 months	276	270	262	532	808
≥ 12 months	126	124	109	233	349
≥ 18 months	0	0	9	9	9

As OLE-012 is an ongoing, uncontrolled extension study, only descriptive statistics for HbA1c will be discussed here. The baseline mean HbA1c values were similar among the 2 completed groups but lower than the rescued group, as expected. The mean HbA1c levels increased slightly in the completers groups but decreased in the rescued group. Without a control group, it is difficult to determine if the slight increase in HbA1c seen in the completers groups was due to the progression of T2D.

	Completed phase 3		Rescued from phase 3	Total
	Alo 12.5 (n=669)	Alo 25 (n=668)	Alo 25 (n=385)	Alo 25 (n=1051)
Baseline	7.3 (0.8)	7.3 (0.8)	9.3 (0.9)	8.1 (1.3)
Week 12 CFB	0.1 (0.6)	0.1 (0.6)	-0.4 (1.0)	-0.1 (0.8)
Month 6 CFB	0.1 (0.6)	0.1 (0.8)	-0.6 (1.2)	-0.2 (1.1)
Month 9 CFB	0.2 (0.9)	0.2 (0.8)	-0.7 (1.2)	-0.3 (1.1)
Month 12 CFB	0.4 (0.5)	0.2 (0.6)	-0.8 (1.5)	-0.6 (1.4)
Month 15 CFB	-	-	-1.4 (1.3)	-1.4 (1.3)
Endpoint CFB	0.1 (0.7)	0.1 (0.7)	-0.5 (1.2)	-0.1 (1.0)

COMMENT: Without a controlled long term extension study, it is difficult to determine the durability of alogliptin's glycemic control beyond 26 weeks. However, as discussed in section 6.1.4 Analysis of Primary Endpoint, in the 5 controlled, pivotal phase 3 trials of alogliptin, both the 12.5 and 25 mg doses achieved statistically significant LS mean reductions in HbA1c reductions from baseline to week 26 compared to placebo, regardless of the add-on therapy. The effect of alogliptin in the controlled phase 3 trials was established by week 12, after which the placebo-adjusted effect of alogliptin remained relatively constant, even though the average change from baseline decreased from week 12 – 26 in the alogliptin and placebo arms. This decrease may have resulted from the progression of diabetes over time. However, the apparent stabilization at week 12 may have also resulted from changes in disposition due to hyperglycemic rescue.

6.1.9 Additional Efficacy Issues/Analyses

The sponsor calculated the homeostasis model assessment of beta cell function (HOMA-BCF) using the National Diabetes Education Initiative formula based on FPG and fasting plasma insulin levels that was developed as a surrogate measurement of beta-cell function:

$$\text{HOMA-BCF} = \frac{20 \times \text{fasting plasma insulin } (\mu\text{IU/ml})}{\text{FPG (mmol/L)} - 3.5}$$

Increases and decreases in HOMA-BCF are indicative of improvements or worsening in beta-cell function, respectively. HOMA-BCF was not determined in INS-011. In the other 4 pivotal studies, alogliptin subjects consistently had a greater LS mean increase in HOMA-BCF at week 26 compared to placebo subjects, although the differences were not statistically significant. In addition, improvement with 12.5 mg was numerically greater than 25 mg in the MET-008 and TZD-009 studies. This modeling has not been adequately validated as a marker of beta-cell function and does not yet rise to the level of evidence to support inclusion in labeling.

NDA 22-271. Change from baseline in HOMA-BCF at week 26 for pivotal phase 3 studies (LOCF)					
Study	N	Baseline HOMA-BCF mean (SD)	Change in HOMA-BCF LS mean (SE)	LS mean difference	p-value
SULF-007					
Alo 25	198	77.2 (120.9)	8.9 (6.6)	9.6	0.4
Alo 12.5	203	73.9 (83.9)	4.1 (6.6)	4.8	0.7
Placebo	99	84.7 (118.0)	-0.7 (9.6)	-	-
MET-008					
Alo 25	207	60.6 (49.6)	17.9 (14.8)	22.8	0.4
Alo 12.5	213	57.1 (39.8)	42.9 (14.3)	47.8	0.1
Placebo	104	61.2 (47.0)	-4.9 (20.7)	-	-
TZD-009					
Alo 25	199	48.9 (35.7)	9.9 (4.0)	1.0	0.9
Alo 12.5	197	47.6 (36.5)	19.8 (4.0)	10.9	0.1
Placebo	97	47.3 (38.6)	8.9 (5.6)	-	-
PLC-010					
Alo 25	131	72.2 (58.5)	9.7 (4.1)	10.0	0.2
Alo 12.5	133	74.5 (59.9)	7.5 (4.0)	7.8	0.3
Placebo	64	73.5 (59.4)	-0.3 (6.0)	-	-

7 Review of Safety

Safety Summary

The safety data consist of all randomized subjects who received ≥ 1 dose of study drug. This review focused on the controlled phase 2 and 3 clinical studies pertinent to the claimed

indication that were originally submitted to NDA 22-271 (i.e. SYR-322 studies 003, SULF-007, MED-008, TZD-009, PLC-010, INS-011).

Due to early concerns about cardiovascular safety, the sponsor also submitted 2 studies of alogliptin + pioglitazone (study 01-05-TL-322OPI-001 and 01-06-TL-322OPI-002), which were originally intended for the fixed dose combination NDA 22-426. The AEs in these studies were also reviewed, as well as the deaths, serious AEs, and marked abnormalities in serum chemistry values that occurred in uncontrolled, long term extension study OLE-012.

As described in sections 6.1.3 Patient Disposition and 7.1.2 Adequacy of Data, miscoding occurred. In the opinion of this reviewer, 7 subjects should have been labeled as having a major protocol deviation for receiving a treatment different from the randomized treatment. One subject was discontinued the same day he experienced an MI, although the reason for discontinuation was listed as “lack of efficacy.” Review of the SAE and AE narratives indicated that as many as 8 additional cases of MI, 7 CVA, and 1 hypersensitivity case may have occurred. A slight discrepancy was noted between tables displaying the cardiovascular TESAEs and SAEs. Although these potential miscodes are each in themselves minor and open to interpretation, together they complicate the interpretation of cardiovascular adverse events which is already limited by the low event rates.

Although the application meets the agency’s current recommendations regarding the extent and duration of exposure, it must be noted that all studies excluding uncontrolled OLE-012 had a controlled, 26 week treatment period. Thus, all exposure data beyond 6.5 months is uncontrolled and its interpretation is limited. Due to the cardiovascular safety concern that has arisen in the data submitted, the lack of long term controlled safety data is a significant deficiency.

The HbA1c lowering effects of 6.25, 12.5, 25, 50, and 100 mg were evaluated in phase 2 studies SYR-322-002 and SYR-322-CPH-002, with the latter taking place in Japan. There was a statistically significant effect on HbA1c at all doses except 6.25 mg. Study results indicated that 12.5 mg was the minimum effective dose, with which a maximum effect was also achieved. Dose titration was not conducted in phase 3 clinical studies, as subjects were randomized to 12.5 or 25 mg. Subjects who met the criteria for rescue were considered to have completed the study and were eligible to enter open label extension study OLE-012.

The effect of alogliptin on QT interval was assessed in a single blind, randomized, placebo, and positive controlled Thorough QT study testing two parallel suprathreshold multiple doses (50 or 400 mg x 7 days; study 019). The QT IRT concluded there was no significant effect of alogliptin on QT prolongation.

Although the sponsor recommends dosage adjustment in moderate, severe, and ESRD, the clinical pharmacology reviewers also recommend dose adjustment for subjects with mild renal impairment. In subjects with mild, moderate, and severe renal impairment and end stage renal disease (ESRD), the AUC_{0-t} increased by 69%, 108%, 219%, and 281%, respectively. This reviewer finds the sponsor’s proposal acceptable to reduce the alogliptin dose to 12.5 mg for subjects with moderate, but not mild, renal impairment for the following reasons:

- When the 1 subject with mild renal impairment who had greater exposures than all moderately renally impaired subjects was excluded, the increase in exposure in the remaining 5 subjects with mild renal impairment was 47% relative to control indicating no need for dose adjustment in subjects with mild renal impairment.
- The controlled phase 3 program studied between 560 and 1,415 subjects (depending on the formula used to calculate creatinine clearance) with mild renal impairment. No trend towards increased AEs was observed in this population.
- No significant difference in the incidence of AEs was seen between the alogliptin 12.5 and 25 mg groups when analyzed by sex and baseline serum creatinine in controlled studies.
- There are very wide margins of safety based on the animal data.
- Having fewer dose adjustment recommendations will simplify use in clinical practice.

Moderate hepatic impairment did not significantly alter alogliptin exposure. (The PK of alogliptin was not evaluated in subjects with mild or severe hepatic impairment.) According to FDA's clinical pharmacology reviewers, elderly white women had a 97% increase in exposure compared to young white men. The creatinine clearance in elderly white women was approximately half that of young white men, suggesting the renal function decrease resulted in the increased exposure in elderly white women. Sex and race, however, did not affect alogliptin exposure.

Metabolic modulators did not significantly affect exposure. Alogliptin did not significantly affect exposure of P450 probe substrates.

In the controlled clinical trials, there were 4 deaths among the alogliptin-treated patients and 1 death in a non-alogliptin-treated patient. These 5 deaths were all cardiovascular-related. The 4:1 ratio of deaths in the controlled portions of the trial is generally consistent with the randomization scheme for these trials. The remaining 6 deaths occurred during the uncontrolled open-label extension trial and were due to cardiovascular causes or cancer.

Approximately 4% of subjects receiving alogliptin experienced a treatment-emergent serious adverse event (TESAE) in phase 2/3 trials of the drug, whereas 2.5% of subjects receiving Alo+Pio experienced a TESAE in the FDC trials. In controlled phase 2 and 3 trials of alogliptin, cardiac serious adverse events (SAEs) were most common (1.2%) followed by infections and infestations (0.8%). In controlled phase 3 studies of the FDC, TESAEs occurred less frequently, but were most common in the infection and infestation disorders SOC (0.5%) followed by cardiac, gastrointestinal, and nervous system disorders (0.4% each).

In controlled phase 2 and 3 studies originally submitted to the NDA, the percentage of subjects who withdrew due to AEs was slightly numerically higher with all alogliptin, and the alogliptin 12.5 mg and alogliptin 25 mg groups compared to placebo (2.8%, 2.7%, 2.6%, and 2.1%, respectively).

In the controlled phase 2 and 3 studies originally submitted to NDA 22-271, the percentage of subjects who experienced hypoglycemia was similar between the placebo and alogliptin 12.5 and 25 mg treatment groups (mild-moderate hypoglycemia: 3.7-6.0%; severe hypoglycemia: 0.1-0.6%).

A higher percentage of subjects in the all alogliptin group had AEs in the immune system SOC when compared to placebo (1.3% vs. 0.4%, respectively). The AEs that contributed to this difference were hypersensitivity and drug hypersensitivity. The only event of angioedema reported in phase 2 and 3 studies was in a placebo subject.

A slightly higher percentage of subjects experienced AEs in the skin and subcutaneous tissue disorders SOC when compared to placebo (11.5% vs. 10.3%, respectively). This difference was due to events of pruritis and rash.

The sponsor analyzed the phase 2 and 3 AEs with 2 different cluster analyses:

- The angioedema standardized MedDRA query (SMQ)
- A customized MedDRA query of potential cutaneous drug reaction (PCDR) events

A deficiency of this analysis was that the customized MedDRA query of PCDR events did not include most ulcers (only venous ulcer pain was included).

Although the percentages of subjects experiencing angioedema cluster events in the placebo and alogliptin groups were similar, the number of events per 100 subject-years of exposure was approximately 25% greater in the alogliptin 12.5 and 25 mg groups. The most common angioedema cluster event was peripheral edema, which occurred similarly in the alogliptin and placebo groups. Eleven angioedema cluster events, however, were reported in alogliptin but not placebo subjects. Hypersensitivity occurred slightly more often in the alogliptin group, especially when events per 100 subject-years exposure was compared (1.4 vs. 0.5).

The percentage and number of PCDR events per 100 subject-years of exposure were slightly higher in the all alogliptin dose group when compared to placebo (9.6% and 28.4 vs. 6.9% and 24.9). This was also true when alogliptin 12.5 and 25 mg were compared to placebo.

The most common AEs in the PCDR cluster were pruritis and rash, which occurred in a higher percentage of subjects in the all alogliptin group than placebo group (pruritis 1.6% vs. 0.4%; rash 1.6% vs. 0.7%). More subjects experienced AEs of contact dermatitis, dermatitis, allergic dermatitis, and atopic dermatitis in the all alogliptin group than in the placebo group (27/1961 [1.4%] vs. 3/534 [0.6%], respectively).

Thirteen of 2,454 (0.5%) subjects in all phase 2 and 3 studies had an event in the PCDR cluster which led to discontinuation (1 placebo, 3 alogliptin 12.5 mg, 7 alogliptin 25 mg, and 2 alogliptin 50 mg). Five of these subjects discontinued from OLE-012. The ratio of placebo: alogliptin discontinuations for PCDR events was 1:7, whereas the ratio of placebo: alogliptin-treated subjects in controlled phase 2 and 3 studies was approximately 1:3.7. Please note, however, that just 1 more placebo event would have resulted in a 1:3.5 ratio, which is consistent with randomization.

Although sponsors of some other DPP-4 inhibitors evaluated infections as an AE of special interest, alogliptin's sponsor did not. However, the incidence of infection and infestation TEAEs in controlled phase 2/3 trials of alogliptin was similar in the alogliptin and placebo groups (0.8% vs. 0.9%); the incidence of infection and infestation TEAEs was less in the alogliptin group when compared to placebo (28.8% vs. 31.3%).

After carefully considering the recommendations of the Endocrinologic and Metabolic Drugs Advisory Committee on July 1 and 2, 2008 and the data submitted, the division determined that additional evidence was needed to address concerns about cardiovascular risk. As two other NDAs were also under review at that time, the division wished to standardize the approach to evaluating cardiovascular risk in these 3 NDAs. In a January 11, 2009 letter to the sponsor, the division clearly stated the analysis population, endpoints, and types of analyses to be conducted for cardiovascular assessment. This included both 1) "SMQ major adverse cardiovascular (MACE) analysis" which was the composite endpoint of cardiovascular death and all preferred terms in the standardized MedDRA queries for "myocardial infarction" and "central nervous system haemorrhages and cerebrovascular accidents" and 2) "custom MACE" which was the composite endpoint of cardiovascular death and a subset of 34 MedDRA preferred terms from the Broad SMQ MACE endpoint.

It was decided that the 3 NDAs currently under review must meet the cardiovascular safety standards of other diabetic drugs in development, as recommended in the December 2008 final diabetes cardiovascular guidance. This meant that, prior to approval, the incidence of important cardiovascular events occurring with the investigational agent should be compared to the incidence of important cardiovascular events occurring with the control group and that the upper bound of the 2-sided 95% confidence interval (CI) for the estimated risk ratio should be < 1.8 . If the integrated analysis approach does not show this, then a single large safety trial should be conducted alone or added to other trials to satisfy this upper bound. On January 21, 2009, the sponsor submitted the requested information, which is described in section 7.3.5 Submission Specific Primary Safety Concerns.

The analysis shows that the upper bound of the 2-sided 95% confidence interval (CI) for the estimated risk ratio is > 1.8 in pooled SMQ and custom analyses and in all individual studies, when it was estimable. The high upper bound of the 2-sided 95% CI is likely due to the low MACE event rates. Nonetheless, NDA 22-271 does not meet current cardiovascular risk safety guidelines for approval. The large fixed dose combination study of alogliptin + pioglitazone (study OPI-001) also likely drove the results of the pooled study comparison.

In total, 10 of 35 (28.6%) Broad SMQ MACE cases were coded as MI or acute MI. Sixteen of the 35 (45.7%) MACE events were AEs, not SAEs. Three of the 16 (18.8%) AEs (725/3005, 716/3021, and 728/3008) were coded as myocardial infarction, causing one to question the coding quality of these events as all myocardial infarctions are potentially life threatening and should be labeled as SAEs. Based on the limited information present, this reviewer considers it possible that as many as an additional 6 MIs and 6 CVAs (2 placebo and 4 alogliptin in each group) may have occurred in the 16 AEs cases. Case 716/3021 is especially concerning as it

describes an AE of myocardial infarction with subject discontinuation on the same day for “lack of efficacy”. This reviewer believes the reasons for discontinuation should have been listed as the AE.

Aside from the fact that several of the AEs described in the MACE analysis may have met criteria for an SAE, MI, and/or CVA, there is also an imbalance in the events the sponsor labeled as SAEs when the alogliptin cardiac SOC is compared to placebo. As shown in section 7.3.2 Nonfatal Serious Adverse Events, in the controlled phase 2 and 3 trials in NDA 22-271, the sponsor described 23 cardiovascular TESAES in alogliptin subjects versus 2 events in the placebo population. However, NDA 22-271 Integrated Analysis of Safety’s table 10.b Listing of Subjects who Experienced an SAE indicates there were 24 cardiac SAEs. As one would expect the SAE table to have a greater or equal number of SAEs as the TESAES table, the sponsor was asked to clarify this point. The sponsor responded that 2 cases (hypertensive heart disease MET-008 520/8010 and palpitations PLC-010 440/4008) were inadvertently not included in table 10.b. Subject 520/8010 died from hypertensive heart disease and is included in the Deaths section. Subject 440/4008 experienced atrial fibrillation with a positive troponin and was included in the review of CV SAEs. When these 25 cardiovascular (CV) SAE cases were internally adjudicated, two possible cases of MI were identified (422/9009 angina pectoris and coronary artery disease; 440/4008 palpitations). Overall, the ratios of CV SAE exceeded the expected 3.7:1 ratio based on randomized patients in the safety population of NDA 22-271.

In controlled phase 2 and 3 studies originally submitted to NDA 22-271, there was an increase in cardiovascular TEAEs when alogliptin was compared to placebo (4.0% vs. 2.4%). The most common AE in this SOC was angina pectoris (0.7% vs. 0%, respectively). A slight increase in immune system disorders was also seen when alogliptin was compared with placebo (1.3% vs. 0.4%). The most common events in this SOC were seasonal allergy (0.5% vs. 0.2%) and hypersensitivity (0.4% vs. 0.2%). Nervous system disorders also occurred more frequently in the alogliptin group (13.0% vs. 9.7%). Headache and dizziness, which occurred at similar rates in the alogliptin and placebo groups, were the most common events in the SOC. The discrepancy in the nervous system reporting rates mainly results from isolated neurologic reports in the alogliptin group rather than a sizable collection of reports under 1 or 2 preferred neurologic terms. Upper respiratory infection, nasopharyngitis, and headache, which are AEs associated with sitagliptin, occurred more commonly in placebo than the all alogliptin doses treatment group (5.2% vs. 3.6%; 5.1% vs. 4.9%; and 3.9% vs. 4.9%).

When OPI-001 and OPI-002 were reviewed for common AEs, the incidence of AEs was similar in the alogliptin and Alo + Pio groups when compared to pioglitazone, except for a slight increase in gastrointestinal disorders (12.6% and 13.3% vs. 10.9%, respectively).

Standard safety laboratory data were obtained in all studies at baseline, during the treatment period, and at study end. Serum CPK, amylase, and lipase were not measured in the phase 3 studies.

The mean changes from baseline to endpoint in laboratory results were small and generally similar between placebo and alogliptin treatment groups. In the controlled phase 2 and 3 studies

originally submitted to NDA 22-271, the mean change in serum creatinine in the alogliptin treatment groups from baseline to endpoint was 0 mg/dl. Small increases from baseline in the alogliptin groups' mean urine albumin/creatinine ratios were seen when compared to placebo (30 and 15 mcg/mg versus 5 mcg/mg). However, the mean values for the placebo group were higher at endpoint than baseline (76.3 vs. 71.2 mcg/mg). The median changes were more similar (-1, -2, and -3 for the placebo and alogliptin 12.5 and 25 mg groups). A greater percentage of alogliptin 12.5 and 25 mg subjects experienced markedly abnormal creatinine values (i.e. creatinine > 1.5x baseline) when compared to placebo (0.9% and 1.0% vs. 0.4%), although case narratives were not provided.

Mean ALT values improved more in subjects on alogliptin 12.5 and 25 mg when compared to placebo (-0.2 and -0.6 vs. -0.1 mU/ml), whereas mean AST increased slightly more in the alogliptin treatment groups when compared to placebo (0.6 and 0.3 vs. 0.2 mU/ml). Thus, no consistent pattern was seen in the effect of alogliptin 12.5 and 25 mg in the change in liver enzymes from baseline to endpoint.

The percentage of subjects with markedly abnormal ALT > 3x or >10x ULN were similar between the alogliptin 12.5 and 25 mg and placebo groups. However, the alogliptin 25 mg group had a greater percentage of subjects with ALT > 5x ULN when compared to placebo or alogliptin 12.5 mg (0.6% vs. 0.2% and 0.2%). AST was more likely than ALT to be markedly abnormal. Both alogliptin 12.5 and 25 mg groups had a higher percentage of subjects with AST > 3x or 5x ULN, when compared to placebo (> 3x ULN: 1.0% and 0.7% vs. 0.4%; > 5x ULN: 0.2% and 0.4% vs. 0%). A similar percentage of subjects in each treatment group had AST > 10x ULN (0-0.1%).

As discussed below, 7 cases were identified with transaminases > 5x ULN but < 10x ULN. Liver enzymes generally returned to normal in these subjects without study drug interruption. Five of the 7 reports described alternative etiologies for the elevations. No subject met Hy's law criteria.

Of the 2 subjects (1 each 12.5 mg and 25 mg) who experienced ALT or AST > 10x ULN which resulted in withdrawal from controlled phase 2 or 3 studies, both had elevated liver enzymes at baseline (1 subject > 10x ULN) and 1 had reported alcohol use.

A consistent effect of alogliptin on liver enzymes was not seen. Transaminase elevation > 5x ULN usually resolved without study drug interruption and may have been due to alternative etiologies. The alogliptin 25 mg subjects who completed the 30 week trials, experienced a small dose-related increase in transaminases (ALT > AST), although this change was not seen when endpoint values were reviewed. The change from baseline to endpoint in alkaline phosphatase in the placebo and alogliptin 12.5 and 25 mg groups was also -0.3, -1.8, and -1.4 mU/ml respectively.

Although the sponsor should have used more rigorous criteria for defining abnormal blood pressure, no significant differences were seen in blood pressure, heart rate, and ECG parameters between treatment groups. Although 2 subjects withdrew from study SULF-007 due to AEs

associated with ECG changes, subject 424/7008's ischemic changes were not likely due to study drug.

Alogliptin poses minimal carcinogenic risk to humans based on high exposure multiples at the NOAEL (32x) for rat thyroid C-cell tumors, very high exposure multiples ($\geq 288x$) at doses that caused increased combined thyroid C-cell adenomas and carcinomas in male rats, and absence of any other drug-related tumors in rats ($> 400x$ female MRHD) or mice (60x MRHD).

There were no remarkable effects on pregnancy or fetal development except at maternally toxic doses that were generally greater than 200x higher than expected human exposure. There was a slight increase in sperm abnormalities in males (NOAEL approximately 67x MRHD). However, rat sperm abnormalities did not affect fertility.

Alogliptin crosses the placenta and is secreted in rat milk at 2x the concentration of maternal plasma.

Two pregnancies were reported in the phase 1 program. Both subjects had completed study drug administration at the time of their first positive pregnancy test and both subjects terminated their pregnancies via induced abortion. Four pregnancies were reported in the alogliptin phase 2 and 3 programs. Two of the 4 subjects delivered healthy, full-term infants. The other 2 subjects experienced spontaneous abortions.

The Sponsor studied alogliptin in patients ≥ 18 years old and requested a deferral for children 10-17 years old and a waiver in children 0-9 years. The sponsor proposed a 4 week oral toxicity study in adolescent Sprague-Dawley rats and phase 1 and 3 clinical studies in T2D children aged 10-17 years. The Pediatric Review Committee (PeRC) met on September 24, 2008 and agreed with the Division's recommendation that alogliptin studies be deferred in ages 10-16 years and waived in ages 0-9 years.

No cases of alogliptin overdose were reported during clinical development. Over a 3 hour hemodialysis session, approximately 7% of the drug was removed. Therefore, hemodialysis is unlikely to benefit an overdose situation.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The safety data consist of all randomized subjects who received ≥ 1 dose of study drug. The table below summarizes the safety database for alogliptin. This review focused on the controlled phase 2 and 3 clinical studies pertinent to the claimed indication that were originally submitted to NDA 22-271 (i.e. SYR-322 studies 003, SULF-007, MED-008, TZD-009, PLC-010, INS-011).

Due to early concerns about cardiovascular safety, the sponsor also submitted 2 studies of alogliptin co-administered with pioglitazone (study 01-05-TL-322OPI-001 and 01-06-TL-

322OPI-002), which were originally intended for the fixed dose combination NDA 22-426. The adverse events (AEs) in these studies were also reviewed, as well as the deaths, serious AEs, and marked abnormalities in serum chemistry values that occurred in uncontrolled, long term extension study OLE-012.

NDA 22-271. Overview of safety data for alogliptin	
Source of data	Details
Controlled safety/ efficacy trials	8 studies: 1 monotherapy phase 3 trials (PLC-010) 6 add-on combination therapy phase 3 studies (SULF-007, MET-008, TZD-009, INS-011, OPI-002, OPI-001) 1 monotherapy phase 2 study (003)
Uncontrolled long-term safety data	1 study: 1 2-year add-on combination therapy phase 3 extension study (OLE-012)
Special safety studies	2 special safety studies in healthy volunteers: 2 Thorough QT studies of cardiac safety (044, 019) 2 special safety studies in renally or hepatically impaired subjects: 1 study in healthy and renally impaired subjects (SYR-322-006) 1 study in healthy and moderately hepatically impaired subjects (SYR-322-023)
Other sources of Safety data	21 other studies: Bioavailability and clinical pharmacology studies Spontaneous reports/literature reports

As discussed in section 5.3 Discussion of Individual Studies, phase 2 dose ranging study 003 investigated alogliptin doses 6.25, 12.5, 25, 50, and 100 mg daily for 12 weeks in T2D subjects. Alogliptin doses 12.5 and 25 mg daily for 26 weeks were evaluated in T2D subjects without (010) and with (SULF-007, MET-008, TZD-009, and INS-011) add-on therapy. More phase 3 study subjects received alogliptin than placebo due to the 1:2:2 (placebo: alogliptin 12.5 mg: alogliptin 25 mg) randomization used in studies SULF-007, MET-008, TZD-09, and PLC-010. Studies INS-011, OPI-022, and OPI-001, which investigated alogliptin as add on therapy to insulin and pioglitazone, had a 1:1 randomization. Please also refer to section 5.1 Tables of Clinical Studies for more information.

7.1.2 Adequacy of Data

The core alogliptin trials were randomized, blinded, and controlled. However, open label extension study OLE-012 was uncontrolled, limiting the interpretability of long-term data. The assessment of cardiovascular risk was limited by a low event rate, trials not designed to measure CV risk, and a lack of prospective adjudication.

In the opinion of this reviewer, the following errors in coding occurred:

- 7 subjects should have been labeled as having a major protocol deviation for receiving a treatment different from the randomized treatment (SULF-007: 1 alogliptin; MET-008: 3 alogliptin subjects; OPI-002: 3 A+P subjects). Please see section 6.1.3 Patient Disposition for more information.
- MACE analysis:

- Case 716/3021 is concerning as it describes an AE of myocardial infarction with subject discontinuation on the same day for “lack of efficacy”. This reviewer believes the reasons for discontinuation should have been listed as the AE.
 - Based on the limited information present, this reviewer considers it possible that as many as an additional 6 MIs and 6 CVAs (2 placebo and 4 alogliptin in each group) may have occurred in the 16 AEs cases in the Broad SMQ.
 - 640/2506 (placebo): This case of cerebral ischemia in a 71 year old male on day 196 should have been coded as a CVA.
 - Please see 7.3.5 Submission Specific Primary Safety Concerns for more information.
- Cardiovascular (CV) SAEs: As shown in section 7.3.2 Nonfatal Serious Adverse Events, in the controlled phase 2 and 3 trials in NDA 22-271, the sponsor described 23 cardiovascular TESAES in alogliptin subjects versus 2 events in the placebo population. However, NDA 22-271 Integrated Analysis of Safety’s table 10.b Listing of Subjects who Experienced an SAE indicates there were 24 cardiac SAEs. As one would expect the SAE table to have a greater or equal number of SAEs as the TESA table, the sponsor was asked to clarify this point. The sponsor responded that 2 cases (hypertensive heart disease MET-008 520/8010 and palpitations PLC-010 440/4008) were inadvertently not included in table 10.b. Subject 520/8010 died from hypertensive heart disease and is included in the Deaths section. Subject 440/4008 experienced atrial fibrillation with a positive troponin and was therefore included in the review of CV SAEs. When these 25 CV SAE cases were internally adjudicated, two possible cases of MI were identified (422/9009 angina pectoris and coronary artery disease; 440/4008 palpitations).
- TZD-009 226/9002: This 52 year old male with T2D was diagnosed with serum sickness on day 32. However, it may have been an event of hypersensitivity. Please see section 7.3.2 Nonfatal Serious Adverse Events for more information.
- In uncontrolled study OLE-012:
 - 2 subjects (452/5001 and 440/9005) really discontinued due to an AE (coronary artery stenosis and MI, respectively). Please see section 6.1.3 Patient Disposition for more information.
 - The death of subject 325/9004 may have been miscoded under the preferred term “hypertensive heart disease”, given the lack of hypertensive history and significant atherosclerosis seen at autopsy.

While the number of potential miscodes is small in comparison to the total population studied, the presence of miscoded MACE events and CV SAEs adds further uncertainty to the cardiovascular data which has already been called into question. Please refer to section 7.3.5 Submission Specific Primary Safety Concerns for more information.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The safety review focuses mainly on the alogliptin 12.5 and 25 mg dose groups from the controlled phase 2 and 3 study group, as this group is most relevant to potential drug approval. Safety data from 27 of 31 completed clinical studies and interim data from the long term, open label safety study 012 were pooled into an integrated safety database, separated by similarity of

design into 4 groups and analyzed according to the statistical analysis plans. Data from the phase 1 renal (006) and hepatic (023) impairments studies were not pooled because of their unique populations.

NOTE: Due to the similarities in study design, I generally agree with the pooled study groups. It must be noted however that monotherapy study PLC-010 was included in the pool. The MET-008 study had stricter creatinine inclusion criteria than other studies (i.e. male serum creatinine < 1.5 mg/dl and female serum creatinine < 1.4 mg/dl versus serum creatinine ≤ 2.0 mg/dl). Furthermore, the different studies included patients on different background therapies, which in themselves are associated with different adverse events. Thus, pooling the studies may have diluted safety signals.

NDA 22-271. Pooled study groups	
Study group	Studies included
Controlled phase 2 and 3	003, 007, 008, 009, 010, 011
All phase 2 and 3 (a)	003, 007, 008, 009, 010, 011, 012
US phase 1 (b)	001, 002, 004, 005, 014, 015, 016, 017, 018, 019, 020, 021, 022, 024, 025, 026, 027, 029
Japanese Phase 1	CPH-001, CPH-002, CPH-006
(a) Includes interim data from study 012 as of August 29, 2007	
(b) Data from the renal (006) and hepatic (023) impairment studies were not pooled.	

Studies OPI-002 and OPI-001 were originally submitted to NDA 22-426, to support the use of alogliptin (12.5 and 25 mg) in a fixed dose combination with pioglitazone (15, 30, and 45 mg). NDA 22-426's integrated analysis pooled studies OPI-002 and OPI-001 were also submitted to NDA 22-271 on August 5, 2008 and pooled with all completed phase 2 and 3 for major adverse cardiovascular events (MACE) analysis.

NDA 22-426. Pooled study groups	
Study group	Studies included
Controlled phase 3 studies with pioglitazone	OPI-002 and OPI-001

NOTE: I agree with the pooling of studies OPI-002 and OPI-001 due to the similarity in design as well as the coadministration of pioglitazone. It should be noted however that study OPI-001 enrolled a population who had inadequate glycemic control on ≥ 1,500 mg (or MTD) metformin.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

At the November 28, 2005 end of phase 2 meeting, the division recommended that at least 400 subjects be exposed to alogliptin for 1 year. However, since then, a draft guidance for industry, *Diabetes Mellitus: developing drugs and therapeutic biologics for treatment and prevention*, was

released in February 2008. The guidance recommends that phase 3 trial data be available for $\geq 2,500$ subjects exposed to investigational product with at least 1,300-1,500 subjects exposed for 1 year or more and at least 300-500 subjects exposed for 18 months or more.

The sponsor was asked to clarify the number of subjects exposed to alogliptin in controlled phase 3 studies and uncontrolled study OLE-012 (up to submission of the 120-day safety update [January 31, 2009]) as well as alogliptin + pioglitazone studies OPI-001 and OPI-002 (up to the time of NDA 22-426 submission). The sponsor submitted this information, which is shown below, on May 6, 2009.

NDA 22-271. Alogliptin exposure from studies 007 – 001 and 012 through January 31, 2008 and OPI-001 and -002. NOTE: All studies, excluding 012, had a controlled, 26 week treatment period. Thus, all exposure data beyond 6.5 months is uncontrolled data.			
Exposure	Alo 12.5 mg	Alo 25 mg	All Alo
≥ 6 mo	1,625	2,125	3,255
≥ 12 mo	409	649	1,443
≥ 18 mo	95	134	422

COMMENT: While the application meets the agency's current recommendations regarding the extent and duration of exposure, it must be noted that all studies excluding OLE-012 had a controlled, 26 week treatment period. Thus, all exposure data beyond 6.5 months is uncontrolled and its interpretation limited. Due to the cardiovascular safety concern that has arisen in the data submitted, the lack of long term controlled safety data is a significant deficiency.

The only DPP-4 inhibitor approved in the United States is sitagliptin (Januvia). Adverse events associated with this class of compounds include serious allergic and hypersensitivity reactions including exfoliative skin conditions, upper respiratory tract infection, nasopharyngitis, headache, and hypoglycemia especially when used with a SULF. Sitagliptin requires dosage adjustment in patients with moderate or severe renal insufficiency and patients with end stage renal disease (ESRD). Furthermore, a minor increase in serum creatinine was seen in patients with moderate and severe renal insufficiency, studied under a dedicated protocol, which prompted a label recommendation to assess renal function prior to and periodically after the initiation of sitagliptin. Unapproved vildagliptin has potential liver and skin toxicities.

The sponsor analyzed major adverse cardiovascular events, angioedema, potential cutaneous drug reactions, and hypoglycemic events as events of special interest, as requested by the agency. It also performed 2 QT studies and one study each assessing the effects of renal and hepatic impairment on alogliptin pharmacokinetics, studies SYR-322-006 and -023, respectively.

Most studies excluded subjects with serum creatinine ≥ 2.0 mg/dl (studies involving metformin had stricter criteria). Therefore, there are limited data in patients with substantial renal impairment, which is an important subgroup of patients who will be prescribed alogliptin, if approved. The sponsor is planning to either 1) conduct 2 dedicated renal safety studies in patients with moderate and severe renal impairment (see below) or 2) include a renal substudy in their

cardiovascular outcomes trial; the agency is still in discussions with the sponsor. The effects of renal impairment on alogliptin PK were evaluated in study SYR-322-006, an open label, parallel group, comparison, single dose (50 mg) alogliptin in 48 subjects (24 healthy subjects and 6 subjects in each of the mild, moderate, severe, and ESRD categories). This study showed that without dose reduction, subjects with moderate to severe renal impairment would be exposed to significantly higher levels of alogliptin than subjects without renal impairment. The sponsor's proposed administration recommendations for subjects with moderate, severe, and ESRD are in agreement with the study's conclusions, which were as follows:

- For patients with mild renal insufficiency ($\text{CrCl} \geq 50$ to ≤ 80 ml/min or serum creatinine levels ≤ 1.7 mg/dl in men and ≤ 1.5 mg/dl in women), no dosage adjustment is required.
- For patients with moderate renal insufficiency ($\text{CrCl} \geq 30$ to ≤ 50 ml/min or serum creatinine levels > 1.7 to ≤ 3.0 mg/dl in men and > 1.5 to ≤ 2.5 mg/dl in women), the dose should be approximately half the dose given to patients with normal renal function or the schedule of drug administration should be prolonged so that dosing is every other day (Q48 hours).
- For patients with severe renal insufficiency ($\text{CrCl} < 30$ 50 ml/min or serum creatinine levels > 3.0 mg/dl in men and > 2.5 mg/dl in women) or with ESRD requiring hemodialysis or peritoneal dialysis, the dose should be approximately one fourth the dose given to patients with normal renal function or the schedule of drug administration should be prolonged so that dosing is approximately twice a week, with at least 3 days in between doses.

Clinical pharmacology, however, recommends dose adjustment to 12.5 mg for subjects with mild renal impairment because of a mean increase in exposure of 69%. Although the sponsor believes the 69% increase in mild renal impairment patients is mostly influenced by 1 subject who had a CrCl of 53 ml/min (Cockcroft-Gault calculation) and that exposure in that subject was higher than all subjects with moderate renal impairment, clinical pharmacology does not view the subject in question as an outlier because the study only included 6 subjects with mild renal impairment. Please refer to the clinical pharmacology review and section 7.4.5 Special Safety Studies for more information.

On June 4, 2008, the sponsor submitted to alogliptin IND 69,707 the following 2 protocols, which include 2 week screening, 26 week treatment, and 2 week follow up periods, to further support alogliptin use in T2D patients with renal impairment:

- Protocol SYR-322_302: A multicenter, randomized, double blind, placebo controlled study to evaluate the efficacy and safety of alogliptin in subject with T2D and moderate renal insufficiency. This study will compare 12.5 mg alogliptin to placebo in at least 210 subjects (105 per arm).
- Protocol SYR-322_304: A multicenter, randomized, double blind, placebo controlled study to evaluate the efficacy and safety of alogliptin in subjects with T2D and severe renal impairment. This study will compare 6.25 mg alogliptin to placebo in at least 160 subjects (80 per arm).

The agency is still in discussions with the sponsor as to whether these 2 dedicated renal studies will be conducted or if the now planned cardiovascular outcomes trial will include a dedicated renal substudy.

The demographic and baseline characteristics of subjects in the controlled phase 2 and 3 study groups were generally adequate, although they had low baseline CV risk, a relatively short duration of diabetes, and no substantial renal impairment. In studies involving alogliptin as well as studies involving alogliptin + pioglitazone, the mean patient age was approximately 54 years. The majority of subjects were White (~74%). The percentage of Asian and Black subjects varied between 4-10%. Approximately half of subjects were male. The majority were obese with a duration of diabetes from 5-7 years and mean HbA1c of 8%.

NDA 22-271. Demographics and baseline characteristics of subjects in controlled phase 2 and 3 study groups		
	Alo studies, n=1961	Alo + Pio studies, n=1107
Age, mean (SD)	55.3 (10.55)	53.1 (9.8)
Male, n (%)	1005 (51.2)	496 (44.8)
Race, n (%)		
White	1438 (73.3)	829 (74.9)
Asian	189 (9.6)	81 (7.3)
Black	145 (7.4)	46 (4.2)
Other	189 (9.6)	151 (13.6)
BMI ≥ 30, n (%)	1137 (58.0)	590 (53.3)
Mean DM duration (years)	7.1 (6.0)	5.4 (5.2)
Mean HbA1c (SD)	8.2 (1.0)	8.6 (0.8)

7.2.2 Explorations for Dose Response

The HbA1c lowering effects of 6.25, 12.5, 25, 50, and 100 mg were evaluated in phase 2 studies SYR-322-002 and SYR-322-CPH-002, with the latter taking place in Japan. There was a statistically significant effect on HbA1c at all doses except 6.25 mg. Study results indicated that 12.5 mg was the minimum effective dose with which a maximum effect was also achieved. However, maintaining higher than 80% DPP-4 inhibition over 24 hours is targeted for achieving desirable chronic glucose lowering in T2D and 25 mg was the minimum dose achieving this DPP-4 inhibition goal.

Dose titration was not conducted in phase 3 clinical studies, as subjects were randomized to 12.5 or 25 mg. Subjects who met the criteria for rescue were considered to have completed the study and were eligible to enter open label extension study OLE-012. Therefore, there is inadequate data to provide specific recommendations for the clinical titration of alogliptin from 12.5 to 25 mg or vice versa, although in general alogliptin may be titrated as needed in individual patients based on glycemic response.

7.2.3 Special Animal and/or In Vitro Testing

The sponsor performed 2 QT studies. The first (SYR-322-004) was an evaluator blinded, active and placebo controlled, multiple dose, crossover study to assess the effects of SYR110322 on the

QTc interval in healthy subjects. Originally, data from 3 heart beats on a single ECG strip were selected and analyzed for each subject. In order to conform with the standard industry practice for thorough QT/QTc studies, data from 2 additional strips (3 heart beats each) were retrospectively collected, after database unblinding and after the initial QT/QTc data were analyzed. Due to the design flaw in this study, the sponsor conducted a second QT/QTc study (SYR-322-019), a single blind, randomized, parallel trial to define the ECG effects of SYR-322 using a clinical and suprathreshold dose (i.e. 50 and 400 mg) compared to placebo and moxifloxacin (a positive control) in healthy men and women. It was concluded that there was no significant effect of alogliptin on QT prolongation. Please refer to the QT IRT review under IND 69,707 for full details.

7.2.4 Routine Clinical Testing

The Sponsor obtained laboratory tests, vital signs, and ECGs at reasonable time points during the studies, and under consistent settings, where applicable. I have reviewed the timing of these assessments in section 5.3 Discussion of Individual Studies. Limitations of this testing include

- Serum bicarbonate was not measured in the key safety studies, although there is no concern for acidosis based on alogliptin's mechanism of action or the non-clinical findings
- The Sponsor did not measure pancreatic enzymes in the key safety studies. A signal for pancreatitis has been identified with at least 2 GLP-1 analogs and possibly 1 DPP-4 inhibitor. (The Office of Surveillance and Epidemiology is currently reviewing reports of sitagliptin-associated pancreatitis.)

7.2.5 Metabolic, Clearance, and Interaction Workup

Approximately 68% of the oral alogliptin dose is excreted in urine, indicating renal excretion is the major elimination pathway. Alogliptin is metabolized to N-dealkylated alogliptin (M1) by CYP2D6 and acetylated alogliptin (M2). M1 and M2 are minor metabolites, with < 1% and < 4% of alogliptin exposure.

Drug interaction studies were evaluated as follows:

- The effect of metabolic modulators (fluconazole, ketoconazole, gemfibrozil, and cyclosporine) on alogliptin exposure
- The effect of alogliptin on other drugs (caffeine, tolbutamine, dextromorphan, midazolam, fexofenadine, glyburide, warfarin, ethinyl estradiol and norethindrone)
- Drug interaction between alogliptin and other drugs (cimetidine, metformin, pioglitazone, atorvastatin, and digoxin)

Alogliptin increased dextromorphan AUC (2D6 substrate) by 26% and fexofenadine AUC (P-gp and OATP substrate) by 32%. However, the increases were not considered clinically meaningful by our clinical pharmacology reviewers. Gemfibrozil and cyclosporine significantly increased M1 exposure but is not thought to be clinically meaningful because of insignificant exposure

(<1% of alogliptin). Please refer to the Clinical Pharmacology review of alogliptin for full details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As discussed in section 2.4 Important Safety Issues with Consideration to Related Drugs, the only DPP-4 inhibitor currently approved in the United States is sitagliptin. Safety issues associated with sitagliptin include the following:

- Dosage adjustment in patients with moderate or severe renal impairment, including ESRD
- Risk of hypoglycemia when used with a SFU
- Serious allergic and hypersensitivity reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome.
- Upper respiratory tract infection, nasopharyngitis, and headache which occur in $\geq 5\%$ of patients treated with sitagliptin and more commonly than placebo-treated patients

Vildagliptin, which remains unapproved, is associated with potential liver toxicity in humans and skin lesions in monkeys.

The sponsor has appropriately evaluated for these potential risks.

- Angioedema and potential cutaneous drug reactions were analyzed as AEs of special interest
- Study SULF-007 was conducted in T2D patients receiving current treatment with SULF. Hypoglycemic events, defined as glucose < 60 mg/dl in the presence of symptoms or < 50 mg/dl regardless of symptoms, as well as severe hypoglycemic events were analyzed in the key safety studies.
- Study SYR-322-006 evaluated alogliptin PK in subjects with renal impairment. Results indicated that dose reduction is needed in patients with moderate to severe renal impairment, including ESRD. Therefore in this application, the sponsor proposed that patients with moderate and severe renal impairment take alogliptin 12.5 mg and 6.25 mg once daily, respectively. The sponsor will conduct renal safety trial(s) in subjects with moderate and severe renal impairment (protocols SYR-322_302, SYR-322_304, and/or SYR-322_402).
- Study SYR-322-023 evaluated the effect of hepatic impairment on the single dose PK of alogliptin.
- Kidney and liver function tests were also monitored with routine laboratories
- Unlike some of the other DPP-4 inhibitors, alogliptin does not cause skin lesions in monkeys near clinically relevant exposures. Nonetheless, skin adverse events were reviewed as an AE of special interest.

As diabetes mellitus is associated with elevated risk of cardiovascular disease, which is the leading cause of morbidity and mortality in this patient population, it is important to provide reassurance that a new treatment does not increase this risk to an unacceptable extent. During the review of alogliptin, concern arose within the division about the drug's cardiovascular safety

profile. After communication with the sponsor and analyses of major adverse cardiovascular events (MACE), it is clear that the sponsor has not fully evaluated the potential for cardiovascular risk. Please refer to sections 7.3.5 Submission Specific Primary Safety Concerns for full details.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in studies 003, SULF-007, PLC-010, and OPI-002. A total of 11 deaths occurred in studies MET-008, TZD-009, INS-011, OLE-012, and OPI-001; 4 of these were reported in the 120 day safety update (April 17, 2008). All but one subject had received alogliptin; OPI-001 subject 907/3016 received pioglitazone 45 mg. During the controlled portions of the clinical trials, there were 4 deaths among the alogliptin-treated patients and 1 death in a non-alogliptin-treated patient. These 5 deaths were all cardiovascular-related. The 4:1 ratio of deaths in the controlled portions of the trial is consistent with the randomization scheme for these trials. The remaining 6 deaths occurred during the uncontrolled open-label extension trial. The narratives of the deaths are as follows:

SYR-322-MET-008:

- 520/8010 (alogliptin 12.5 mg; metformin 2500 mg): 49 year old female with a history of T2D, hypertension, high cholesterol, obesity, prolonged QTc interval, bipolar disorder, and seizures. On day -21 (October 12, 2006), the subject experienced 3 short episodes of retrosternal pain lasting 2-3 minutes; it was felt the pain was muscular. For 6 months prior to her death, the subject's blood pressure had been increased; it was 153/119 mmHg on October 13, 2006. On day 42, the subject was seen in the emergency room for viral gastroenteritis. On day 44, she was visited by an emergency room physician for vomiting and generalized aches. She had an irregular heart beat. That night, she was rushed to the hospital with shallow breathing and worsening abdominal symptoms. She died prior to arrival on day 45. Autopsy and the death certificate noted the cause of death as hypertensive heart disease.
- 448/8001 (alogliptin 25 mg; metformin 2000 mg): 57 year old male with a history of T2D, hypercholesterolemia, diabetic neuropathy, and smoking who died more than 14 days after his last dose of study drug. On day 47, the subject was admitted to the hospital for cholelithiasis. Study drug had been stopped on day 44 due to the cholelithiasis with the plan of restarting the study medication post cholecystectomy. On day 53, the subject underwent cholecystectomy. At that time, the liver appeared cirrhotic, and there was ascitic fluid in the abdomen. On day 63, following surgery and while in the recovery room, the subject experienced a myocardial infarction and died. Autopsy revealed a thrombosis of the intermediate section of the right coronary artery, stenosis and calcifications between 80-90% of the left anterior descending artery and liver enlargement.
 - **COMMENT: Subject 448/8001 had 3 cardiovascular risk factors as well as recent surgery, which may have contributed to the myocardial infarction.**

SYR-322-TZD-009:

- 463/9003 (alogliptin 12.5 mg; pioglitazone 30 mg): 62 year old male with a history of T2D, hyperlipidemia, and previous smoking. Concomitant medications also included glibenclamide 2 mg/day and simvastatin 20 mg/day. After shopping on day 42, the subject collapsed at home and was later pronounced dead. His ECG during the study showed left anterior hemiblock but no arrhythmia.
 - **COMMENT: Due to the limited information available, an effect of the study drug cannot be fully excluded.**

SYR-322-INS-011:

- 464/5005 (alogliptin 12.5 mg): 72 year old male with a history of T2D, myocardial infarction, coronary artery disease, arterial hypertension, congestive heart failure, cerebral infarction, hyperlipoproteinemia, neuropathy, and smoking (55 years). Screening and baseline ECGs revealed complete left bundle branch block (PR interval 364 ms and 354 ms, respectively). The subject died at home in bed on day 71. A used bottle of nitrospray was found next to the bed. The last dose of study drug was on day 70. The cause of death was recorded as cardiovascular standstill with contributory causes of coronary heart disease and diabetes.
 - **COMMENT: Subject 464/5005 had an extensive history of cardiac disease.**

SYR-322-OLE-012 (including 120 day safety update [April 17, 2008]):

- 228/9002 (alogliptin 25 mg): 73 year old male with a history of T2D, hyperlipidemia, smoking (46 years), early Parkinson's disease, and prior enrollment in study TZD-009, in which he was randomized to alogliptin 25 mg. On day 116, he was hospitalized for severe pneumonia. Oxygen saturation on 3 liters of oxygen was 84%. His last dose of study drug was on day 115. On day 117, the subject's oxygen saturation was 95% on room air but decreased to 87% with labored breathing after ambulation. Home oxygen was arranged. He was instructed on the use of incentive spirometry. He was started on nebulizer treatments and placed on CPAP machine while asleep. The subject recovered from pneumonia and was discharged on day 118. On day 121, his daughter found him face down and unresponsive. The subject was noted to be in ventricular fibrillation and was given CPR. The subject presented to the hospital in pulseless electrical activity and asystole. Oxygen saturation on room air was 70%. Glucose was 247 mg/dl. At the hospital, laboratory evaluations showed elevated liver enzymes and creatinine, hypocalcemia, and normal MB creatinine kinase and troponin. A chest x-ray could not exclude pulmonary embolism. Following do not resuscitate orders, he was pronounced dead after his blood pressure continued to decrease. The cause of death was recorded as acute cardiopulmonary arrest with pneumonia as a contributory factor.
 - **COMMENT: The subject had a recent hospitalization for severe pneumonia and increased oxygen requirements which may have contributed to his death.**
- 325/9004 (alogliptin 25 mg): 63 year old male with a history of T2D and prior enrollment in study TZD-009, in which he took alogliptin 25 mg. However, he discontinued study TZD-009 on an unspecified date due to lack of efficacy. On day 68, the subject was arranging flowers when he collapsed. He was later pronounced dead. Autopsy showed 90% stenosis of the left anterior descending and main arteries, 80% stenosis of the right coronary artery, and 60% stenosis of the left circumflex artery. The cause of death was determined to be arteriosclerotic and hypertensive heart disease.

- **COMMENT: The lack of cardiac risk factors other than T2D suggests that the death may be related to study drug. However, the significant atherosclerotic disease suggests a more chronic process is at fault. Due to the lack of hypertensive history and significant atherosclerosis seen at autopsy, this death may have been miscoded under the preferred term “hypertensive heart disease.”**
- 244/4001 (alogliptin 12.5 mg): 60 year old female with a history of T2D, arthritis, and completion of study PLC-010, in which she was randomized to alogliptin 25 mg. On day 490, she was hospitalized with mental status changes and pneumococcal pneumonia. Blood cultures were positive for gram positive cocci pneumoniae. Cerebral spinal fluid (CSF) culture was positive for *Streptococcus pneumoniae*. She died in the hospital on day 491 following cardiorespiratory collapse and hypotension.
 - **COMMENT: This is the only cause of death due to an infection.**
- 383/7013 (alogliptin 25 mg): 60 year old male with a history of T2D, myocardial infarction, angina pectoris, ischemic cardiomyopathy, peripheral vascular disorder, hypercholesterolemia, hypertension, previous smoking, and hyperglycemic rescue in study SULF-007 in which he was randomized to alogliptin 12.5 mg. On day 301, the subject was evaluated in the emergency room for dyspnea. He had complained of precordial chest pain twice in the prior week, although symptoms were relieved by sublingual isosorbide dinitrate. The subject was admitted to the hospital on day 302 for decompensated chronic obstructive pulmonary disease (COPD) and acute coronary syndrome. The ECG showed elevated ST segments and inverted T waves; troponin was positive. The subject was started on enoxaparin and oral anticoagulant therapy. On day 302, the subject experienced sudden dyspnea and vasovagal symptoms followed by cardiogenic shock and cardiac arrest unresponsive to cardiopulmonary resuscitation. The cause of death was myocardial infarction.
 - **COMMENT: The patient had a significant cardiac history.**
- 882/2505 (alogliptin 12.5 mg): 60 year old male with a history of T2D, hypertension, and previous enrollment in study OPI-002. On March 18, 2008, the subject died suddenly. The death certificate listed the death as acute heart and respiratory failure with chronic ischemic cardiopathy and stage IIIC arterial hypertension as the intermediary morbid conditions leading to the direct cause.
 - **COMMENT: A detailed narrative, including the preferred term, was not provided as this death occurred after the January 31, 2008 database lock.**
- 485/8008 (alogliptin 25 mg): 72 year old male with a history of T2D, ischemic heart disease, stable angina, arterial hypertension, hypercholesterolemia, premature ventricular beats, and prior enrollment in study MET-008. On day 352, the subject died of multiorgan trauma (mainly head and thorax) after a fall on the stairs, which rendered him unconscious. The subject was transported to the hospital and died from the injuries 7 days later.
 - **COMMENT: A detailed narrative, including the preferred term, was not provided as this death occurred after the January 31, 2008 database lock. If the fall was related to hypoglycemia, the cause of death would be study drug related.**

- 907/3016 (pioglitazone 45 mg): 62 year old female with a history of T2D, obesity, asthma, chronic bronchitis, arterial hypertension, menopause, and current smoking (30 year history). The subject died of sudden cardiac arrest on day 156, although liver enzymes were > 3x ULN on day 128 (ALT 77 mU/ml and AST 74 mU/ml). The subject's screening ECG was abnormal with ventricular hypertrophy and an abnormal QTc of 471 ms. The subject had laid down at work and was found unconscious a few hours later. Concomitant medications included fosinopril sodium, metoprolol tartrate, and hydrochlorothiazide. The cause of death was recorded as acute coronary insufficiency.
 - COMMENT: The patient was not exposed to alogliptin. She also had a significant cardiac history.**

NDA 22-271. Deaths in subjects who received alogliptin in the alogliptin clinical studies up to April 17, 2008				
Subject	Age/Sex	Day of death (Days after last dose)	Preferred term	Possible contributing factors
MET-008				
520/8010	49 F	45 (44)	Hypertensive heart disease	CVD history, viral gastroenteritis
448-8001	57 M	63 (44)	Cholelithiasis, myocardial infarction	CVD risk factors, surgery
TZD-009				
463/9003	62 M	42 (42)	Sudden death	Abnormal ECG
INS-011				
464/5005	72 M	71 (70)	Sudden death	CVD history
OLE-012				
228/9002	73 M	121 (115)	Pneumonia, cardio-respiratory arrest	Recent pneumonia, hospitalization
325/9004	64 M	68	Hypertensive heart disease*	
244/4001	60 F	491 (490)	Streptococcus pneumoniae pneumonia	
383/7013	61 M	302 (301)	Acute myocardial infarction	CVD history
882/2505	60 M	**	**	Chronic ischemic cardiomyopathy and arterial hypertension
485/8008	72 M	352	**	Fall from stairs
*Possible miscode; atherosclerotic heart disease may have been more appropriate. **Information not provided. Causes of death were cardiorespiratory failure (882/2505) and trauma (485/8008).				

7.3.2 Nonfatal Serious Adverse Events

A total of 226 subjects experienced a treatment-emergent serious adverse event (TESAE), which was defined as any event occurring or worsening on or after the date of first dose of study medication and within 14 days after the last dose of study medication, in all phase 2 and 3

studies of alogliptin and controlled phase 3 studies conducted to support the fixed dose combination (FDC) of alogliptin + pioglitazone (Alo+Pio).

Approximately 4% of subjects receiving placebo and approximately 4% of subjects receiving alogliptin experienced a TESA in phase 2 or 3 trials of the drug, whereas 2.5% of subjects receiving Alo+Pio experienced a TESA in the FDC trials. None of the TESAs had a convincing relationship to alogliptin dose. In controlled phase 2 and 3 trials of alogliptin, cardiac events were most common (1.2%) followed by infections and infestations (0.8%). There were few TESAs reported in the remaining system-organ-classes. There was an imbalance in the cardiac TESAs when alogliptin was compared to placebo (23 vs. 2 events). Please refer to section 7.3.5 Submission Specific Primary Safety Concerns for full details. The most common TESAs in the infection SOC were cellulitis (0.4% placebo, 0.1% alogliptin) and pyelonephritis (including acute: 0.2% placebo, 0.1% alogliptin).

In controlled phase 3 studies for the FDC, TESAs occurred less frequently, but were most common in the infection and infestation disorders SOC (0.5%) followed by cardiac, gastrointestinal, and nervous system disorders (0.4% each). In uncontrolled study OLE-12, infections and infestations (1.1%) were more common than cardiac events (0.9%).

NDA 22-271. Incidence rates of TESAs by system organ class in phase 2 and 3 controlled studies of alogliptin.
NOTE: Please also refer to section 7.3.5 for full details.

	Placebo (n=534)	A 6.25 (n=42)	A 12.5 (n=922)	A 25 (n=910)	A > 25 (n=87)	All Alo (n=1961)
Subjects w \geq 1 TESA	20 (3.7)	1 (2.4)	36 (3.9)	42 (4.6)	1 (1.1)	80 (4.1)
Cardiac	2 (0.4)	0	11 (1.2)	11 (1.2)	1 (1.1)	23 (1.2)
Congenital	1 (0.2)	0	0	0	0	0
Gastrointestinal	1 (0.2)	0	3 (0.3)	2 (0.2)	0	5 (0.3)
General disorders & adm site	0	1 (2.4)	4 (0.4)	3 (0.3)	0	8 (0.4)
Hepatobiliary	1 (0.2)	0	2 (0.2)	1 (0.1)	0	3 (0.2)
Immune system	0	0	0	2 (0.2)	0	2 (0.1)
Infections & Infestations	5 (0.9)	0	5 (0.5)	11 (1.2)	0	16 (0.8)
Injury, poisoning, & procedures	3 (0.6)	0	1 (0.1)	3 (0.3)	0	4 (0.2)
Investigations	0	0	1 (0.1)	0	0	1 (0.1)
Metabolism & nutrition	1 (0.2)	0	1 (0.1)	0	0	1 (0.1)
Musculosk & connective tissue	1 (0.2)	0	3 (0.3)	2 (0.2)	0	5 (0.3)
Neoplasms	4 (0.7)	0	3 (0.3)	2 (0.2)	0	5 (0.3)
Nervous system	2 (0.4)	0	1 (0.1)	3 (0.3)	0	4 (0.2)
Psychiatric	0	0	1 (0.1)	0	0	1 (0.1)
Renal & urinary	1 (0.2)	0	1 (0.1)	1 (0.1)	0	2 (0.1)
Reproductive system & breast	0	0	0	1 (0.1)	0	1 (0.1)
Respiratory, thoracic & mediastinal	0	0	0	3 (0.3)	0	3 (0.2)
Vascular	0	0	1 (0.1)	1 (0.1)	0	2 (0.1)

NDA 22-271. TESAs that occurred in \geq 2 subjects in any treatment group in the controlled phase 2 and 3 study group

System organ class – Preferred term	Placebo n=534	All Alo n=1961	Alogliptin			
			6.25 n=42	12.5 n=922	25 n=910	50/100 n=87
Any SAE	20 (3.7)	80 (4.1)	1 (2.4)	36 (3.9)	4 (4.6)	1 (1.1)

Cardiac	2 (0.4)	23 (1.2)	0	11 (1.2)	11 (1.2)	1 (1.1)
Angina pectoris	0	7 (0.4)	0	1 (0.1)	5 (0.5)	1 (1.1)
Angina unstable	2 (0.4)	1 (0.1)	0	0	1 (0.1)	0
Atrial fibrillation	0	2 (0.1)	0	2 (0.2)	0	0
Cardiac failure congestive	0	4 (0.2)	0	1 (0.1)	3 (0.3)	0
Coronary artery disease	0	2 (0.1)	0	2 (0.2)	0	0
Myocardial infarction	0	4 (0.2)	0	2 (0.2)	2 (0.2)	0
General disorders & administration site	0	8 (0.4)	1 (2.4)	4 (0.4)	3 (0.3)	0
Noncardiac chest pain	0	6 (0.3)	1 (2.4)	2 (0.2)	3 (0.3)	0
Sudden death	0	2 (0.1)	0	2 (0.2)	0	0
Hepatobiliary disorders	1 (0.2)	3 (0.2)	0	2 (0.2)	1 (0.1)	0
Cholecystitis	0	2 (0.1)	0	2 (0.2)	0	0
Infections & infestations	5 (0.9)	16 (0.8)	0	5 (0.5)	11 (1.2)	0
Cellulitis	2 (0.4)	2 (0.1)	0	0	2 (0.2)	0
Pyelonephritis	0	2 (0.1)	0	0	2 (0.2)	0
Musculoskeletal & connective tissue	1 (0.2)	5 (0.3)	0	3 (0.3)	2 (0.2)	0
Arthralgia	0	3 (0.2)	0	2 (0.2)	1 (0.1)	0

NDA 22-426. Treatment-emergent SAEs by system organ class in phase 3 controlled studies of alogliptin + pioglitazone

	Alogliptin	Pioglitazone	Alo+Pio
Subjects w ≥ 1 TESAE	12 (2.9)	19 (3.5)	28 (2.5)
Cardiac	1 (0.2)	2 (0.4)	4 (0.4)
Eye	0	0	1 (0.1)
Gastrointestinal	2 (0.5)	1 (0.2)	4 (0.4)
General disorders & administrative Site	1 (0.2)	3 (0.5)	1 (0.1)
Hepatobiliary	3 (0.7)	1 (0.2)	2 (0.2)
Infections & Infestations	3 (0.7)	6 (1.1)	5 (0.5)
Injury, poisoning, & procedures	0	1 (0.2)	1 (0.1)
Investigations	0	1 (0.2)	0
Metabolism & nutrition	0	1 (0.2)	0
Musculosk & connective tissue	0	1 (0.2)	0
Neoplasms	0	1 (0.2)	0
Nervous system	4 (1.0)	3 (0.5)	4 (0.4)
Pregnancy, puerperium, and perinatal	1 (0.2)	0	0
Psychiatric	0	1 (0.2)	0
Renal & urinary	0	0	3 (0.3)
Reproductive system & breast	0	0	1 (0.1)
Respiratory, thoracic & mediastinal	1 (0.2)	0	3 (0.3)
Vascular	0	0	2 (0.2)

NDA 22-426. SAEs which occurred in ≥ 2 subjects overall

System organ class – Preferred term	Alo n=421	Pio n=550	Alo+Pio n=1107
Overall	12 (2.9)	19 (3.5)	28 (2.5)
Cardiac disorders			
Angina unstable	1 (0.2)	0	1 (0.1)
Gastrointestinal disorders			
Gastritis	0	0	3 (0.3)
Pancreatitis	1 (0.2)	0	1 (0.1)
General disorders & administration site			
Noncardiac chest pain	1 (0.2)	2 (0.4)	0

Hepatobiliary disorders			
Cholecystitis	1 (0.2)	0	1 (0.1)
Infections & infestations			
Appendicitis	1 (0.2)	0	1 (0.1)
Pneumonia	0	1 (0.2)	1 (0.1)
Nervous system disorders			
Syncope	1 (0.2)	1 (0.2)	1 (0.1)
Respiratory, thoracic, & mediastinal			
Pulmonary embolism	1 (0.2)	0	1 (0.1)

NDA 22-271. Treatment-emergent SAEs by SOC in uncontrolled study OLE-012 (120 day safety update)					
	A 12.5 (Completed double-blind study) (n=1145)	A 25 (Completed double-blind study) (n=1150)	A 25 (Rescued from double- blind study) (n=519)	A 25 (Total) (n=1669)	Total (n=2815)
Subjects w \geq 1 TESAE	45 (3.9)	39 (3.4)	34 (6.6)	73 (4.4)	118 (4.2)
# TESAE	50	49	43	92	142
Blood and lymphatic	0	0	1 (0.2)	1 (0.1)	1 (0.0)
Cardiac	8 (0.7)	10 (0.9)	7 (1.3)	17 (1.0)	25 (0.9)
Eye	0	2 (0.2)	1 (0.2)	3 (0.2)	3 (0.1)
Gastrointestinal	2 (0.2)	1 (0.1)	0	1 (0.1)	3 (0.1)
General dis & admin site	1 (0.1)	2 (0.2)	1 (0.2)	3 (0.2)	4 (0.1)
Hepatobiliary	2 (0.2)	2 (0.2)	0	2 (0.1)	4 (0.1)
Immune system	1 (0.1)	1 (0.1)	0	1 (0.1)	2 (0.1)
Infections & infestations	9 (0.8)	8 (0.7)	13 (2.5)	21 (1.3)	30 (1.1)
Injury, poisoning, & proced.	4 (0.3)	2 (0.2)	3 (0.6)	5 (0.3)	9 (0.3)
Metabolism & nutrition	2 (0.2)	0	2 (0.4)	2 (0.1)	4 (0.1)
Musculosk & connect. tissue	2 (0.2)	2 (0.2)	2 (0.4)	4 (0.2)	6 (0.2)
Neoplasms	7 (0.6)	3 (0.3)	1 (0.2)	4 (0.2)	11 (0.4)
Nervous system	5 (0.4)	3 (0.3)	4 (0.8)	7 (0.4)	12 (0.4)
Psychiatric	0	0	1 (0.2)	1 (0.1)	1 (0.0)
Renal & urinary	1 (0.1)	3 (0.3)	0	3 (0.2)	4 (0.1)
Reproduct. system & breast	1 (0.1)	2 (0.2)	1 (0.2)	3 (0.2)	4 (0.1)
Resp., thoracic & mediastinal	1 (0.1)	2 (0.2)	0	2 (0.1)	3 (0.1)
Skin and subcut tissue	0	0	2 (0.4)	2 (0.1)	2 (0.1)
UNCODED	0	1 (0.1)	0	1 (0.1)	1 (0.0)
Vascular	3 (0.3)	1 (0.1)	0	1 (0.1)	4 (0.1)

I reviewed all cardiac, neurologic, hypoglycemic, hypersensitivity, accidental (to assess for hypoglycemia), and uncommon TESAE narratives, including pregnancies. Narratives for major adverse cardiovascular events (MACE), including cardiovascular and neurologic events, are reviewed under section 7.3.2 Significant Adverse Events. (Deaths are reviewed in section 7.3.1.) Hypoglycemic, hypersensitivity, and uncommon TESAEs narratives are listed below by study.

SULF-007:

- 420/7021 (Alogliptin 12.5 mg): 62 year old male with T2D who was admitted to the hospital due to severe hypoglycemia. Concomitant medications included glyburide 10 mg and acetylsalicylic acid. On day 137, the subject was semiconscious, disoriented, and not responding to commands, with a glucose of 27 mg/dl. The narrative did not describe

any different events or activities that day which may have contributed to hypoglycemia. Upon arrival at the hospital, the subject's glucose was 47 mg/dl. He was treated with dextrose 25% IV and D5W IV. The ECG was normal. Study medication was discontinued. On day 156, when the subject was not on oral hypoglycemic agents or study medication, his fasting sugars ranged from 120-140 mg/dl with a post prandial blood sugar of 146 mg/dl.

TZD-009:

- 226/9002 (Alogliptin 25 mg): 52 year old male with T2D was diagnosed with serum sickness on day 32, four days after study drug discontinuation on day 28. Concurrent medications included pioglitazone, glyburide, ezetimibe, pravastatin, metoprolol, lisinopril, propranolol, and cetirizine. The patient initially reported a red papular rash over the body that started as palm pruritus. The rash progressed to a diffuse, confluent papular erythematous rash with periorbital edema. Symptoms also included nausea, diarrhea, diffuse arthralgias, joint and eye lid swelling, malaise, fatigue, chills followed by warmth, and an 8 pound weight gain. On day 57, the patient was seen for a follow up visit. He had residual scaling of his palms as well as new onset patches of raised erythema in a linear distribution that was diagnosed as contact dermatitis. He reported chemical exposure and yard work in relation to the event of contact dermatitis.
 - **COMMENT: This event may be a case of hypersensitivity.**
- 332/9013 (Alogliptin 25 mg): 69 year old female with a relevant medical history of T2D, ankle and humerus fracture, peripheral neuropathy, and prior antero-septal MI, was hospitalized on day 37 for a road traffic accident with resultant blunt chest trauma. Paramedics and police were called to the scene and noted the subject seemed confused with an unusual history. Prior to the accident, she experienced a warm, flushed feeling with chest pain and shakiness after shopping and rushing around. Vital signs at the scene showed hypertension but normal pulse oximetry. Blood glucose was 146 at 12:20. Physical exam at the hospital revealed a tender sternum, right hip pain with rotation in a sitting position, and lateral right ankle tenderness. X-rays were negative for new fracture. An ECG showed normal sinus rhythm without acute ischemia. CT scans only showed post-CABG changes, coronary artery calcification, and diverticulosis. She was to be released from the hospital but fell faint and was hospitalized until day 40, when symptoms improved.
- **COMMENT: This does not appear to be related to hypoglycemia.**

INS-011:

- 328/5007 (Alogliptin 25 mg): 60 year old female with a history of T2D, hypertension, transient ischemic attack, stroke with left-sided weakness, and enlarged thyroid experienced Stevens-Johnson Syndrome on day 109. Symptoms included bilateral scaling of the skin on her feet, ankles, and toes. Relevant concomitant medications included insulin, clopidogrel, amlodipine, quinapril, oxybutynin extended-release, cefadroxil, and ibuprofen. The subject was treated with prednisone 4 mg, and the event resolved on day 128. On day 71, the subject was admitted to the hospital for arthralgia, underwent elective spinal fusion, and was discharged. Study medication was discontinued on day 70 as a result of the first hospitalization.

- **COMMENT: As this event occurred 39 days after alogliptin discontinuation, it is not likely to be study drug related.**
- 370/5013 (Alogliptin 25 mg): 34 year old male with a history of T2D, arterial hypertension, and appendectomy was admitted to the hospital on day 4 for hypersensitivity. Symptoms included difficulty breathing, trouble talking, and swallowing difficulties. Concomitant medications included losartan, candesartan, hydrochlorothiazide, and long acting insulin. Physical examination was positive for edema of the uvula, face, and neck. The subject was treated with chlorpheniramine and the event resolved on day 5. Study medication was interrupted and restarted on day 4. The subject was discontinued from the study on day 167 due to lack of efficacy.
 - **COMMENT: Rechallenge with alogliptin did not result in another event of hypersensitivity in this patient during the core trial although angioedema was reported to have occurred on Day 174 (during the extension trial). Concomitant medication included valsartan on both occasions.**
- 452/5007 (Alogliptin 25 mg): 58 year old male with a history of T2D, hypertension, hyperuricemia, diabetic retinopathy, left cataract, glaucoma, microalbuminuria, peptic ulcer, prior hypoglycemic events, and microaneurysms of the right eye was admitted to the hospital for hypoglycemic coma on day 75. The event occurred while the subject was sleeping. The subject was treated with dextrose for 8 hours until glucose levels stabilized. The event resolved on day 77. The subject discontinued the study on day 101 due to lack of efficacy. The investigator clarified that the cause of the hypoglycemic coma was attributed to alcohol.
 - **COMMENT: The hypoglycemic event was likely not study drug related although insulin may have contributed to this event.**

OLE-012:

- 329/8013 (Alogliptin 12.5 mg): 64 year old male with a relevant history of T2D, hypertension, hyperlipidemia, osteoarthritis, diabetic neuropathy, bilateral cataracts, left hip replacement, smoking, and previous enrollment in study MET-008 experienced a fall under icy conditions on day 114. The subject hit the back of his head and subsequently reported headaches, loss of fine motor skills, and intermittent numbness and tingling in his right hand. A CT scan revealed bilateral subdural hematomas measuring 2 cm on the right and 1.5 cm on the left. On day 161, the subject was hospitalized. Neurological exam revealed mild right facial weakness, right pronator drift, and diminished light touch sensation in both feet and distal legs. A MRI of the brain confirmed the CT findings and revealed intracranial hemorrhage. Bur hole drainage of the right chronic subdural hematoma was performed. On day 165, the event was considered resolved. Study medication was interrupted from day 162-165.
 - **COMMENT: The fall was likely due to icy conditions and not hypoglycemia.**
- 370/5002 (Alogliptin 12.5 mg): 54 year old female with a history of T2D, menopause, and previous enrollment in study INS-011 experienced syncope on day 136. She fainted for approximately 30 minutes and experienced prodromal symptoms, including feet numbness and discomfort, before the episode of syncope. The subject reported glucose of 142; it was 179 in the emergency room. The ECG was normal. The subject was

hospitalized. The event was considered resolved and the subject was discharged on day 137. Study medication was temporarily interrupted and restarted on day 138.

- 447/5024 (Alogliptin 25 mg): 33 year old female with a history of T2D, hypertension, diabetic nephropathy, hypertriglyceridemia, and previous enrollment in study INS-011 experienced a road traffic accident on day 86. The subject was hospitalized due to a motor vehicle accident with blunt abdominal injury. On day 87, the subject was discharged in stable condition. She later returned to the emergency room where x-ray confirmed a right rib fracture. The subject was later discharged. The event was considered resolved on day 168.
 - **COMMENT: The narrative did not provide information regarding the cause of the accident.**
- 452/5001 (Alogliptin 25 mg): 50 year old male with a history of T2D, hypertension, ischemic heart disease, family history of heart disease, smoking (30 years), and previous enrollment in study INS-011 was diagnosed with coronary artery stenosis on day 24 of the open-label extension study. On day 1, ECG showed ventricular premature complexes, which were assessed as not clinically significant. On day 24, coronary artery stenosis was diagnosed following a routine stress ECG which suggested myocardial ischemia. The subject was asymptomatic. A coronary angiogram on day 24 showed 100% RCA occlusion, 80-90% proximal mid-LAD lesion and other lesions. The end of treatment ECG was described as not clinically significant. A prolonged QTc interval (472 ms) was described, although the day 1 QTc interval was 431 ms. On day 34, the subject was admitted for elective coronary artery bypass grafting which was performed on day 35. The subject experienced respiratory failure following the operation and was intubated for 7 days. On day 44, the event was considered resolved, and the subject was discharged. The subject discontinued study OLE-012 on day 27 due to lack of efficacy (pending clarification). The last dose of study drug was given on day 28.
 - **COMMENT: Despite describing 100% RCA occlusion, this event does not meet the WHO criteria for a nonfatal myocardial infarction and is most consistent with stable, chronic coronary artery disease. The reason for discontinuation from study OLE-012 was miscoded as lack of efficacy, although this case does not describe hyperglycemia and the subject experienced an AE of coronary artery stenosis 3 days prior to study drug discontinuation.**
- 485/8008 (Alogliptin 25 mg): 71 year old male with T2D and prior enrollment in study MET-008 was diagnosed with an anaphylactic reaction after 3 wasp bites to the knee and both ankles on day 79. Symptoms included slight facial and lip swelling, leg rash, and general weakness with normal muscle tone. Treatment included IV epinephrine, antazoline, hydrocortisone, dexamethasone 8 mg IM, and oral cetirizine, and calcium. The subject's symptoms resolved within minutes of treatment.
- 228/9007 (Alogliptin 12.5 mg): 70 year old male with a history of T2D, peripheral edema, back pain, peripheral neuropathy, hypertension, and previous enrollment in study TZD-009 presented with severe back and leg pain on day 362. Two months earlier, he had a traumatic fall and onset of back pain. MRI revealed a mild compression fracture at L5 and central canal stenosis at L4-5 and L5-S1. On day 370, the subject underwent L4-

5 laminectomy with bilateral foraminotomies and L5 kyphoplasty. On day 371, the event was considered resolved and the subject was discharged.

- **COMMENT: Although the case of the fall on approximately day 302 was not specified, the severe back and leg pain which resulted in hospitalization and the SAE label was due to the fall.**
- 236/8001 (Alogliptin 12.5 mg): 79 year old female with a history of T2D, hypertension, and previous enrollment in study MET-008 had a left femur fracture on day 402. She fell on an icy step and was admitted for surgical intervention and repair. Study drug was interrupted from day 405 – 409. The event was considered resolved on day 405. The subject was discharged from the hospital on day 408.
 - **COMMENT: The patient fell under icy conditions.**
- 269/5001 (Alogliptin 12.5 mg): 52 year old male with a history of T2D, bilateral hip surgery, left hip replacement, obesity, osteoarthritis, disc degeneration, and previous enrollment in study MED-008 experienced a rib fracture and nervous system disorder on day 416. That day, the subject was hospitalized for fractured ribs following an accident. He was hospitalized for 5 days and the study drug was interrupted. During hospitalization, a CT scan was done which showed a right frontal lobe lesion. On day 435, the subject was hospitalized for removal of the lesion, which was a benign familial tumor. The event was considered resolved and the subject was discharged on day 437.
 - **COMMENT: The reason for the accident was not provided, although the investigator considered the events not related to study drug.**
- 440/5006 (Alogliptin 12.5 mg): 50 year old male with a history of T2D, central obesity, hypertension, and previous enrollment in study INS-001 experienced loss of consciousness and a convulsion on day 273. The subject collapsed in his garden following heavy physical labor. The subject's son witnessed the event and reported that he was unconscious for 10 minutes. Blood sugar at the time of the event was reported as 5.5 mol/L, although this reviewer suspects 5.5 mmol/L (99 mg/dl) was intended. Physical examination was within normal limits. ECG showed sinus tachycardia with a heart rate of 104 bpm. Cardiac enzymes were normal. The event was considered resolved and the subject discharged from the hospital on day 274.
- 487/7013 (Alogliptin 12.5 mg): 72 year old male with a history of T2D, back pain, hypertension, and previous enrollment in study SULF-007 experienced allergic edema of the right side of the face on day 230. The cause was not found. The event resolved on day 232. No action was taken with the study drug.
 - **COMMENT: This event was likely not related to the study drug as the allergic event resolved despite continued therapy.**
- 029/2506 (Alogliptin 25 mg): 49 year old male with a history of T2D, osteoarthritis, and previous enrollment in study OPE-002 who fractured the left tibia in a work-related accident on day 39. The subject underwent open reduction internal fixation without complication. The event was considered resolved with sequelae on day 42.
 - **COMMENT: The fracture was not study drug related as it occurred in a work-related accident.**
- 234/5005 (Alogliptin 25 mg): 70 year old male with a history of T2D, peripheral edema, hyperlipidemia, obesity, osteoarthritis, neuropathy, sciatica, hypertension, and previous

enrollment in study INS-011 had a fall on day 201. He slipped and fell down 4 steps onto a cement surface, landing on his right side. He was transported to the hospital via ambulance. Exam revealed right upper extremity swelling and ecchymosis. Radiological studies confirmed a right hip spiral subtrochanteric fracture and probably right shoulder massive rotator cuff tear. An ECG revealed right bundle branch block; no old ECG was available for comparison. The subject was admitted for open reduction and intramedullary nailing of the right femoral fracture, which was performed on day 202. On day 205, the subject experienced hemorrhagic anemia that was described as continuing. On day 206, the event was considered resolved and the subject was discharged to a skilled nursing rehabilitation facility.

- **COMMENT: Although the patient slipped and fell down 4 steps, ECG on the day of the fall showed a right bundle branch block. No old ECG was available for comparison.**
- 370/5013 (Alogliptin 25 mg): 35 year old male with a history of T2D, hypertension treated with valsartan, and previous enrollment in study INS-011 experienced angioedema on day 174. The subject was hospitalized due to swallowing difficulties and trouble talking. The event resolved after 2 doses of chlorpheniramine maleate and the subject was discharged that day. The subject had an allergic reaction of the facial and uvula area on day 4 of study INS-011, which was considered a hypersensitivity reaction. The investigator considered the event not related to study drug based on the negative rechallenge and the subject continued in the study. Study drug was interrupted from day 174-175. On day 174, valsartan was discontinued and verapamil was started.

OPI-001:

- 296/3007 (Alo 25 mg + Pio 45 mg): 48 year old male with a history of T2D, smoking (25 years), hypertension, dyslipidemia, fatty liver, and obesity experienced myocardial ischemia on day 174. The subject's day 1 ECG showed incomplete right bundle branch block, which was reported as nonclinically significant. On day 146, the subject had 2-3 mm ST segment depression in leads V3-V6, aVF, II-III, and a high probability of myocardial ischemia. A repeat stress test showed similar findings. The subject was hospitalized on day 174 for chest pain which radiated to the left arm. The subject reported similar pain for the prior 2 months. ECG showed normal sinus rhythm with no ST-T changes or Q waves. A coronary angiogram on day 176 revealed 100% left circumflex artery occlusion that could not be opened, although there was a collateral supply. There was a 60% occlusion in the mid-RCA. The event resolved and the subject was discharged with atenolol.
- 412/3119 (Alogliptin 12.5 mg): 32 year old female with a history of T2D, spontaneous abortion, 2 Caesarean sections, and concurrent vaginal mycosis experienced a spontaneous abortion on day 80. The subject had vaginal bleeding and pain in the hypogastrium from day 80-81. Serum pregnancy test on day 85 was positive (beta human gonadotropin [β HCG] level 52.62 mIU/ml, suggesting 1 week gestation). However, a transvaginal ultrasound that day showed a normal uterus without signs of pregnancy. An additional pregnancy test on day 92 confirmed the subject was not pregnant (β HCG 6.6 mIU/ml). It was determined that the pregnancy aborted on day 80.

The subject stopped taking study drug on day 84 because of the pregnancy and did not resume it afterwards. Her last study visit was day 106.

- 833/3004 (Alo 12.5 mg + Pio 45 mg): 44 year old male with a history of T2D and hypertension experienced “angina unstable” on day 9. The subject developed syncope while driving lasting approximately 15 seconds that day. He was hospitalized and stated that he had chest pain, diaphoresis, and palpitations after taking the study drug. His ECG was normal at admission, although CK was 211 IU/L (30-170 IU/L). Other cardiac enzymes were within normal limits. Approximately 7 hours after admission, his CK value improved to 178 IU/L. The subject was discharged on day 10. A dobutamine stress echocardiogram was negative for ischemic heart disease on day 19. The event resolved. Study drug was discontinued on day 9.
 - **COMMENT: Alternatively, this event could have been coded as syncope.**
- 830/3002 (Alo 25 mg + Pio 45 mg): 46 year old female with a history of T2D and 4 pregnancies (1 live birth, 3 spontaneous abortions) experienced a spontaneous abortion on day 197. The subject had a positive serum pregnancy test on day 183 and positive urine and serum pregnancy tests on day 188. β HCG was 390.7 mIU/ml. On day 199, the subject presented with 2 days of vaginal bleeding. A transvaginal ultrasound confirmed a spontaneous abortion, and the event resolved. Previous spontaneous abortions were due to fall, lack of glycemic control, and premature rupture of membranes. The subject took her last dose of study medication on day 180.

OPI-002:

- 012/2524 (Pioglitazone 30 mg): 43 year old female with a history of T2D and hysterectomy who experienced syncope on day 5 while on vacation. Her blood sugars at the time of admission were unknown. She also had a fainting episode prior to hospital admission. The syncope was considered resolved and the subject was discharged on day 7. Study drug was discontinued and the subject was withdrawn from the study on day 53 due to a major protocol violation (the subject had received another medication for her diabetes).
- 040/2513 (Alo 25 mg + Pio 30 mg): 43 year old female with a history of T2D, dyslipidemia, headache, hypertension, neck pain, and urinary tract infection experienced syncope on day 146. She completed a study visit the same day without incident or complaint. She fainted at home. The subject was discharged on day 147 and the event considered resolved.

7.3.3 Dropouts and/or Discontinuations

In controlled phase 2 and 3 studies originally submitted to the NDA, reasons provided for voluntary withdrawal from phase 3 studies included moving, family illness, personal reasons, and conflicts with work schedules. The percentage of subjects who withdrew due to AEs was numerically higher in the all alogliptin (2.8%), the alogliptin 12.5 mg (2.7%) and alogliptin 25 mg (2.6%) groups compared to placebo (2.1%) but no dose response relationship was seen.

NDA 22-426. AEs leading to discontinuation (≥ 2 subjects) in controlled phase 2 and 3 studies			
SOC-PT	Placebo	All Alo	Alogliptin

	n=534	n=1961	6.25 n=42	12.5 n=42	25 n=910	50/100 n=87
Any AE that lead to discontinuation	11 (2.1)	48 (2.4)	0	21 (2.3)	22 (2.4)	5 (5.7)
Cardiac	1 (0.2)	5 (0.3)	0	2 (0.2)	3 (0.3)	0
Cardiac failure congestive	0	2 (0.1)	0	0	2 (0.2)	0
General & admin site	0	5 (0.3)	0	3 (0.3)	2 (0.2)	0
Sudden death	0	2 (0.1)	0	2 (0.2)	0	0
Investigations	0	7 (0.4)	0	4 (0.4)	3 (0.3)	0
Liver function test abnl	0	3 (0.2)	0	2 (0.2)	1 (0.1)	0
Nervous system	2 (0.4)	8 (0.4)	0	3 (0.3)	2 (0.2)	3 (3.4)
Headache	1 (0.2)	4 (0.2)	0	1 (0.1)	1 (0.1)	2 (2.3)

In the studies originally submitted to NDA 22-426 (i.e. OPI-001 and OPI-002), subjects in the combination groups discontinued less often for all reasons except voluntary withdrawal when compared with the pioglitazone group (3.5% vs. 3.7%, respectively). Compared with the alogliptin group, subjects in the combination group discontinued more often due to AEs (2.3% vs. 1.4%) and a major protocol deviation (3.1% vs. 1.4%). The AEs leading to discontinuation in ≥ 2 subjects overall are shown in the table below. The SAEs that led to discontinuation and were judged by the investigator to be related to study drug were acute myocardial infarction (OPI-002: 665/2509) and unstable angina (OPI-001: 833/3004) in the combination group, and lower respiratory tract infection (OPI-001: 694/3023) and musculoskeletal pain (OPI-002: 665/2506) in the pioglitazone group.

NDA 22-426. AEs leading to discontinuation (≥ 2 subject overall) in pooled studies OPI-001 and OPI-002			
	Alogliptin (n=421) N (%)	Pioglitazone (n=550) N (%)	Alo+Pio (n=1107) N (%)
Discontinuation due to any AE	6 (1.4)	19 (3.5)	26 (2.3)
Gastrointestinal			
Diarrhea	0	1 (0.2)	2 (0.2)
Nausea	0	0	2 (0.2)
General & admin site			
Edema peripheral	0	2 (0.4)	3 (0.3)
Investigations			
Weight increased	0	0	2 (0.2)
Liver tests abnormal	0	1 (0.2)	1 (0.1)
Nervous system			
Dizziness	0	1 (0.2)	1 (0.1)

Please refer to section 6.1.3 Patient Disposition for more information.

7.3.4 Significant Adverse Events

Hypoglycemia was an AE of special interest. Subjects reported hypoglycemic events and were instructed to record each incident's blood glucose values and any signs or symptoms in a diary. Data from the diary was entered into the clinical database, although hypoglycemic events were

not summarized as AEs unless they met the criteria for an SAE. The following definitions were used:

- Mild to moderate hypoglycemia: Blood glucose < 60 mg/dl with symptoms or blood glucose < 50 mg/dl with or without symptoms
- Severe hypoglycemia: Any episode requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions, associated with a documented blood glucose < 60 mg/dl unless the clinical situation makes obtaining a blood glucose difficult (e.g. if it involves coma or seizure)

The percentage of subjects who experienced hypoglycemia was similar between treatment groups, except for the 6.25 and 50/100 mg groups which had a slightly higher incidence symptomatic or asymptomatic hypoglycemia with glucose < 50 mg/dl and asymptomatic hypoglycemia with glucose ≥ 50 mg/dl and ≤ 60 mg/dl. The 6.25 mg group also had a small increase in symptomatic events with glucose > 60 mg/dl. Note however that the 6.25 and 50/100 mg groups were the smallest in size (n=42 and 87, respectively). Thus, a small difference in the number of events may have affected the percent incidence. The lack of a dose-related trend in hypoglycemic events is reassuring.

NDA 22-271. Hypoglycemic events in the controlled phase 2 and 3 study group						
Hypoglycemic event	Placebo (n=534)	All Alo doses (n=1961)	Alogliptin (mg)			
			6.25 (n=42)	12.5 (n=922)	25 (n=910)	50/100 (n=87)
Mild - Moderate						
Symptomatic & glucose <60 mg/dl	32 (6.0)	109 (5.6)	3 (7.1)	53 (5.7)	51 (5.6)	2 (2.3)
Symptomatic or asymptomatic & glucose <50 mg/dl	24 (4.5)	82 (4.2)	4 (9.5)	34 (3.7)	35 (3.8)	9 (10.3)
Severe						
Any episode that required assistance w/ glucose <60 mg/dl	3 (0.6)	4 (0.2)	1 (2.4)	2 (0.2)	1 (0.1)	0
Additional categories						
Symptomatic, no blood glucose	9 (1.7)	26 (1.3)	0	15 (1.6)	11 (1.2)	0
Asymptomatic & glucose ≥50 mg/dl & ≤60 mg/dl	1 (0.2)	22 (1.1)	3 (7.1)	6 (0.7)	2 (0.2)	11 (12.6)
Symptomatic & glucose > 60 mg/dl	13 (2.4)	62 (3.2)	3 (7.1)	28 (3.0)	28 (3.1)	3 (3.4)

Five subjects (2 alogliptin 12.5 mg; 3 alogliptin 25 mg) experienced adverse events of hypoglycemia. Two of these were SAEs, one occurring in a patient also taking glyburide 10 mg daily and the other attributed to alcohol intake in a patient also taking insulin. Please refer to section 7.3.2 Nonfatal Serious Adverse Events.

Hypersensitivity reactions, included anaphylaxis, angioedema, rash, urticaria, and exfoliative skin conditions including Stevens-Johnson syndrome have been reported in patients receiving DPP-4 inhibitors. Thus, these were AEs of interest in alogliptin clinical studies.

A higher percentage of subjects in the all alogliptin group had AEs in the immune system SOC when compared to placebo (1.3% vs. 0.4%, respectively). The preferred terms that contributed to this difference were hypersensitivity and drug hypersensitivity. Furthermore, a slightly higher

percentage of subjects experienced AEs in the skin and subcutaneous tissue disorders SOC when compared to placebo (11.5% vs. 10.3%, respectively). This difference is due to events of pruritis and rash. The only event of angioedema reported in phase 2 and 3 studies was in a placebo subject.

The sponsor analyzed the phase 2 and 3 AEs with 2 different cluster analyses:

- The angioedema standardized MedDRA query (SMQ) version 10.0 includes preferred terms from 11 SOCs, including reactions such as angioedema and hypersensitivity as well as localized swelling, urticaria, and some respiratory events such as wheezing and throat tightness.
- A customized MedDRA query of potential cutaneous drug reaction (PCDR) events, including high level group terms in the immune system disorders SOC and skin and subcutaneous disorders SOC from MedDRA version 10.0.

A full list of the preferred terms included in these clusters can be found in the NDA 22-271's Integrated Analysis of Safety End of Text Table 8.4.2.1.9. No rationale was provided for how the sponsor decided which preferred terms to include in the customized cluster.

COMMENT: The customized MedDRA query of PCDR events did not include most ulcers; only venous ulcer pain was included.

The ratio of alogliptin: placebo-treated subjects in controlled phase 2 and 3 studies was approximately 3.7:1. Subjects in the placebo group discontinued due to hyperglycemic rescue earlier than alogliptin subjects. Because exposure was less in the placebo than the alogliptin dose groups, the sponsor calculated the number of AEs per 100 subject-years of exposure.

Angioedema cluster

A similar percentage of subjects in the controlled phase 2 and 3 placebo and alogliptin study groups used antipruritics prior to screening (1.1% vs. 1.5%). A similar percentage of subjects used agents acting on the renin-angiotensin system in the placebo and alogliptin groups (48.1% and 44.6%, respectively). Although the percentages of subjects experiencing angioedema cluster events in the placebo and alogliptin groups were similar, the number of events per 100 subject-years of exposure was approximately 25% greater in the alogliptin 12.5 and 25 mg groups. The number of events per 100 subject-years of exposure was greatest in the alogliptin 50/100 mg group (38.1 vs. 9.8 for placebo).

NDA 22-271. Treatment-emergent angioedema cluster events in controlled phase 2 and 3 studies						
Cluster, n (%) (a)	Placebo (n=534)	All Alo (n=1961)	Alogliptin			
			6.25 (n=42)	12.5 (n=922)	25 (n=910)	50/100 (n=87)
Angioedema	18 (3.4) [9.8]	88 (4.5) [13.0]	2 (4.8) [27.6]	36 (3.9) [11.4]	45 (4.9) [13.3]	5 (5.7) [38.1]
(a) Number of events per 100 subject-years of exposure						

The most common angioedema cluster event was peripheral edema, which occurred similarly in the alogliptin and placebo groups. Eleven angioedema cluster events, however, were reported in alogliptin but not placebo subjects (see list below). Eight of these eleven events each occurred in 1 alogliptin-treated patient only, and absence in the placebo group may reflect the ~4:1 randomization. Angioedema and urticaria chronic were reported in placebo but not alogliptin

subjects. Hypersensitivity occurred slightly more often in the alogliptin group, especially when events per 100 subject-years exposure was compared (1.4 vs. 0.5). However, urticaria occurred at a similar rate in alogliptin and placebo subjects.

NDA 22-271. Treatment emergent AEs in the angioedema cluster by preferred term in the controlled phase 2 and 3 study group (n, %, events per 100 subject-years of exposure)		
Angioedema cluster & preferred terms	Placebo (n=534)	All alogliptin doses (n=1961)
Angioedema cluster	18 (3.4) [9.8]	88 (4.5) [13.0]
Edema peripheral	14 (2.6) [7.3]	58 (3.0) [7.9]
Wheezing	0	8 (0.4) [1.0]
Hypersensitivity	1 (0.2) [0.5]	7 (0.4) [1.4]
Urticaria	2 (0.4) [1.0]	7 (0.4) [0.9]
Drug hypersensitivity	0	4 (0.2) [0.6]
Face edema	0	2 (0.1) [0.2]
Conjunctival edema	0	1 (0.1) [0.1]
Eyelid edema	0	1 (0.1) [0.1]
Local swelling	0	1 (0.1) [0.1]
Edema	0	1 (0.1) [0.1]
Scrotal swelling	0	1 (0.1) [0.1]
Swelling face	0	1 (0.1) [0.1]
Swollen tongue	0	1 (0.1) [0.1]
Tongue edema	0	1 (0.1) [0.1]
Angioedema	1 (0.2) [0.5]	0
Urticaria chronic	1 (0.2) [0.5]	0

One subject (INS-011 370/5013) who received alogliptin 25 mg had an SAE of hypersensitivity, which resulted in discontinuation of study drug. No recurrence of symptoms occurred with reintroduction of study drug, although angioedema was reported to have occurred on Day 174 during the extension trial. Concomitant medication included valsartan on both occasions.

Three subjects had an event in the angioedema cluster, which lead to discontinuation, 2 of which occurred in uncontrolled study OLE-012.

- 366/5014 (INS-011; alogliptin 25 mg): A 54 year old female who developed mild urticaria on day 99. The investigator reported a red urticarial rash with multiple lesions that covered the entire body. Concomitant medications included atenolol, chlorthalidone, losartan, metformin, ASA, rosuvastatin, benzaifibrate, NPH insulin, omeprazole, flixonase acqua, salmeterol, fluticasone, allopurinol, citalopram, alprazolam, and ciprofloxacin. Eosinophil count was 32% on day 113 and 4% on day 121. Study drug was discontinued on day 127 and the event considered resolved on day 134.
- 369/8006 (OLE-012; alogliptin 25 mg): A 50 year old female with no relevant medical history was diagnosed with urticaria on day 3, which lead to study withdrawal on day 3. The reaction was generalized on the whole body, required no treatment, and resolved by day 7.
- 452/5007 (OLE-012; alogliptin 25 mg): A 58 year old male, with a history of hypertension, hyperuricemia, gallstones, and microalbuminuria, experienced a moderate, but not clinically significant hepatic enzyme elevation on day 29 and moderate peripheral edema on day 35. Relevant concomitant medications were actraphane, atenolol, disprin,

puricos, ramipril, Cosopt drops, and felodipine. Study medication was discontinued on day 42 due to both events.

NDA 22-271. AEs that lead to discontinuation in the angioedema cluster in all phase 2 and 3 studies					
Study	Subject	Age Gender	Treatment	Day	Preferred term
INS-011	366/5014	54 F	Alogliptin 25 mg	99	Urticaria
OLE-012	369/8006	50 F	Alogliptin 25 mg (12.5 mg in MET-008)	3 (184 cumulative)	Urticaria
OLE-012	452/5007	58 M	Alogliptin 25 mg (25 mg in INS-011)	135	Edema peripheral

PCDR Cluster

Skin AEs were classified as AEs of special interest in controlled phase 3 studies due to reports of necrotic skin lesions in monkey studies with other DPP-4 inhibitors. Four- and 13-week monkey studies were designed specifically to examine the potential for drug induced skin lesions. There was no evidence of drug-related skin lesions in clinical observations, macroscopic analyses at necropsy, or histological analyses at necropsy in either monkey study. The NOAEL from skin-related toxicity in the 13 week monkey study was 30 mg/kg/d, which provided approximately 31x expected human exposure. Nonetheless, investigators were directed to examine the integrity of the skin and digits at each visit. High level terms included in the PCDR cluster included the following.

NDA 22-271. High level group terms included in the PCDR cluster	
SOC	High level terms
Immune system disorders	Allergic conditions NEC
	Allergies to foods, food additives, drugs, and other chemicals
	Anaphylactic responses
	Angioedemas
	Urticarias
Skin and subcutaneous tissue disorders	Angioedemas
	Urticarias
	Rashes, eruptions, and exanthems NEC
	Dermal and epidermal condition NEC
	Dermatitis and eczema
	Dermatitis ascribed to specific agent
	Erythemas
	Exfoliative conditions
	Papulosquamous conditions
	Pruritis NEC

COMMENT: The customized MedDRA query of PCDR events did not include most ulcers; only venous ulcer pain was included.

The percentage and number of PCDR events per 100 subject-years of exposure were slightly higher in the all alogliptin dose group when compared to placebo (9.6% and 28.4 vs. 6.9% and 24.9). This was also true when alogliptin 12.5 and 25 mg were compared to placebo with an apparent dose response relationship except for the 50/100 mg dose group that was of small size.

NDA 22-271. Treatment-emergent PCDR cluster events in controlled phase 2 and 3 studies						
Cluster, n (%) (a)	Placebo (n=534)	All Alo (n=1961)	Alogliptin			
			6.25 (n=42)	12.5 (n=922)	25 (n=910)	50/100 (n=87)
PCDR	37 (6.9) [24.9]	188 (9.6) [28.4]	1 (2.4) [13.8]	81 (8.8) [26.4]	100 (11.0) [30.1]	6 (6.9) [44.4]
(a) Number of events per 100 subject-years of exposure						

The most common AEs in the PCDR cluster were pruritis and rash, which occurred in a higher percentage of subjects in the all alogliptin group than placebo group (pruritis 1.6% vs. 0.4%; rash 1.6% vs. 0.7%). More subjects experienced AEs of contact dermatitis, dermatitis, allergic dermatitis, and atopic dermatitis in the all alogliptin group than in the placebo group (27/1961 [1.4%] vs. 3/534 [0.6%], respectively). Skin exfoliation, exfoliative rash, and dermatitis exfoliative were reported in 10/1961 (0.5%) subjects in the all alogliptin group and 1/534 (0.2%) subject in the placebo group. The preferred terms described in this paragraph accounted for the differences between the alogliptin and placebo groups with respect to the PCDR cluster.

Only 3 of the 225 AEs reported in the PCDR cluster in all phase 2 and 3 studies were classified as SAEs. All 3 subjects received alogliptin 25 mg. One subject with an SAE discontinued the study as a result of the SAE. (Please refer to case narratives above.) Subject 370/5013's hypersensitivity reaction, which included difficulty breathing and swallowing with edema of the uvula, face, and neck, may not have been due to alogliptin. Alogliptin was stated 3 days prior and candesartan was started 10 days earlier. Both drugs were interrupted and later restarted without symptom recurrence. Subject 485/8008's anaphylactic reaction occurred after a wasp bite.

NDA 22-271. SAEs in PCDR cluster in all phase 2 and 3 studies						
Study	Subject	Age Gender	Treatment	Day	Preferred term	Action
TZD-009	226/9002	59 M	25 mg	32	Serum sickness	Discontinued
INS-011	370/5013	34 M	25 mg	4	Hypersensitivity (allergic reaction in facial and uvula area)	Interrupted
OLE-012	485/8008	71 M	25 mg (Placebo in MET-008)	79	Anaphylactic reaction after wasp bite	None

Thirteen of 2,454 (0.5%) subjects in all phase 2 and 3 studies had an event in the PCDR cluster which led to discontinuation (1 placebo, 3 alogliptin 12.5 mg, 7 alogliptin 25 mg, and 2 alogliptin 50 mg). Only one of the PCDR cluster events that led to study discontinuation was an SAE. Five of these subjects discontinued from OLE-012. Thus the ratio of placebo: alogliptin discontinuations for PCDR events in controlled phase 2 and 3 studies was 1:7, which is not inconsistent with the randomization scheme of 1:4 given the very low event rates. Example narratives are as follows:

- 272/2002 (alogliptin 50 mg): A 71 year old female, with a history of high cholesterol, right and left hip replacements, sleep apnea, hypertension, diabetes, microalbuminuria, nephropathy, menopause, and allergies to sulfa and ditropan (both of which cause rash), experienced a moderate rash on the extremities on day 11 of study drug. Study drug was discontinued on day 12 and the AE resolved on day 16. Concomitant medications were atorvastatin and acetylsalicylic acid. The investigator judged the AE as definitely related to study drug.

- 327/9009 (alogliptin 12.5 mg): A 53 year old male with a relevant history of sulfa drug allergy and smoking for 9 years was diagnosed with rash on day 83. He had a nonserious, small maculopapular rash with mild redness on both feet ascending to lower extremities. The subject was treated with butenafine cream and the event resolved on day 85. Study medication was discontinued on day 84 as a result of this event. The investigator reported the relationship to study medication as definitely related.

Although sponsors of some other DPP-4 inhibitors evaluated infections as an AE of special interest, alogliptin's sponsor did not. However, the incidence of infection and infestation TESAEs in controlled phase 2/3 trials of alogliptin was similar in the alogliptin and placebo groups (0.8% vs. 0.9%); the incidence of infection and infestation TEAEs was less in the alogliptin group when compared to placebo (28.8% vs. 31.3%).

When the NDA 22-271's Integrated Analysis of Safety was searched for the term "pancreatitis", 2 of 1,961 (0.1%) alogliptin subjects were identified in the controlled phase 2 and 3 studies. These events were coded to the preferred terms "pancreatitis" and "pancreatitis acute". Both events occurred in Caucasian females < 65 years of age with baseline serum creatinine < 1.5 mg/dl after 30 days to 6 months exposure to study drug. Subject 269/5004's adverse event was serious; subject 256/5004's adverse event resulted in discontinuation. Narratives are listed below. Overall, however, the pancreatitis event rate was low and similar to placebo (0%).

- 269/5004 (INS-011; alogliptin 12.5 mg group): A 55 year old female, with a history of obesity, MI, hypertension, hypothyroidism, back pain, and soft tissue mass right abdomen, was admitted to the hospital on day 88 with a 3 week history of intermittent nausea and abdominal pain secondary to cholecystitis and pancreatitis. An ultrasound was negative and an upper gastrointestinal endoscopy performed on day 83 showed normal esophagus with nonbleeding erythematous gastrophyl and no gross lesions in the duodenum. A CT scan of the abdomen and pelvis showed a fatty liver but was otherwise negative. The subject was diagnosed with acute pancreatitis, acute cholecystitis, urinary tract infection, and dehydration and treated with intravenous ampicillin/sulbactam. On day 91, the amylase and lipase levels were reported as normal and the subject underwent a laparoscopic cholecystectomy with cholangiogram. On day 92, the subject was discharged from the hospital and the event resolved. Study drug was interrupted from day 88 – 93 due to this event. On day 140, the subject was withdrawn due to lack of efficacy. The last dose of study drug was taken on day 136.
- 256/5004 (INS-011; alogliptin 25 mg group): A 45 year old female, with history of hyperlipidemia and neuropathy, experienced pancreatitis acute on day 73 which led to withdrawal from the study. Study drug was discontinued on day 78. Concomitant medications included acetaminophen, naproxen, metformin, insulin glargine, atorvastatin, diphenhydramine, evening primrose, black cohosh, and clotrimazole cream. The patient was medically managed and the event resolved with sequelae on day 89. The subject experienced additional AEs of heart palpitations, pedal edema, athlete's foot, and depression on days 2, 6, 15, and 150, respectively.

7.3.5 Submission Specific Primary Safety Concerns

After carefully considering the recommendations of the Endocrinologic and Metabolic Drugs Advisory Committee on July 1 and 2, 2008 and the data submitted, the division determined that all new therapies developed for the treatment of type 2 diabetes should rule out unacceptable cardiovascular risk (see December 2008 Final Guidance titled *Diabetes mellitus: Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes*). The Division has determined that even those therapies with a submitted NDA at FDA and those in advanced stages of development at the time the December 2008 guidance was issued should also rule out unacceptable cardiovascular risk. On August 5, 2008, the sponsor submitted additional analyses of cardiovascular events observed in the pooled dataset. The analysis evaluated all deaths, MACE (Major Adverse Cardiovascular Events), cardiovascular SAEs and AEs and defined clusters of ischemic heart disease, cardiac failure, and cardiac arrhythmia related events. On November 13, 2008, the sponsor submitted a revised MACE table which calculated patient-years of exposure by dividing patient days by the more customary 365.25 (rather than 365) and submitted a MACE analysis by individual study, as requested by the division on November 5, 2008.

In these analyses, the sponsor retrospectively adjudicated events of nonfatal myocardial infarction (MI) and nonfatal stroke. MedDRA SMQs and the World Health Organization (WHO) definitions were used to determine events of cardiovascular death, nonfatal MI, and nonfatal stroke:

- Nonfatal MI: ischemic symptoms, ECG changes consistent with ischemia, and elevated enzyme levels (either troponin-I or CK-MB) above the upper limit of normal (2 of the 3 conditions are required)
- Stroke: An acute focal neurologic dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to the involvement of focal areas in the brain. If the symptoms and signs disappear completely within a few minutes or hours (< 24 hours), the event is termed a transient ischemic attack. If the symptoms and/or signs last > 24 hours, the event is a completed stroke.

As two other NDAs without prospective cardiovascular event adjudication were also under review at that time, the division wished to standardize the approach to evaluating cardiovascular risk across all 3 programs. In a January 11, 2009 letter to the sponsor, the division clearly stated the analysis population, endpoints, and types of analyses to be conducted. This included both 1) “SMQ major adverse cardiovascular analysis (MACE) analysis” which was the composite endpoint of cardiovascular death and all preferred terms in the standardized MedDRA queries for “myocardial infarction” and “central nervous system haemorrhages and cerebrovascular accidents” and 2) “custom MACE” which was the composite endpoint of cardiovascular death and 34 MedDRA preferred terms.

The “custom MACE” was created as follows. Without considering which events had actually occurred, a panel of 3 FDA clinical reviewers independently reviewed the list of all PTs included in the “SMQ MACE” with the following question in mind, “If I had a patient who actually had a

MI or stroke, is this a preferred term that I might actually have chosen for such an event?” The goal was to select only those PTs that seemed highly likely to represent true events of MI or stroke with a mechanism of atherosclerotic plaque development followed by plaque rupture or thrombosis. The lists generated by the 3 clinical reviewers were compared and any PTs for which there was not unanimous agreement to include or exclude were open for discussion. Consensus was reached regarding inclusion or exclusion for all PTs. The complete list of “custom MACE” PTs is included in the agency’s January 11, 2009 information request letter.

As stated above, it was decided that the 3 NDAs currently under review must meet the cardiovascular safety standards of other diabetic drugs in development, as recommended by the July 2008 Endocrinologic and Metabolic Drugs Advisory Committee. This meant that, prior to approval, the incidence of important cardiovascular events occurring with the investigational agent should be compared to the incidence of important cardiovascular events occurring with the control group and that the upper bound of the 2-sided 95% confidence interval (CI) for the estimated risk ratio should be < 1.8. If the integrated analysis approach does not show this, then a single large safety trial should be conducted alone or added to other trials to satisfy this upper bound. On January 21, 2009, the sponsor submitted the requested information, which is shown below. Note that this information was only requested for controlled clinical trials; therefore, the events from the uncontrolled open-label extension trial are not included.

NDA 22-271 & 22-426. MACE events sorted by treatment group and type of events						
Patient	Treatment	Preferred term	Day	Serious	SMQ MACE	Custom MACE
SULF-007						
422/7017	12.5	MI	41	Yes	Yes	Yes
104/7016	25	Hemiparesis*	108	No	Yes	No
244/7001	25	Blood creatinine phosphokinase increased	182	No	Yes	No
MET-008						
315/8016	Placebo	Coronary artery occlusion*	84	No	Yes	No
263/8006	12.5	CVA	99	No	Yes	Yes
520/8010	12.5	Hypertensive heart disease	45	Yes	Yes	Yes
448/8001	25	MI	63	Yes	Yes	Yes
TZD-009						
452/9004	Placebo	Acute coronary syndrome	-40	Yes	Yes	No
107/9005	12.5	MI	32	Yes	Yes	Yes
246/9002	12.5	Transient ischemic attack	54	No	Yes	No
463/9003	12.5	Sudden death	42	Yes	Yes	Yes
252/9006	25	MI	139	Yes	Yes	Yes
320/9003	25	MI	20	Yes	Yes	Yes
387/9001	25	Carotid artery occlusion	127	Yes	Yes	No
INS-011						
395/5009	Placebo	Ischaemic stroke	50	Yes	Yes	Yes
447/5009	12.5	Transient ischemic attack	79	No	Yes	No
464/5005	12.5	Sudden death	71	Yes	Yes	Yes
OPI-001						
265/3001	Placebo	CVA	14	Yes	Yes	Yes
632/3003	Placebo	MI	144	Yes	Yes	Yes
888/3029	Placebo	Cerebrovascular insufficiency*	141	No	Yes	No

907/3016	Placebo	Sudden cardiac death	156	Yes	Yes	Yes
725/3005	12.5	MI	186	No	Yes	Yes
395/3022	25	Lacunar infarct*	149	Yes	Yes	Yes
694/3017	25	Hemiparesis*	27	No	Yes	No
704/3001	25	Carotid artery occlusion	122	Yes	Yes	No
716/3021	25	MI	175	No	Yes	Yes
728/3008	25	MI	84	No	Yes	Yes
919/3007	25	Ischaemic stroke	35	Yes	Yes	Yes
OPI-002						
053/2513	Placebo	Electrocardiogram ST segment elevation*	1	No	Yes	No
640/2506	Placebo	Cerebral ischaemia*	196	Yes	Yes	No
673/2501	Placebo	Cerebrovascular insufficiency*	-11	No	Yes	No
291/2501	12.5	Vertebrobasilar insufficiency*	164	No	Yes	No
741/2506	12.5	Carotid artery stenosis*	171	No	Yes	No
067/2506	25	Transient ischaemic stroke	102	No	Yes	No
665/2509	25	Acute MI	26	Yes	Yes	Yes
* Cases in which this reviewer disagrees with the sponsor-designated preferred terms. Please refer to case narratives and comments below.						

NOTE: Sixteen of the 35 SMQ MACE events were AEs, not SAEs, including 3 events of MI in study OPI-001 (725/3005, 716/3021, and 728/3008).

Narratives for the 35 MACE events are provided below.

SULF-007:

- 422/7017 (Alogliptin 12.5 mg): 52 year old male with a history of T2D, class II coronary artery disease, dyslipidemia, hypertension, bilateral shoulder pain, and typhoid was hospitalized on day 41 for a myocardial infarction (MI). He was also taking open-label SULF 15 mg at the time of the event. At 11 AM on day 41, the subject experienced left-sided chest pain which increased and led him to visit the hospital at 3 PM. At 5 PM, he was admitted to the general hospital's intensive care unit for a severe ST-elevation MI. CPK and CPK-MB were 580 and 40, respectively. After the diagnosis of anteroseptal MI was established, streptokinase was given. Echocardiogram revealed an ejection fraction (EF) of 44% with evidence of mitral regurgitation and hypokinesia of the left ventricle. The event resolved on day 49 and the subject was discharged.

COMMENT: Although the subject had cardiac risk factors for an MI, the event which occurred on day 41 may have been drug related.

- 104/7016 (Alogliptin 25 mg): 43 year old female with a history of T2D, diabetic neuropathy, and headache who experienced left-sided hemiparesis and memory impairment on day 108. The AEs resolved on day 148. The subject was treated with ciprofloxacin from day 85 to 103 for a urinary tract infection. The subject voluntarily withdrew from the study on day 162.

COMMENT: Although few details are provided, the preferred term of hemiparesis lasting > 24 hours meets the criteria for a CVA.

- 244/7001 (Alogliptin 25 mg): 69 year old female with a history of T2D, hypercholesterolemia, hypertension, asthma, COPD, and previous smoking, was hospitalized for an asthma exacerbation on day 182. She experienced AEs of creatinine

phosphokinase elevation, worsening of GERD, worsening of hypertension, and BUN elevation. The pre-randomization ECG showed extensive ST-T segment changes suggestive of myocardial ischemia but were considered not clinically significant. During hospitalization, CPK levels were 69 U/l, CKMB 1.4 ng/ml, and troponin 0.22 ng/ml and 0.24 ng/ml. Serum creatinine was 1.3 mg/dl and BUN was 32 mg/dl. ECG showed stable ST-T abnormalities. Myocardial perfusion scan was essentially normal and myocardial infarction was ruled out. Study drug was discontinued on day 181 due to asthma.

MET-008:

- 315/8016 (Placebo): 65 year old male with a history of T2D, coronary artery disease, hyperlipidemia, hypertension, ventricular fibrillation, and implantable defibrillator experienced an AE of coronary artery occlusion on day 84. Baseline serum creatinine was 1.4 mg/dl. The subject also experienced renal failure on days 83 – 106 when serum creatinine was 1.6 and 1.4 mg/dl and BUN was 25 and 15 mg/dl, respectively. The subject also experienced anemia on day 29 – 133 when hematocrit values were 34.5% and 34.1% and hemoglobin values 11.6 and 11.5 g/dl, respectively.
COMMENT: This reviewer wonders, if more information was provided, if this AE of coronary artery occlusion would meet criteria for an SAE or myocardial infarction.
- 263/8006 (Alogliptin 12.5 mg): 54 year old male with a history of T2D, benign bradycardia, gait disturbance, hypertension, bilateral cerebellar hemispheric infarct, and old myocardial infarction was admitted to the hospital on day 68 due to bradycardia and day 155 for weakness due to a fall. The subject began alogliptin 12.5 mg on October 9, 2006 and was receiving metformin 2,000 mg at the time of the events. On day 68, the subject received a dual chamber permanent pacemaker for symptoms due to worsening bradycardia with a Mobitz type II, second degree AV block. On day 71, the subject underwent a revision and replacement of the atrial lead. Bradycardia resolved and he was discharged on day 72. On day 154, the subject became lightheaded, fell, and was hospitalized on day 155. Physical exam revealed swelling of the left knee, bilateral knee abrasions, 1+ pitting edema to the mid-shin bilaterally, and weakness. Hypoglycemic was not suspected. The subject was seen by neurology in January 2007 for gait unsteadiness with the resulting impression of a possible stroke. CT of the head revealed an old bilateral cerebellar infarct. A repeat CT scan during the hospitalization was normal. The subject's strength increased with physical therapy but he was unable to walk without assistance. He was transferred to a nursing home for continued therapy and discharged on day 173. Study medication was interrupted from day 68 to 72 and day 155 to 172.
- 520/8010 (Alogliptin 12.5 mg): See above section 7.3.1 Deaths.
- 448/8001 (Alogliptin 25 mg): See above section 7.3.1 Deaths.

TZD-009:

- 452/9004 (Placebo): 51 year old male with a history of T2D, hyperlipidemia, hypertension, MI, and coronary angioplasty who experienced acute coronary syndrome

on day -41. The event resolved after 2 days. Prebaseline ECG showed anterior infarct and was considered nonclinically significant. The subject completed the study.

COMMENT: Event occurred prior to exposure to placebo.

- 107/9005 (Alogliptin 12.5 mg): 45 year old male with a history of T2D, smoking (30 years), hypertension, and hyperlipidemia who was admitted to the hospital on day 32 for an MI. The subject complained of intermittent chest discomfort and diaphoresis for 3 days. The ECG showed < 1 mm lateral ST segment depression and inferior T wave inversion. Cardiac enzymes were as follows: CK 142 IU/L (26-221), CKMB 7.1 ng/ml (0.0-5.0), and troponin-I 3.1 ug/ml (0.0-0.5). A drug eluting stent was placed in the proximal to mid right coronary artery (RCA) that day. His EF at the time of the procedure was 35% with eccentric stenosis of 90-95% of the proximal RCA. The subject was also treated with medical therapy. Study drug was interrupted on days 33-34 and resumed on day 35. The event was considered resolved and the subject was discharged on day 34.

COMMENT: This alogliptin subject experienced an MI on day 32. The onset of the event after approximately one month's exposure to alogliptin reduces the likelihood but does not eliminate an association with the study drug.

- 246/9002 (Alogliptin 12.5 mg): 64 year old male with a history of T2D, hyperlipidemia, and hypertension who experienced a transient ischemic attack on day 54, which resolved that day. The subject completed the study.
- 463/9003 (Alogliptin 12.5 mg): See above section 7.3.1 Deaths.
- 252/9006 (Alogliptin 25 mg): 62 year old male with a history of T2D and hypercholesterolemia was admitted on day 139 for an inferior MI. He was also taking pioglitazone 30 mg at the time of the event. The patient complained of a 3 day history of substernal chest pressure which radiated to the left shoulder, worsened with exertion, was better at rest, and associated with nausea and diaphoresis. The subject reported that the pain got so intense that he lost consciousness and hit his left knee and wrist, resulting in a knee contusion and left wrist fracture. Laboratory results were as follows: CPK 481 and 1214 (49-397 IU/L), CKMB 37.3 and 105.7 (0.6-6.3 ng/ml), and troponin 1.4 and 18.0 (< 0.3 ng/dl). ECG showed subendocardial ischemia with ST segment depression in V2-V5. Echocardiogram showed minimal aortic valvular thickening, possible inferoseptal hypokinesis, and an EF of 55-60%. On day 145, coronary angiogram showed 3 vessel disease with an EF of 50-55%. Angioplasty of the left anterior descending (LAD) artery failed, but stent placement of the circumflex and RCA were successful. Medical management was also provided. Study medication was interrupted on day 139 and resumed on day 148. The event was considered resolved and the subject discharged on day 147.

COMMENT: This event of MI on day 139 in a subject whose only risk factors were T2D and hypercholesterolemia may be drug related.

- 320/9003 (Alogliptin 25 mg): 50 year old male with a history of T2D, hypercholesterolemia, and chronic smoking was hospitalized on day 20 for an MI. He was also taking pioglitazone 30 mg at the time of the event. The subject complained of severe indigestion. ECG and CK confirmed an MI. The subject was treated with clopidogrel bisulfate and nitroglycerin. Cardiac catheterization showed 70+% stenosis in

the first and second obtuse marginal vessels. The posterior descending showed diffuse disease. His LAD was totally occluded after the first diagonal vessel with the first diagonal vessel noted to be 60-70% narrowed. A stent was placed in the mid-LAD. The subject had excellent TIMI grad III flow after the procedure, although there was residual stenosis in the first and second obtuse marginal as well as first diagonal vessels. The event was considered resolved and the subject discharged on day 25. The subject was withdrawn from the study due to this event and his last dose of study medication given on day 25.

COMMENT: This occurrence of MI on day 20 in a subject whose risk factors included T2D, hypercholesterolemia, and smoking may not be drug related.

- 387/9001 (Alogliptin 25 mg): 70 year old woman with a history of T2D, hypertension, coronary artery disease, hypercholesterolemia, peripheral vascular disease, and diabetic neuropathy was hospitalized on day 127 with carotid artery occlusion. On day 63, the subject had a cerebrovascular duplex exam completed for an indication of carotid bruit. The results showed severe 50-69% stenosis in the right internal carotid artery and critical 70-99% stenosis in the left internal carotid artery. Antegrade flow was noted in both arteries. On day 127, the subject went to the hospital for a routine carotid angiographic evaluation. According to the narrative, there were no signs or symptoms that triggered the decision to perform the arteriogram. The investigator reported that the angiogram revealed 50% and 70% blockages of the right and left carotid arteries, respectively. An elective carotid endarterectomy was done on day 129. The subject was discharged on day 131, when the event resolved. Study medication was interrupted from day 127 to 131.

COMMENT: This patient may have been picked up incidentally, as the narrative does not describe signs or symptoms.

INS-011:

- 395/5009 (Placebo): 66 year old male with a history of T2D, hypertension, overweight, and dyslipidemia who was admitted on day 50 for an ischemic stroke.
- 447/5009 (Alogliptin 12.5 mg): 48 year old female with a history of T2D and hypertension experienced a transient ischemic attack on day 79, which resolved that day. Baseline blood pressure was 140/82 mmHg. Endpoint blood pressure was 124/80 mmHg. The subject completed the study.
- 464/5005 (Alogliptin 12.5 mg): See above section 7.3.1 Deaths.

OPI-001:

- 265/3001 (Placebo): 64 year old male with T2D, hypertension, dyslipidemia, and bilateral peripheral neuropathy experienced a cerebrovascular accident on day 14. Symptoms included slurred speech, heaviness in the chest and neck, and headache. Head CT showed a left basal ganglia subacute ischemic lacunar infarct. He was treated with clopidogrel, amlodipine besylate, fenofibrate, and insulin. The event resolved with sequelae (slight left-sided facial numbness) on day 19, and the subject was discharged. The study drug was discontinued on day 19 due to this SAE. The subject also reported facial hypoesthesia on day 24, which resolved on day 29.

- 632/3003 (Placebo): 61 year old female with a history of T2D, previous smoking, hyperlipidemia, hypertension, and hypothyroidism experienced an MI on day 144. The subject was hospitalized for chest pain on day 144 and diagnosed with an acute lateral inferior MI. Cardiac catheterization found triple vessel disease. An emergency triple vessel coronary artery bypass graft was performed of the left internal mammary artery to the LAD artery and right internal mammary artery to the right coronary artery and a saphenous vein graft to the left posterior descending artery. After surgery, she developed a wound infection and post cardiectomy syndrome with a right pleura effusion, which were treated medically. The subject was discharged on day 156 when the MI resolved but ischemia was continuing. Study drug was discontinued on day 143 due to the MI.
COMMENT: Case of MI in a female subject with cardiac risk factors who took pioglitazone 45 mg.
- 888/3029 (Placebo): 65 year old male with a history of T2D and hypertension experienced cerebrovascular insufficiency on day 141 that was considered ongoing at the time of study completion. Baseline blood pressure was 156/99 mmHg.
COMMENT: The narrative provided was brief. This reviewer wonders if more information was provided if the subject would meet criteria for a CVA.
- 907/3016 (Placebo): See above section 7.3.1 Deaths.
- 725/3005 (Alogliptin 12.5 mg): 73 year old male with a history of T2D, arteriosclerosis, hypercholesterolemia, and hypertension who experienced an AE of MI on day 186, which resolved on day 200. The screening ECG showed ST-T segment changes in inferior leads that were considered nonclinically significant. The ECG on day 186 was interpreted as an inferior infarction, probable old septal infarction. The subject completed the study.
COMMENT: This subject may have experienced a silent MI while on study drug.
- 395/3022 (Alogliptin 25 mg): 69 year old female with a history of T2D, menopause, dyslipidemia, hypertension, hypothyroidism, and obesity experienced a lacunar infarction on day 149. The subject experienced right arm tremor which began and resolved on day 148. The subject was hospitalized on day 149 for an unknown neurological disorder. No neurological signs or symptoms were reported at admission. A head CT showed lacunar infarcts in the paraventricular region. The event resolved on day 153 and the subject was discharged.
COMMENT: Unclear whether the lacunar infarcts were acute or old. Insufficient information was provided to conclude that the patient had an acute cerebrovascular event.
- 694/3017 (Alogliptin 25 mg): 39 year old female with a history of T2D who experienced an AE of right sided hemiparesis on day 27 that resolved on day 32. The subject had received omeprazole with domperidone on days 1-5 and day 27-32. The subject completed the study.
COMMENT: Without additional information, one may assume that hemiparesis lasting 5 days is due to a CVA.
- 704/3001 (Alogliptin 25 mg): 65 year old woman with history of T2D and hypercholesterolemia experienced cholecystitis and carotid artery occlusion on days 115 and 122, respectively. The subject was hospitalized on day 115 for abdominal pain due

to cholecystitis and was scheduled for cholecystectomy. During the preoperative visit on day 122, carotid bruits were present on exam and a duplex ultrasound revealed severe stenosis. Therefore, a right carotid endarterectomy was performed on day 128 and the event resolved. The subject was discharged on day 130 and readmitted on day 169 for a laproscopic cholecystectomy. She was discharged again on day 170. Although study drug was interrupted, the subject completed the study.

COMMENT: Probable longstanding carotid artery occlusion detected incidentally during preoperative evaluation for cholecystectomy.

- 716/3021 (Alogliptin 25 mg): 47 year old male with a history of T2D experienced an AE of myocardial infarction based on extensive ST-T changes on ECG on day 175. The subject had a presystolic cardiac murmur concurrent with the ECG changes. The subject also had an AE of hypertension on days 143 – 175. The ECG on day 175 showed prolonged QT interval (QTcF 474.1 msec, a 32 msec change from baseline) and extensive ST-T changes suggesting MI. The ECG changes were considered not clinically significant. The subject discontinued study drug on day 175 due to lack of efficacy.

COMMENT: This subject experienced an MI while on study drug (there is no information on whether he had symptoms or elevated cardiac biomarkers), which was labeled as an AE (not an SAE). In this reviewer's opinion, the reason for the subject's discontinuation should have been labeled "AE", not "lack of efficacy."

- 728/3008 (Alogliptin 25 mg): 33 year old male with a history of T2D, hyperlipidemia, and hypertension experienced an AE of MI on day 84 that was continuing at the time of study completion. The prescreening ECG was reported as abnormal but not clinically significant with premature atrial complexes. On day 84, the ECG was reported as abnormal not clinically significant with septal infarct. An unscheduled ECG on day 198 was reported as normal and improved. The subject completed the study.

COMMENT: The brief information presented is conflicting. The ECG on day 84 indicates a septal infarct, although the ECG on day 198 was normal. This reviewer will err on the side of safety and consider the event as a silent MI.

- 919/3007 (Alogliptin 25 mg): 52 year old female with a history of T2D, arteriosclerosis, chronic obstructive pulmonary disease, dyslipidemia, hypertension, myocardial ischemia, and obesity experienced an ischemic stroke on day 35. Head CT revealed acute dysfunction of the cerebral circulation of ischemic type in the left medial cerebral artery with moderate atrophic changes. The subject was discharged on day 51. The event resolved with sequelae (paresis of the left leg).

OPI-002:

- 053/2513 (Placebo): 45 year old male with a history of T2D, hypertension, and first degree cardiac murmur experienced an ECG ST segment elevation on day 1. The screening ECG was normal. The day 1 ECG report stated it was abnormal, clinically significant, and showing worsening with sinus rhythm and left anterior fascicular block. The principal investigator stated the interpretation should include ST segment elevation. The subject was lost to follow up and no additional data available after day 1.

COMMENT: While the narrative suggests this subject may have experienced an MI, little information is provided and it occurred on day 1 of placebo administration.

- 640/2506 (Placebo): 71 year old male with a history of T2D, cerebral ischemia, cerebrovascular accident (April 1995), and hypertension experienced cerebral ischemia on day 196. The subject experienced vertigo and was hospitalized for cerebral ischemia. On admission, ataxia was detected that was accompanied by residual neurologic symptoms, including left-sided marked facial paresis. Finger-nose test and heel-knee tests were slightly ataxic on the left. The Romberg test revealed a tendency to lean to the right; the subject could only stand with help. Treatment included circulation-improving infusion therapy, piracetam, and acetylsalicylic acid. The subject's condition improved and he was discharged on day 200, when the event was considered resolved.
COMMENT: The presence of neurologic symptoms which began on day 196 and did not resolve until day 200 suggests the event should have been coded as a cerebrovascular accident.
- 673/2501 (Placebo): 61 year old female with a history of T2D, angina pectoris, cardiac failure, cerebral ischemia, hypertension, hypertensive cardiomyopathy, mitral valve calcification, and myocardial ischemia experienced an AE of cerebrovascular insufficiency on day -12 during prerandomization. The event resolved after 9 days. The ECG worsened from day 1 to 86 and was considered clinically significant.
COMMENT: The patient experienced 9 days of cerebrovascular insufficiency during the prerandomization period and a worsening ECG on days 1 – 86. This reviewer wonders, if more information was provided, whether the event would have qualified as a CVA in this placebo-exposed patient.
- 291/2501 (Alogliptin 12.5 mg): 57 year old female with a history of T2D, arteriosclerosis, arteriosclerosis coronary artery, cardiomyopathy, hypertension, hypertensive cardiomyopathy, myocardial ischemia, and vascular encephalopathy experienced an AE of vertebrobasilar insufficiency on day 164 that was ongoing at the time of study completion. The subjects ECG showed left ventricular hypertrophy from prerandomization that was considered not clinically significant and remained unchanged throughout the study.
COMMENT: The presence of ongoing vertebrobasilar insufficiency suggests this subject may have experienced a CVA.
- 741/2506 (Alogliptin 12.5 mg): 62 year old male with a history of T2D, angina pectoris, blood cholesterol increased, coronary artery disease, hypertension, MI, and ongoing renal failure (baseline creatinine 1.9 mg/dl) experienced an AE of carotid artery stenosis on day 171 that was ongoing at the time of study completion.
COMMENT: Again, little information is provided for this AE. If the patient was symptomatic, he would meet criteria for a CVA.
- 067/2506 (Alogliptin 25 mg): 55 year old female with a history of T2D and hypertension experienced an AE of transient ischemic attack on day 102, that resolved the next day. The subject completed the study.
- 665/2509 (Alogliptin 25 mg): 57 year old male with a history of T2D, previous smoking, dyslipidemia, hypertension, hypothyroidism, obesity, prior MI (1997), and myocardial ischemia experienced a MI on day 26. On day 1, the baseline ECG was read as normal sinus rhythm with negative T waves in V4-V6; these changes were assessed as nonclinically significant. On day 26, the subject was hospitalized for several hours of

angina pectoris, which did not subside with nitroglycerin tablets. Initial laboratories were significant for hyperglycemia and glycosuria. On day 27, troponin was positive and the ECG showed negative coronary T waves in I and VL and in precordial recordings. The event was considered resolved and the subject was discharged on day 33. Study drug was discontinued and the subject withdrawn from the study on day 51 due to the MI.

NDA 22-271. Incidence of SMQ MACE events in the main analysis population, combined across doses of study drug, reported separately by study							
Study	Group	N	Exposure (Pt-Yrs)	# Events	Incidence (%) (Events/N)	Incidence ratio 95% CI	Incidence rate (Events/100 pt-years)
003	Alo	218	48.1	0	0.00	NE	0.0000
	Plb	41	7.2	0	0.00		0.0000
SULF-007	Alo	401	182.1	3	0.75	NE	1.6484
	Plb	99	42.3	0	0.00		0.0000
MET-008	Alo	420	194.8	2	0.48	0.50	1.0267
	Plb	104	44.6	1	0.96	(0.07, 3.77)	2.2422
TZD-009	Alo	397	179.8	6	1.51	NE	3.3370
	Plb	97	42.3	0	0.00		0.0000
PLC-010	Alo	265	119.6	0	0.00	NE	0.0000
	Plb	64	26.3	0	0.00		0.0000
INS-011	Alo	260	109.9	2	0.77	0.99	1.8198
	Plb	129	48.1	1	0.78	(0.13, 7.55)	2.0790
OPI-001	Alo	1037	481.0	7	0.68	0.87	1.4553
	Plb	516	221.9	4	0.78	(0.27, 2.78)	1.8026
OPI-002	Alo	491	222.2	4	0.81	0.66	1.8002
	Plb	163	72.0	2	1.23	(0.14, 3.08)	2.7778
Pooled	Alo	3489	1537	24	0.69	1.04	1.5615
	Plb	1213	504.9	8	0.66	(0.48, 2.27)	1.5845
NE = Not estimable							

NDA 22-271. Incidence of custom MACE events in the main analysis population, combined across doses of study drug, reported separately by study							
Study	Group	N	Exposure (Pt-Yrs)	# Events	Incidence (%) (Events/N)	Incidence ratio 95% CI	Incidence rate (Events/100 pt-years)
003	Alo	218	48.1	0	0.00	NE	0.0000
	Plb	41	7.2	0	0.00		0.0000
SULF-007	Alo	401	182.1	1	0.25	NE	0.5491
	Plb	99	42.3	0	0.00		0.0000
MET-008	Alo	420	194.8	2	0.48	NE	1.0267
	Plb	104	44.6	0	0.00		0.0000
TZD-009	Alo	397	180.3	4	1.01	NE	2.2185
	Plb	97	42.3	0	0.00		0.0000
PLC-010	Alo	265	119.6	0	0.00	NE	0.0000
	Plb	64	26.3	0	0.00		0.0000
INS-011	Alo	260	110.2	1	0.38	0.50	0.9074
	Plb	129	48.1	1	0.78	(0.05, 4.74)	2.0790
OPI-001	Alo	1037	481.6	5	0.48	0.83	1.0382

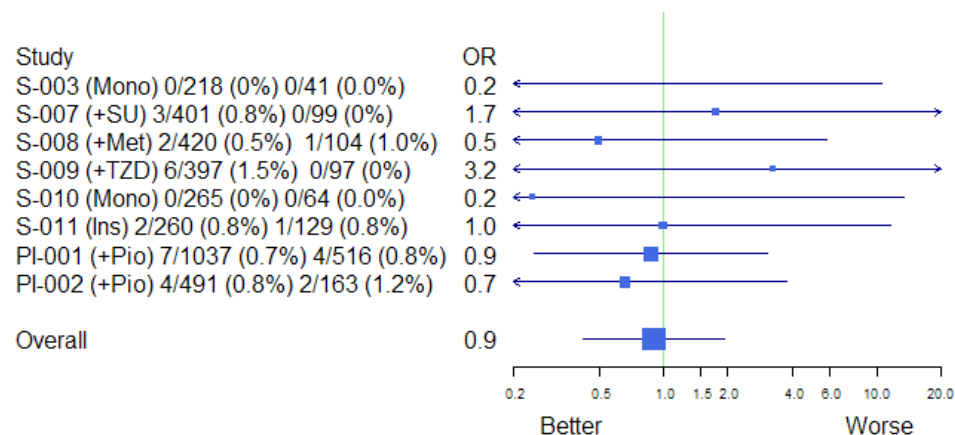
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 Alogliptin (Nesina) 6.25, 12.5 or 25 mg daily

	Plb	516	222.1	3	0.58	(0.22, 3.13)	1.3507
OPI-002	Alo	491	222.5	1	0.20	NE	0.4494
	Plb	163	72.2	0	0.00		0.0000
Pooled	Alo	3489	1539	14	0.40	1.22	0.9097
	Plb	1213	505.2	4	0.33	(0.42, 3.51)	0.7918
NE = Not estimable							

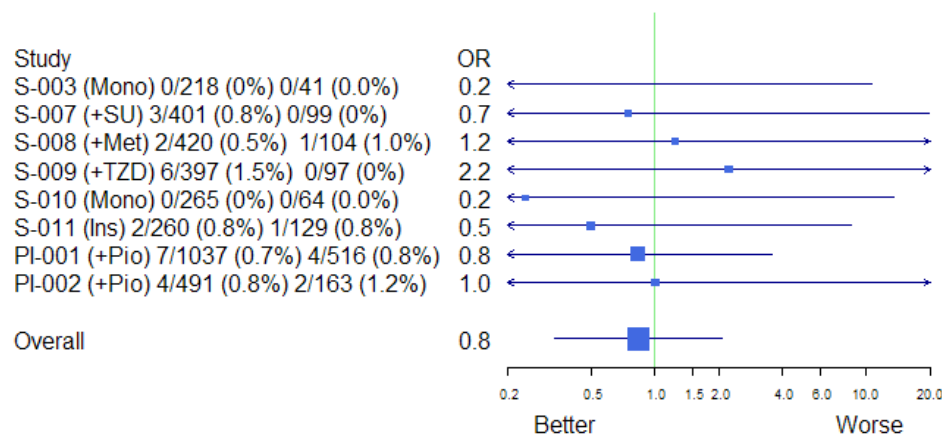
A proportion of this analysis was recalculated by statistician Janice Derr and is shown below.

NDA 22-271. Alogliptin vs. Placebo, Main Analysis Population A for SMQ MACE (combined across 8 studies) ¹					
Group	N	Exposure (Pt-Yrs)	# of events	Incidence (%) Events/N	Incidence Rate Events/ 100 pt-yrs
Alogliptin	3489	1537	24	0.69%	1.562
Placebo	1213	505	8	0.66%	1.585
Method			Incidence Ratio (95% CI)		Incidence Rate Ratio (95% CI)
<i>Stratified, asymptotic (MH)</i> ²			1.09 (0.48, 2.47)		<i>Stratified, asymptotic</i> 1.02 (0.45, 2.32)
<i>Stratified, exact</i>			1.09 (0.47, 2.84)		<i>Stratified, exact</i> 1.02 (0.44, 2.65)
Stratified, fixed effects MH meta-analysis with a continuity correction ³			0.90 (0.43, 1.89)		
<i>Notes:</i> ¹ The tallies of SMQ MACE events are from Takeda, Table 3a, submitted in response to FDA request for information 1/11/2009. For the stratified analyses with no continuity correction: 6 of the 8 studies were included in the analyses; 2 studies were omitted because they had 0 events in both arms. This excluded 12.5% of cases and 9.8% of patient-years. Test of homogeneity across studies: For incidence rate, the p-value was 0.816; for incidence rate ratio, the p-value was 0.776. ² MH = Mantel-Haenszel ³ A continuity correction of 0.5 was added to groups with 0 mace events: Depicted in the forest plot (Figure 1)					

NDA 22-271. SMQ MACE, Odds Ratios and 95% CIs from stratified asymptotic method (M-H) with continuity correction



NDA 22-271. Custom MACE, Odds Ratios and 95% CIs from stratified asymptotic method (M-H) with continuity correction



NDA 22-271. Alogliptin vs. Placebo, Main Analysis Population A for Custom MACE (8 studies; stratified analyses) ¹						
Group	N	Exposure (Pt-Yrs)	# of events	Incidence (%) Events/N	Incidence Rate Events/ 100 pt-yrs	
Alogliptin	3489	1539	14	0.40%	0.9097	
Placebo	1213	505	4	0.33%	0.7918	
Method				Incidence Ratio (95% CI)	Incidence Rate Ratio (95% CI)	
Stratified, asymptotic (MH) ²				1.36 (0.43, 4.30)	Stratified, asymptotic	1.26 (0.39, 4.07)
Stratified, exact				1.34 (0.41, 5.65)	Stratified, exact	1.24 (0.39, 5.23)
Stratified, fixed effects MH meta-analysis with a continuity correction ³				0.83 (0.34, 2.04)		

Notes:

¹ The tallies of SMQ MACE events are from Takeda, Table 3b, submitted in response to FDA request for information 1/11/2009. For the stratified analyses with no continuity correction: 6 of the 8 studies were included in the analyses; 2 studies were omitted because they had 0 events in both arms. This excluded 12.5% of cases and 9.8% of patient-years. Test of homogeneity across studies: For incidence rate, the p-value was 0.771; for incidence rate ratio, the p-value was 0.803.

² MH = Mantel-Haenszel

³ A continuity correction of 0.5 added to groups with 0 mace events: Depicted in the forest plot (Figure 2)

The analysis shows that the upper bound of the 2-sided 95% confidence interval (CI) for the estimated risk ratio is > 1.8 in pooled SMQ and custom analyses and in all individual studies, when it was estimable. The high upper bound of the 2-sided 95% CI is likely due to of the low MACE event rates. Nonetheless, NDA 22-271 does not meet current cardiovascular risk safety guidelines for approval. Figure 1 also indicates that the large fixed dose combination study of alogliptin + pioglitazone (study OPI-001; which had the most events) likely drove the results of the pooled study comparison.

Furthermore, 16 of the 35 (45.7%) MACE events were AEs, for which only brief narratives were provided. Three of the 16 (18.8%) AEs were coded as myocardial infarction. Based on the limited information present, this reviewer considers it possible that as many as an additional 6 MIs and 6 CVAs (2 placebo and 4 alogliptin in each group) may have occurred in the 16 AEs cases. However, even if these events were miscoded, they were still included in the MACE analysis, such that the agency's analysis would not have been affected. These cases are listed below, and the narratives are described above. Case 716/3021 is especially concerning as it describes an AE of myocardial infarction with subject discontinuation on the same day for "lack of efficacy". This reviewer believes the AE should have been listed as the reason for discontinuation.

NDA 22-271. Distribution of MACE events which were AEs between studies		
Study	Placebo	Alogliptin
SULF-007	0	2
MET-008	1	0
TZD-009	1 (prebaseline)	1
INS-011	0	1
OPI-001	1	4
OPI-002	2 (prerandomization & day 1)	3
Total	5	11

NDA 22-271. Potential AE cases of MI and CVA in the MACE analysis that were not coded as such by the sponsor. NOTE: Subjects received alogliptin during the treatment period unless otherwise mentioned. (study-subject ID)	
MI	CVA
007-244/7001	007-104/7016
008-315/8016: Placebo	001-694/3017
001-716/3021	001-888/3029: Placebo
001-725/3005	002-291/2501
001-728/3008	002-673/2501: Placebo (prerandomization)
002-053/2513: Placebo (day 1)	002-741/2506

Aside from the fact that several of the AEs described in the MACE analysis may have met criteria for an SAE, MI, and/or CVA, there is also an imbalance in the events the sponsor labeled as SAEs when the alogliptin cardiac SOC is compared to placebo. As shown in section 7.3.2 Nonfatal Serious Adverse Events, in the controlled phase 2 and 3 trials in NDA 22-271, the sponsor described 23 cardiovascular TESAEs in alogliptin subjects versus 2 events in the placebo population. However, NDA 22-271 Integrated Analysis of Safety's table 10.b Listing of Subjects who Experienced an SAE indicates there were 24 cardiac SAEs. As one would expect

the SAE table to have a greater or equal number of SAEs as the TESAE table, the sponsor was asked to clarify this point. The sponsor responded that 2 cases (hypertensive heart disease MET-008 520/8010 and palpitations PLC-010 440/4008) were inadvertently not included in table 10.b. Subject 520/8010 died from hypertensive heart disease and is included in the Deaths section. Subject 440/4008 experienced atrial fibrillation with a positive troponin and is included in the review of SAEs below.

When tables 10.b Listing of Subjects who Experienced an SAE in controlled studies in NDAs 22-271 and 22-426 were reviewed and subject 440/4008 included, a total of 32 SAE cases were found. Cardiovascular SAE narratives, excluding those included in the MACE analysis above, are listed below. Please note that, although the MACE analysis includes death and CVA- and MI-related events, the analysis of cardiovascular SAEs does not include death or CVA-related events. The only preferred term shared between the cardiovascular SAE list and the SMQ or custom MACE lists is MI.

NDA 22-271. This reviewer's adjudication of cardiovascular SAEs					
Patient ID*	Study	Treatment	Day	Preferred Term	Event*
422/7017	SULF-007	Alo	41	MI	MI
107/9005	TZD-009	Alo	32	MI	MI
252/9006	TZD-009	Alo	139	MI	MI
320/9003	TZD-009	Alo	20	MI	MI
665/2509	OPI-002	Alo+Pio	26	Acute MI	MI
422/9009-	TZD-009	Alo	71	Angina pectoris; Coronary artery disease	MI?
632/3003	OPI-001	Pio	144	MI	MI
440/4008-	PLC-010	Alo	102	Palpitations	MI?
105/2019	003	Alo	43	Angina pectoris	Angina
249/2004	003	Alo	82	Angina pectoris	Angina
268/2005	003	Alo	8	Coronary artery disease	Angina
239/7001	SULF-007	Alo	74	Angina pectoris	Angina
315/7002	SULF-007	Alo	125	Arteriosclerosis	Angina
383-7021	SULF-007	Alo	173	Angina pectoris	Angina
244/5024	INS-011	Alo	115	Coronary artery disease	Angina
296/3007	OPI-001	Alo+Pio	174	Myocardial ischemia	Angina
397/3011	OPI-001	Alo+Pio	77	Coronary artery stenosis	Angina?
422/9009+	TZD-009	Alo	71	Angina pectoris; Coronary artery disease	Angina?
301/9005	TZD-009	Alo	172	Angina pectoris	Angina?
442/4005	PLC-010	Alo	77	Angina pectoris	Angina?
774/3014	OPI-001	Pio	58	Coronary artery disease	Angina
395/5008	INS-011	Alo	18	Angina unstable	Un angina
833/3004	OPI-001	Alo+Pio	9	Angina unstable	Un angina?
678/2526	OPI-002	Alo	85	Angina unstable	Un angina
485/8008	MET-008	Plb	114	Angina unstable	Un angina
484/5001	INS-011	Plb	3	Angina unstable	Un angina
256/7021-	SULF-007	Alo		Cardiac failure congestive	CHF
223/8006	MET-008	Alo		Cardiac failure congestive	CHF
107/9011-	TZD-009	Alo+TZD	124	Cardiac failure congestive	CHF
429/9002	TZD-009	Alo+TZD		Cardiac failure congestive	CHF

307/5003	INS-011	Alo		Atrial fibrillation; Cargiogenic shock	A fib/flutter
329/5006	INS-011	Alo		Atrial fibrillation	A fib/flutter
256/7021+	SULF-007	Alo		Cardiac failure congestive	A fib/flutter
107/9011+	TZD-009	Alo	124	Cardiac failure congestive	A fib/flutter
440/4008+	PLC-010	Alo	102	Palpitations	A fib/flutter
263/8006	MET-008	Alo		Bradycardia; fall	Bradycardia
*Event as adjudicated by this reviewer. Question marks signify a possible diagnosis. Note: 4 subjects (422/9009, 256/7021, 107/9011, and 440/4008) were given 2 diagnoses.					

NDA 22-271. Summary of this reviewer's adjudication of cardiovascular SAEs. NOTE: Subjects 422/9009, 256/7021, 107/9011, and 440/4008 which had 2 diagnoses were only tallied once in this table.				
Study	Treatment	N	Exposure (Pt-Yrs)	# CV SAE Events
SYR-322-003	Alogliptin	218	48.1	3
	Placebo	41	7.2	0
SYR-322-SULF-007	Alogliptin	401	182	5
	Placebo	99	42.3	0
SYR-322-MET-008	Alogliptin	420	194.8	2
	Placebo	104	44.6	1
SYR-322-TZD-009	Alogliptin	397	179.8	7
	Placebo	97	42.3	0
SYR-322-PLC-010	Alogliptin	265	119.6	2
	Placebo	64	26.3	0
SYR-322-INS-011	Alogliptin	260	109.9	4
	Placebo	129	48.1	1
01-05-TL-322OPI-001	Alogliptin	1037	481	3
	Plb or Pio	516	221.9	2
01-06-TL-322OPI-002	Alogliptin	491	222.2	2
	Plb (Pio)	163	72	0

SYR-322-003:

- 105/2019 (Alogliptin 25 mg): 65 year old female with a relevant history of T2D, hypertension, hysterectomy, palpitations, hypothyroidism, hypercholesterolemia, and coronary artery disease (CAD) was hospitalized on day 43 for one week of intermittent chest discomfort. The pressure type sensation occurred with ambulation and at rest. ECG revealed sinus rhythm with occasional premature ventricular contractions but no acute ST abnormalities. Cardiac catheterization showed 2 vessel disease which was treated with drug-eluting stents. The event was noted as resolved the following day, when the subject was discharged. Discharge labs included cholesterol 254 mg/dl, triglycerides 158 mg/dl, HDL 46 mg/dl, LDL 183 mg/dl, very low density lipoprotein cholesterol 25 mg/dl, and negative troponin. Study medication was temporarily interrupted on day 43 due to this SAE.
 - COMMENT: This event of CAD on day 43 could be an event of unstable angina as the subject had chest pain at rest.**
- 249/2004 (Alogliptin 100 mg): A 57 year old male with a relevant history of T2D, hypertension, hyperlipidemia, atherosclerotic cardiovascular disease, Raynaud phenomena, myocardial infarction, 5 heart catheterizations, and occasional dyspnea who experienced angina pectoris on day 82. Symptoms included intermittent left-sided chest

pain, shortness of breath, and nausea. A recent stress test was negative. The subject was started on a chest pain protocol which included intravenous heparin and a cardiology consult was placed. On day 82, creatine kinase cardiac muscle was 2.5 ng/ml (0.3-5.0 ng/ml) and troponin was 0.02 ng/ml (0.01-0.5 ng/ml). On day 83, creatine kinase cardiac muscle was 1.3 ng/ml and troponin 0.01 ng/ml. No abnormalities were noted on ECG. Angiogram revealed mild triple vessel disease. Medical management and lifestyle changes were recommended. The subject recovered and was discharged on day 84. Study drug dosage was temporarily interrupted as a result of this SAE.

- 268/2005 (Alogliptin 12.5 mg): 36 year old male with a relevant history of T2D and dyslipidemia who experienced an SAE coronary artery disease on day 8. He was noted to have a history of chest squeezing discomfort after exercise beginning 2 months prior to entering the study. His primary care physician noted an abnormal ECG and referred him to a cardiologist. Cardiac workup revealed severe left ventricular dysfunction. Echocardiogram showed a 56 mm left ventricle with an ejection fraction of 40%. A stress echocardiogram was positive for dyspnea, ST segment depression, and a severely hypokinetic anterior apical wall. A cardiac catheterization was recommended due to possible ischemia. ECG showed normal sinus rhythm with intra ventricular conduction delay and ST depression in the inferior leads and poor R wave progression. A treadmill test noted significant fatigue after 7 minutes on the Bruce protocol, although he did achieve 85% of the predicted maximal heart rate for his age. Carvedilol 3.125 mg twice daily was recommended. The subject was noted to have coronary artery disease and possible cardiomyopathy secondary to alcohol and drug use in the past. On day 23, the subject was hospitalized for stent placement in a 95% stenosed left anterior descending (LAD) artery. The ejection fraction measured by left ventriculogram was improved compared to the prior measurement (55%). Mild hypokinesis of the anteroapical area was also noted. On day 24, the event was resolved and the subject discharged.

SULF-007:

- 239/7001 (Alogliptin 25 mg): 44 year old woman with a relevant history of T2D, gallstones, hypertension, hypothyroidism, and hypercholesterolemia was admitted to the hospital on day 74 for angina pectoris. Symptoms included shortness of breath and tingling in her left arm. ECG was normal on admission. Symptoms resolved with no recurrence overnight. No wheezing was noted during hospitalization. On day 75, oxygen saturation was 100% on room air and lungs were clear on exam and x-ray. Troponin measurements were 0.02, < 0.01, and < 0.01. It was felt that her symptoms were suggestive of asthma since her complaints were mostly shortness of breath after mowing her lawn and improved somewhat with allergy medicine. The subject was discharged on day 75 with the event resolved. On day 90, a stress test was negative for ischemic changes.
 - **COMMENT: Perhaps this event should have been coded as an asthmatic attack, although the normal lung exam and presence of left arm tingling do not support that diagnosis.**
- 256/7021 (Alogliptin 12.5 mg): 61 year old male with a relevant history of T2D, hypertension, and hyperlipidemia was admitted to the hospital on day 78 for cardiac failure congestive. On days 51-58 and 74-77, the subject complained of shortness of breath. On day 78, the subject presented to the emergency room complaining of a one

month history of intermittent mild substernal chest discomfort, orthopnea, 10 pound weight loss, shortness of breath, inability to lie flat, and palpitations. He denied diaphoresis, fevers, and cough. Pulse was 115 beats per minute, blood pressure 134/95 mmHg, and respiratory rate 16 breaths per minute. Exam revealed 1+ lower extremity edema, slightly elevated jugular vein distension, notable S1, bibasilar crackles, and tachycardia. Chest x-ray showed borderline cardiomegaly with normal pulmonary vasculature and questionable right subpulmonic effusion. ECG showed atrial flutter with variable block, rapid ventricular response, and T wave abnormalities consistent with inferior ischemia or digitalis. Furosemide was given and the subjects admitted to rule out myocardial infarction. Decompensated heart failure, atrial flutter, and pleural effusion were later diagnosed. He was medically converted to normal sinus rhythm with metoprolol and diltiazem. On day 79, an echocardiogram showed an ejection fraction < 30%, dilated right atrium and ventricle, and moderate to severe mitral regurgitation. Labs included CK-MB values of 3.4, 2.85, and 2.59 ng/ml (0-0.5); troponin T 0.03 ng/ml and 0.01 (0-0.01); and pro-BNP 7760 pg/ml (0-900). On day 81, ECG showed normal sinus rhythm with nonspecific T wave abnormalities. Cardiac catheterization showed severe left ventricle dysfunction and single vessel CAD (90% first diagonal). The subject was referred for AICD implantation. On day 82, the subject was discharged and event resolved with the sequelae of mild congestive heart failure. Study medication was interrupted due to this event from day 78 – 82.

- **COMMENT: History and exam are consistent with congestive heart failure and atrial flutter. The elevated cardiac enzymes may have resulted from increased myocardial demand in the setting of tachycardia. The occurrence of this event after approximately 3 months of study drug exposure suggests it may be drug-related. However, the low frequency of arrhythmia (3 alogliptin; 0 placebo) and heart failure (4 alogliptin; 0 placebo) SAEs, when considering the 4:1 randomization scheme, does not support an association.**
- 315/7002 (Alogliptin 12.5 mg): 45 year old male with a relevant history of T2D, hypercholesterolemia, hypertension, dyspnea, chest pain, and intermittent noncardiac chest pain was admitted to the hospital on day 125 for atherosclerosis coronary artery. The subject complained of 2 months' history of episodic pressure type chest pain and dyspnea occurring with progressively less exertion. ECG showed sinus rhythm with marked ST and T wave changes with borderline first degree AV block and left ventricular hypertrophy. On day 125, CK-MB was 6.2 ng/ml (0.1-3.9) and troponin I 0.04 ng/ml (< 0.1). On day 126, a cardiac catheterization was performed and revealed 95% proximal obstruction of the LAD with normal left main coronary artery. The circumflex showed 80% and 90% lesions of the distal third of the vessel. A stent was placed in the LAD and 2 stents were placed in the circumflex system. On day 127, the event was considered resolved with sequelae.
- 383/7021 (Alogliptin 25 mg): 68 year old male with a history of T2D, overweight, hypercholesterolemia, and smoking (23 years) was admitted to the hospital for coronary angiography on day 173 secondary to angina pectoris. On day 55, he experienced a nonserious AE of angina pectoris, and on day 83 he experienced worsening hypercholesterolemia and hypertriglyceridemia. On day 91, a stress test was performed and angina confirmed. On day 173, the subject was hospitalized and underwent coronary

angiography for the angina pectoris which started on day 55. The procedure showed small caliber arteries, right dominant circulation, severe stenosis (>80%) of the intermediate branch and distal circumflex artery, and mild stenosis of the right coronary artery (40%) and anterior descending artery (30%). The subject was discharged on day 174 with the event resolved.

- 422/7017 (Alogliptin 12.5 mg): See above MACE analysis.

MET-008:

- 223/8006 (Alogliptin 25 mg): 69 year old female with a history of T2D, gastroesophageal reflux disease, and hypertension was admitted to the hospital on day 128 for cardiac failure congestive. The subject complained of shortness of breath. An evaluation showed pulmonary congestion. Relevant laboratory results included glucose 324 mg/dl, CK-MB 4.5 (< 3.0), HbA1c 7.4%, NT-proBNP 5705 pg/ml (< 353), and troponin normal. ECG showed normal sinus rhythm with left bundle branch block. A chest x-ray showed mild pulmonary congestion consistent with congestive heart failure. A preliminary echocardiogram review noted an ejection fraction of 25%. She was diagnosed with New York Heart Association (NYHA) class II congestive heart failure (CHF). On day 131, the subject was discharged and the event resolved. Study medication was interrupted on days 128-131 and the subject withdrawn due to the SAE on day 139.
 - **COMMENT: This relatively well-controlled diabetic, whose only other risk factor was hypertension, developed class II CHF approximately 4 months after exposure to alogliptin.**
- 263/8006 (Alogliptin 12.5 mg): 54 year old male with a history of benign bradycardia, gait disturbance, hypertension, bilateral cerebellar hemispheric infarct, and old myocardial infarction was admitted to the hospital on day 68 due to bradycardia and day 155 for weakness due to a fall. On day 68, the subject underwent elective implantation of a dual chamber permanent pacemaker for symptoms due to worsening bradycardia with a Mobitz type II, second degree AV block. On day 71, the subject underwent revision and repositioning of the atrial lead of the dual chamber pacer system. On day 72, the subject was discharged and the event resolved. On day 154, the subject became lightheaded, fell, and was hospitalized. Physical exam revealed swelling of the left knee, bilateral knee abrasions, 1+ pitting edema to the mid-shin bilaterally, and weakness. Hypoglycemic was not suspected. The subject was seen by neurology in January 2007 for gait unsteadiness with the resulting impression of a possible stroke. CT of the head revealed an old bilateral cerebellar infarct. A repeat CT scan during the hospitalization was normal. The subject's strength increased with physical therapy but he was unable to walk without assistance. He was transferred to a nursing home for continued therapy and discharged on day 173. Study medication was interrupted from day 68 to 72 and day 155 to 172.
 - **COMMENT: The neurology assessment describes a possible stroke, which may have occurred when the patient was on study drug, although it did not result in hospitalization (and the investigator did not assess as life-threatening) and thus cannot be considered an SAE.**
- 485/8008 (Placebo): 71 year old male with a relevant history of arterial hypertension, ischemic heart disease, stable angina, hypercholesterolemia, and premature ventricular

beats was admitted to the hospital for unstable angina on day 114 and later hospitalized on day 177 for hydrocele surgery. On day 113, the subject experienced moderate retrosternal chest pain, vomiting, and diarrhea, which resolved after 2 hours without medication. On day 114, the pain reoccurred with weak intensity and the patient was admitted. Cardiac enzymes were negative. ECG showed sinus rhythm, rate 90/min, and 0.5 mm ST depression in leads II, III, aVG, and V5-V6. Echocardiography revealed and EF of 60%, enlarged left atrium, hypertrophy of left ventricular septum and walls, and traits of abnormal left ventricular relaxation. An exercise test was positive. The patient qualified for elective coronary angiography. On day 119, the event resolved and the subject was discharged with a referral to the outpatient cardiology and endocrinology clinics. The subject was hospitalized for coronary arteriography day 170 – 171. No significant stenoses were found.

- **COMMENT: This placebo patient experienced worsening of angina from stable to unstable approximately 4 months into study MET-008.**

TZD-009:

- 107/9005 (Alogliptin 12.5 mg): See above MACE analysis.
- 107/9011 (Alogliptin 25 mg): 72 year old female with a relevant history of sarcoidosis, hypertension, obesity, right-sided breast cancer, hyperlipidemia, 2 episodes of pneumonia, chronic obstructive pulmonary disease (COPD), pulmonary embolus, deep vein thrombosis, and hypothyroidism was diagnosed on day 94 with pneumonia and day 124 with congestive heart failure and recurrence of pneumonia. On day 94, the subject was hospitalized for pneumonia. Symptoms included shortness of breath, wheezing, COPD exacerbation, weakness, decreased management of diabetic control, anemia, chest pain, and tachycardia. Laboratory results included WBC 5300 and elevated BUN and creatinine levels. Chest x-ray showed left lower lobe pneumonia. The subject was treated with IV antibiotics, steroids, aggressive bronchodilator therapy, and insulin sliding scale. On day 103, the subject was discharged to a skilled nursing facility. However, on day 105, the subject was readmitted to the hospital for sudden onset chest pain with tachycardia which began after a nebulizer treatment. ECG showed possible atrial fibrillation with a heart rate > 140 bpm. The subject converted to sinus rhythm with metoprolol and diltiazem drip. She was placed on digoxin and the diltiazem was weaned. From day 107 – 113, the subject resided at the skilled nursing unit until discharge home. On day 124, the subject returned to the hospital for 2 days' increasing shortness of breath, cough with scant phlegm, fatigue, leg swelling, and decreased activity. The subject was hospitalized for recurrence of pneumonia with congestive heart failure. The subject was treated with diuresis, IV antibiotics, oxygen, Solu-Medrol, continuation of home medications including bronchodilator therapy, and a blood transfusion. On day 127, the subject was discharged and the event considered resolved.
- 252/9006 (Alogliptin 25 mg): See above MACE analysis.
- 301/9005 (Alogliptin 25 mg): 37 year old male with a history of T2D and sinus bradycardia was hospitalized on day 172 for angina pectoris. On day 172, the subject presented to the emergency department complaining of mild, intermittent, left sided chest pain for 3 days. ECG revealed normal sinus rhythm with nonspecific lateral T abnormalities. Troponin was < 0.2 twice. The subject was treated with sublingual nitroglycerin and aspirin. On day 173, the subject was discharged and the event resolved.

- **COMMENT: The event is correctly coded as possible angina pectoris (diagnostic testing was not revealing and a cardiac stress test was not performed to confirm the diagnosis), although its occurrence on day 172 in a subject whose only risk factor is T2D suggests the event may be drug related.**
- 320/9003 (Alogliptin 25 mg): See above MACE analysis.
- 422/9009 (Alogliptin 12.5): 44 year old male with history of T2D, hyperlipidemia, exertional angina, submandibular jaw and neck pain, and smoking (15 year history) was diagnosed on day 71 with angina pectoris and day 85 with coronary artery disease. He was also taking pioglitazone 30 mg at the time of the event. On day 71, the subject was hospitalized due to jaw pain. A stress test was positive. On day 72, the subject underwent coronary arteriography which revealed 3-vessel disease and adequate LV function. The subject was treated with angizem, escosprin, and a low fat diet. He was discharged from the hospital on day 73. On day 85, the subject was readmitted to the hospital for postmeal angina. He denied dyspnea on exertion. Results on day 86 included serum CK 740 IU/L and CK-MB 50 IU/L (CK-MB/CK = 6.8%). The ECG was within normal limits. The subject underwent coronary artery bypass surgery with 3 grafts and endoscopic vein harvesting. A repeat echocardiogram on day 93 revealed good LV function. The subject was discharged the next day.
- 429/9002 (Alogliptin 25 mg): 62 year old female with a history of T2D, MI, ischemic heart disease, hypertension, aortic valve stenosis, aortic regurgitation, menopause, exertional angina, and iron deficiency anemia was diagnosed on day 121 with congestive cardiac failure and on day 124 with acute respiratory distress syndrome. She was taking pioglitazone 45 mg at the time of the event. On day 121, the subject came to the site complaining of orthopnea and generalized body and facial swelling for 2 days. The subject was hospitalized for class IV CHF, which the investigator felt was precipitated by pneumonia. Physical exam revealed raised jugular venous pressure, blood pressure 140-150/90 mmHg, dyspnea at rest, bilateral rhonchi, and end inspiratory and expiratory crepitations in both lungs. The abdomen was distended with epigastric tenderness. An ejection systolic murmur grade 3/6 was heard in the aortic area conducted to carotids. ECG revealed sinus rhythm with T wave inversion in AVL. On day 122, a 2D echocardiogram showed moderate aortic stenosis and trivial aortic regurgitation with an EF of 52%. A chest x-ray showed cardiomegaly with bilateral lower zone infiltration. The subject was treated with IV antibiotics, oxygen, diuretics, digoxin, and vasodilators. On day 124, the subject's hospitalization was prolonged due to severe acute respiratory distress syndrome (ARDS), which the investigator felt was due to the left lower lobe pneumonia. The subject's respiratory failure worsened over 2 days. Examination showed poor respiratory effort and bilateral coarse crepitations. SPO2 was 44% with oxygen by mask. The subject was intubated and placed on a ventilator. Treatment for ARDS included furosemide, IV antibiotics, digoxin, potassium, and oxygen. The subject's pneumonia improved and she was weaned off the ventilator. On day 134, the subject was discharged in stable condition on oral antibiotics and room air, as the events had resolved. Study medication was discontinued on day 121 due to congestive heart failure. The investigator reported the CHF event as possibly related to alogliptin and probably related to pioglitazone.

- **COMMENT: Although the CHF event occurred after 4 months' exposure to alogliptin, the subject's complicated cardiovascular history and coadministration of pioglitazone are more likely explanations for the SAE.**

PLC-010:

- 440/4008 (Alogliptin 12.5 mg): 37 year old male with a history of T2D, gastroesophageal reflux disease, alcohol abuse, alcohol detoxification, multiple hospital admissions for injuries, falls, unconsciousness related to alcohol abuse, laparoscopic Nissen fundoplication, cholecystitis, sleep apnea, major depressive illness, hypertension, irritable bowel syndrome, and obesity was admitted to the hospital on day 102 for palpitations. The palpitations lasted for 45 minutes while ingesting alcohol and were associated with chest pain. Troponin I was 0.04 mcg/l (reference range 0.0-0.03 mcg/l). ECG did not confirm atrial fibrillation and did not show changes consistent with myocardial ischemia. The hospital diagnosis was alcohol-induced atrial fibrillation. On day 103, the investigator also reported the subject experienced intermittent chest pain following discharge from the hospital that day. Study medication had been discontinued on day 92 due to dizziness.
 - **COMMENT: Although the event occurred 10 days after discontinuation of study medication, the subject had taken alogliptin for > 3 months and the event may be drug related. Although troponin is elevated, ECG did not show changes consistent with ischemia. The elevated troponin may be due to the demand placed on the heart by the palpitations although no formal diagnosis of arrhythmia was made.**
- 442/4005 (Alogliptin 25 mg): 59 year old male with a relevant history of obstructive sleep apnea, chest pain possible angina, hypertension, dyslipidemia, gastroesophageal reflux disease (GERD), and smoking was admitted on day 77 for angina pectoris and day 104 for intermittent claudication. On day 77, the subject was hospitalized for a 9 hour episode of chest pain, which started gradually, was sharp, and left sided with radiation to the left arm. The pain was associated with shortness of breath, sweats, and nausea and resolved with morphine. ECG showed flat T waves inferiorly but not acute ST changes. Troponin I level was < 0.04 µg/L (0-0.04 µg/L). An exercise tolerance test was negative for myocardial ischemia although only 81% of maximum heart rate was reached after 6 minutes when the test had to be aborted due to leg claudication. Laboratory results included triglycerides 3 mmol/L (< 2 mmol/L), GGT 83 U/L (0-60 U/L), and ALT 50 U/L (< 45 U/L). According to the investigator, the subject was admitted to the hospital on several occasions in the past with chest pain and on each occasion the investigations were normal, including serial cardiac enzymes and ECGs. An exercise stress test in February 2000 was negative. These events of chest pain were treated as GERD. The subject was not previously diagnosed with angina nor treated with medications for angina. The investigator also reported that the subject had a history of similar frequent episodes of chest pain, not associated with exertion and lasting 5-10 minutes in the previous 4 weeks. On day 79, the subject was discharged from the hospital and the event resolved. On day 170, the subject was seen by a cardiologist for follow up. He denied any anginal symptoms at rest or exertion. On day 104, the subject was hospitalized for worsening left leg claudication which began on day 58. Bilateral lower limb angiogram showed no vascular pathology with 3 good vessels run off bilaterally. On day 106, the

subject was discharged. At follow up with a vascular surgeon on day 125, physical examination revealed absent dorsalis pedal pulses on the left after a 10 minute walk. Lower limb angiography again showed 3 good vessels run off bilaterally. The subject was encouraged to discontinue smoking and placed on short-acting diltiazem, which improved the symptoms.

- **COMMENT: The characteristics of the chest pain and its associated symptoms on day 77 suggest angina (the negative cardiac stress test results are inconclusive given the short duration of testing), despite the previous episodes of chest pain which were treated as GERD. The occurrence of these symptoms after 2.5 months' exposure to alogliptin suggest the symptoms may be drug related. This patient also experienced leg claudication although an atherosclerotic lesion was not seen during angiography.**

INS-011:

- 244/5024 (Alogliptin 12.5 mg): 71 year old female with a relevant history of T2D, hypertension, coronary artery heart disease, Palmaz stent, angina pectoris, and hypercholesterolemia was admitted day 115 for coronary artery disease. On day 105, the subject experienced chest discomfort. On day 115, she was admitted to the hospital for elective stent placement secondary to worsening coronary artery disease. On admission, the lipids were normal, glucose 128 mg/dl, and the activated clotting time 292 seconds (98-159 seconds). The subject underwent left heart catheterization, selective left and right coronary arteriography, cutting balloon angioplasty and stenting of the right coronary artery (RCA). Catheterization showed severe stenosis or total occlusion of the mid-distal RCA proximal to a previously implanted stent of a collateral to the distal RCA from the LCA system, and of the first marginal branch of the circumflex as well as diffuse atherosclerotic disease of the left descending diagonal and circumflex with no critical focal lesions. The subject had successful placement of a 3 mm x 23 mm stent in the distal right coronary artery. On day 116, the subject was discharged from the hospital and the event resolved. Study medication was interrupted from day 115 to 116.
 - **COMMENT: The patient's history of stent placement may have contributed to the development of severe stenosis or total occlusion proximal to the previously implanted stent. However, upon admission, the subject's lipids were normal and she was anticoagulated. Furthermore, atherosclerotic lesions were also seen in the first marginal branch, LAD, and circumflex arteries. Thus, one cannot fully exclude a relationship between study drug and these events which occurred after almost 4 months of therapy.**
- 307/5003 (Alogliptin 12.5 mg): 58 year old male with a relevant history of T2D, hypertension, smoking, hypercholesterolemia, COPD, atrial fibrillation, and bilateral extremity peripheral vascular disease experienced atrial fibrillation on day 48, worsening atrial fibrillation on day 81, and cardiogenic shock on day 82. On day 48, the subject was hospitalized for atrial fibrillation. Symptoms included shortness of breath, racing heart, intermittent dizziness, nonproductive cough, and left upper quadrant nonradiating abdominal pain. The cardiac profile was normal, although the glucose level was 39 mg/dl. On examination, the subject had decreased breath sounds bibasilarly, mild to moderate JVD, and peripheral edema. The chest x-ray was compatible with congestive heart failure with left > right pleural effusions, cardiomegaly, and underlying COPD.

ECG showed atrial fibrillation with a rate of 121 bpm. The patient was treated with diltiazem, topical nitroglycerin, and lasix. Echocardiogram showed his ejection fraction to be globally suppressed at 40%. A pulmonary consultation was obtained due to shortness of breath; a therapeutic thoracentesis was recommended. On day 56, the event was considered resolved and the subject was discharged. On day 81, the subject was hospitalized for worsening atrial fibrillation and underwent a bilateral thoracentesis. Approximately 1,000 cc of blood tinged fluid was withdrawn from the left pleural cavity and 800 cc from the right. Creatinine and BUN measurements were abnormal, 1.9 mg/dl and 43 respectively. On day 82, the subject experienced severe cardiogenic shock. He was admitted to the ICU with bilateral pleural effusions, cardiogenic shock, and managed with chest tubes and mechanical ventilation. ECG revealed atrial fibrillation with rapid ventricular response. Echocardiogram showed mild left atrial dilation and left ventricular ejection fraction of approximately 50%. On day 85, the cardiogenic shock resolved. On day 97, a transesophageal echocardiogram revealed that the left atrial appendage was free of thrombus. The subject underwent unsuccessful elective external cardioversion the same day. On day 98, the subject was discharged from the hospital and the event considered resolved. The subject discontinued from the study on day 58 due to the onset of new health conditions.

- **COMMENT: This reviewer wonders when the subject received his last dose of study medication, as it is not specified in the provided narrative.**
- 329/5006 (Alogliptin 12.5 mg): 53 year old male with a relevant history of T2D, hypertension, grade 2/6 heart murmur and hyperlipidemia was admitted to the hospital on day 115 for atrial fibrillation. On day 115, the subject complained of palpitations (150-160 bpm) while resting with sweating, shortness of breath, and light nonradiating chest pain. He denied nausea, vomiting, dizziness, and syncope. Symptoms were similar to those experienced 2 weeks prior, which were the first of their kind. The subject was treated with diltiazem and heparin drips, digoxin, metoprolol, metformin, and insulin. Troponin levels were normal (0.09 to < 0.04); LDL cholesterol was 109. On the night of the admission, the subject's rhythm converted to sinus rhythm with a heart rate 70-80 bpm. On day 116, an echocardiogram showed a normal ejection fraction, mild concentric left ventricular hypertrophy, a mildly dilated left atrium, and mild tricuspid regurgitation. On day 117, a stress echocardiogram showed rare premature ventricular contractions and 1 episode of nonsustained ventricular tachycardia (3 beats). Enoxaparin injections and warfarin were started to increase the international normalization ratio from 1.2 to therapeutic values. On day 118, the subject was discharged from the hospital and the event considered resolved.
- 395/5008 (Alogliptin 25 mg): A 40 year old female with a history of T2D, hypertension, ischemic cardiomyopathy secondary to coronary artery disease, dyslipidemia, overweight, and hypokalemia was admitted to the hospital on day 18 for angina unstable. Results from the coronary catheterization were not reported. The subject was treated with isosorbide dinitrate, enalapril, and spironolactone. She was asymptomatic and the event considered resolved when she was discharged from the hospital on day 29. Study medication was interrupted on days 18 – 29 due to this event. The subject was withdrawn from the study due to lack of efficacy with the last dose of study drug on day 123.

- 484/5001 (Placebo): 77 year male with a history of ischemic heart disease, coronary artery bypass grafts, hypertension, pulmonary edema, and transient brain ischemia who was hospitalized on day 3 for angina unstable. The ECG showed marked Q waves in II, III, ST segment elevation in III, aVF and ST segment depression in I. Treatment included unfractionated heparin, nitrates, and clopidogrel. On day 8, the severe chest pain recurred with increased ischemic changes on ECG and the subject was transferred to another hospital for further diagnosis and treatment. The peak CK was 176.9 with CK-MB of 28.0. Troponin T was normal. Angiography on day 8 revealed that both venous bypasses were patent but significant stenosis of the posterolateral branch. Percutaneous angioplasty was carried out with implantation of a 2.5 x 18 mm stent into the stenosed vessel, resulting in full revascularization. On day 14, the subject was discharged. The last dose of study drug was on day 2.
 - **COMMENT: The severe chest pain, “increased ischemic ECG changes” as compared to day 3’s ECG with Q waves, and an elevated “peak” CK and CK-MBs (where “peak” implies a rise and fall) suggest this placebo subject had an MI according to the universal definition of MI.¹**

OPI-001:

- 296/3007 (A25 + P45): 48 year old male with a history of T2D, smoking (25 years), hypertension, dyslipidemia, fatty liver, and obesity experienced myocardial ischemia on day 174. The subject’s screening and day 1 ECG revealed incomplete right bundle branch block. On day 146, cardio stress test revealed 2-3 mm ST depression in leads V3-V6, aVF, II-III, and a high probability of myocardial ischemia. A repeat stress test showed similar findings. The subject was hospitalized on day 174 for chest pain that radiated to his left arm and was similar to pain experienced for the past 2 months. There were no associated symptoms. ECG showed normal sinus rhythm with no ST-T or Q wave changes. A coronary angiogram was performed on day 176 that showed 100% occlusion of the left circumflex artery, which could not be opened, although there was a collateral supply (which implies that this obstruction was chronic). There was also 60% occlusion of the mid RCA. Ventricular function was normal with a restrictive ventricular filling pattern. The right ventricular size and function were normal. The event resolved and the subject was discharged. NonSAEs of angina pectoris and myocardial ischemia were reported on days 141 and 176, respectively. The angina resolved on day 174, although the ischemia continued.
 - **COMMENT: This SAE may have been drug related as it occurred after > 5 months exposure.**
- 397/3011 (A25 + P45): 66 year old male with history of T2D, dyslipidemia, and hypertension experienced coronary artery stenosis on day 77. An exercise tolerance test on day 27 showed myocardial ischemia. A single-photon-emission CT scan with Tc99 MIBI on day 29 revealed transient hypoperfusion in the inferior wall after exercise, an EF of 58% (normal > 45%), and normal left ventricular global function at rest. The subject was hospitalized on day 77 for a cardiac catheterization which showed coronary artery stenosis. At discharge on day 77, the ischemia had resolved but the stenosis was

¹ Thygesen, Kristian et al. Universal definition of myocardial infarction. Circulation. 2007 Nov 27;116(22):2634-53.

continuing. Atenolol and isosorbide mononitrate were prescribed for stenosis on day 97. Study drug was interrupted on days 73-80 due to myocardial ischemia.

- 632/3003 (P45): See above MACE section.
- 774/3014 (P45): 57 year old male with a history of T2D, previous smoking, hyperlipidemia, and hypertension experienced CAD on day 58. The subject also had an ALT value on day 141 that was >3x ULN. The subject experienced chest pain after exertion for 3-4 weeks. ECG was normal but stress test revealed exercise-induced chest pain and ST segment changes at 4.5 minutes into exercise that was reported as a nonSAE of angina pectoris on day 38. The subject was hospitalized on day 58 and underwent a catheterization which showed 95% proximal LAD artery stenosis with a diagonal stenosis of 60%. Angioplasty was performed in both arteries and a stent placed in the LAD. Ventricular function was normal. The diagnoses were progressive angina pectoris and CAD, which resolved on day 59 when the subject was discharged. Study drug was interrupted on days 58 – 59 due to this event.
- 833/3004 (A12.5 + P45): 44 year old male with a history of T2D and hypertension experienced angina unstable on day 9. The subject developed a 15 second syncope while driving on day 9. He was hospitalized and stated that he had chest pain, diaphoresis, and palpitations after taking his study drug. ECG at admission was normal, but CK was 211 (30-170 IU/L). Other cardiac enzymes were normal. An echo-color Doppler test was unremarkable. Approximately 7 hours after admission, his CK was 178 IU/L. The subject was held for 24 hours observation and discharged on day 10 with plans of cardiac follow up. A dobutamine stress echocardiogram on day 19 was negative for ischemic heart disease. The event resolved. Study drug was discontinued on day 9 because of the SAE.
 - **COMMENT: Although this SAE occurred on day 9, symptoms began after taking the study drug and were severe enough for study discontinuation. It is possible that the reported symptoms were due to an arrhythmia rather than unstable angina given the normal cardiac stress test.**

OPI-002:

- 665/2509 (A25 + P30): 57 year old male with a history of T2D, previous smoking, dyslipidemia, hypertension, hypothyroidism, obesity, and an MI in 1997 experienced an acute MI on day 26. Baseline ECG on day 1 was normal sinus rhythm with negative T waves in V4-V6. On day 26, the subject was hospitalized for angina pectoris that lasted several hours. The pain did not subside with nitroglycerin tablets. Admission laboratories showed hyperglycemia and glycosuria, although initial cardiac enzymes were negative. On day 27, the subject was diagnosed with an acute MI. ECG showed inverted T-waves in I and VL and in precordial recordings and troponin was positive. The subject was medically managed. On day 29, an echocardiogram showed EF of 50% and significant hypertrophy of the LV wall. He was discharged on day 33 when the event resolved. Study drug was discontinued and the subject withdrawn on day 51 due to the acute MI.
- 678/2526 (A25): 51 year old female with a history of T2D, menopause, and dyslipidemia who experienced unstable angina on day 85. Her screening ECG showed Q waves in lead III and aVF. On day 83, an ECG at the week 12 visit showed changes suggestive of

anterolateral subepicardial ischemia. The subject was asymptomatic and treatment was initiated with acetylsalicylic acid. At a follow up visit on day 85, the subject stated she had precordial pain lasting < 10 minutes associated with exertion. The pain did not radiate and resolved with rest. An ECG on day 85 showed progression of inverted T waves in V5 and the subject was hospitalized with a diagnosis of severe unstable angina. Cardiac enzymes ruled out myocardial infarction. Serum glucose was 220 mg/dl. A stress ECG on day 86 was positive for signs of ischemia when the subject reached 78% of maximum permissible heart rate. The subject was treated medically and discharged on day 97. Myocardial ischemia was reported as an AE on day 83 for the occurrence of anterolateral subepicardial ischemia, and CAD was reported as an AE on day 97 as an ongoing event. Study drug was interrupted on days 85 – 87. The subject continued in the study but was eventually withdrawn on day 176 due to a major protocol violation (she received misallocated study drug).

- **COMMENT: The coding of the events is correct. The occurrence of the events after approximately 3 months exposure suggests that they may be drug related.**

The expected ratios of cardiovascular SAEs based on randomized patients in the safety population are as follows:

- NDA 22-271 1,961 Alogliptin: 534 Placebo or 3.7: 1
- NDA 22-426 1,528 Alogliptin: 679 Comparator or 2.25: 1
- NDA 22-271 + 22-426 3,489 Alogliptin: 1,213 Comparator or 2.9: 1

The ratios of cardiovascular SAEs observed in NDA 22-271 + NDA 220426, based on this reviewer's adjudication of events, were greater than the expected ratios and are shown below:

- MI 5-7:1
- Angina 8-12:1
- Unstable angina 1.5:1
- Angina/Unstable angina 3.33-5:1
- Heart failure 4:0
- A fib/flutter 5:0
- Bradycardia 1:0

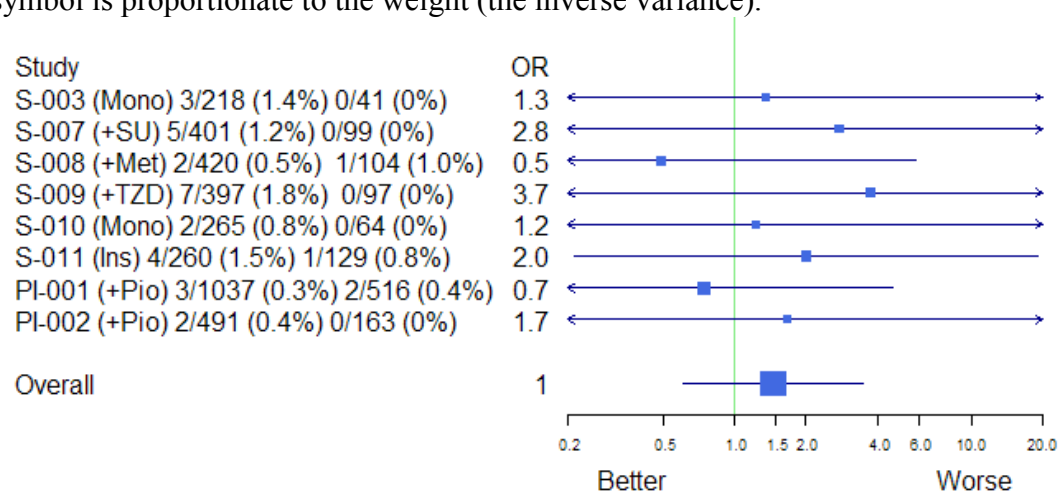
Note, however, that a handful more events in the comparator groups or a handful less events in the alogliptin group, would yield ratios consistent with what is expected for the randomization scheme. The low event rates limit definite conclusions regarding cardiac risk, as occurred with the MACE analyses.

When Dr. Janice Derr of statistics calculated the incidence ratio, it exceeded 1.8 with the stratified asymptotic and exact methods (2.31 and 2.24, respectively). The 95% CI were again broad.

NDA 22-271. Alogliptin vs. Placebo, Stratified Analysis of Cardiac SAEs (combined across 8 studies) ¹					
Group	N	Exposure (Pt-Yrs)	# of events	Incidence (%) Events/N	Incidence Rate Events/ 100 pt-yrs
Alogliptin	3489	1537	28	0.80%	1.821
Placebo	1213	505	4	0.33%	0.793
Method				Incidence Ratio (95% CI)	Method ⁴ Incidence Rate Ratio (95% CI)
Stratified, asymptotic (MH) ²				2.31 (0.78, 6.78)	Stratified, asymptotic 2.10 (0.70, 6.29)
Stratified, exact				2.24 (0.77, 8.88)	Stratified, exact 2.05 (0.71, 8.11)
Stratified, fixed effects MH meta-analysis with a continuity correction ³				1.46 (0.62, 3.45)	
Notes:					
¹ The tallies of cardiac SAE were provided by V. Pratt, as of 3/12/09. For the stratified analyses with no continuity correction, all 8 studies were included in the analyses because none of the studies had 0 events in both groups. Test of homogeneity across studies: For incidence ratio, the p-value was 0.713; for incidence rate ratio, the p-value was 0.713.					
² MH = Mantel-Haenszel					
³ A continuity correction of 0.5 was added to groups with 0 events: Depicted in the forest plot (Figure 1)					

NDA 22-271. Cardiac SAEs, Odds Ratios and 95% CIs from stratified asymptotic method (M-H) with continuity correction.

The forest plot depicts the odds ratio and 95% confidence intervals for each study and for the combined estimate from the stratified, fixed effects Mantel-Haenszel meta-analysis, with a continuity correction of +0.5 applied to studies with zero events in either arm or both arms. Studies with more precise results were given more weight in the computation of the common odds ratio. The size of the symbol is proportionate to the weight (the inverse variance).



7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The incidence rates of TEAEs in the controlled phase 2 and 3 studies originally submitted to the NDA were reviewed. Events which occurred in $\geq 1\%$ of an alogliptin dose group are listed by SOC and preferred term below. None of the preferred terms (except perhaps hypersensitivity) had a convincing relationship to alogliptin dose. There was an increase in cardiovascular TEAEs when alogliptin was compared to placebo (4.0% vs. 2.4%). The most common AE in this SOC was angina pectoris (0.7% vs. 0%, respectively). A slight increase in immune system disorders was also seen when alogliptin was compared with placebo (1.3% vs. 0.4%). The most common events in this SOC were seasonal allergy (0.5% vs. 0.2%), hypersensitivity (0.4% vs. 0.2%), drug hypersensitivity (0.2% vs. 0), and food allergy (0.1% vs. 0). Nervous system disorders also occurred more frequently in the alogliptin group (13.0% vs. 9.7%). Headache and dizziness, which occurred at similar rates in the alogliptin and placebo groups, were the most common events in the SOC.

DPP-4 is present on immune cells, therefore, some sponsors of other DPP-4 inhibitors have evaluated infections as an AE of special interest. Alogliptin's sponsor did not do this, but still collected and analyzed reports of infection AEs as is typically done for all NDAs. This reviewer has analyzed these data and notes no concerning signal for increased infections with alogliptin. Of note, infection and infestation disorders were more common in the placebo group (31.3% vs. 28.8%). Upper respiratory infection, nasopharyngitis, and headache, which occurred in $\geq 5\%$ of subjects treated with sitagliptin and more commonly than placebo, occurred in $< 5\%$ of alogliptin subjects and were more common in placebo subjects (3.6% vs. 5.2%; 4.9% vs. 5.1%; and 4.9% vs. 3.9%, respectively).

NDA 22-271. Percent incidence of TEAEs in controlled phase 2 and 3 studies originally submitted to the NDA ($\geq 1\%$ alogliptin group). Source: Integrated analysis of safety Table 8.4.2.1.1 (p. 542-605)						
	Placebo (n=534)	Alogliptin (mg)				
		6.25 (n=42)	12.5 (n=922)	25 (n=910)	> 25 (n=87)	All doses (n=1961)
% w ≥ 1 TEAE	65.0	40.5	66.1	64.4	55.2	64.3
Blood & lymphatic disorders	2.2	2.4	2.3	2.0	0	2.0
Anemia	0.6	0	1.2	1.0	0	1.0
Lymphocytosis	0	2.4	0	0.1	0	0.1
Cardiac disorders	2.4	0	4.2	4.2	1.1	4.0
Angina pectoris	0	0	0.3	1.0	1.1	0.7
Ear & labyrinth disorders	1.9	2.4	1.2	1.2	0	1.2
Ear pain	0.4	2.4	0.3	0.2	0	0.3
Tinnitus	0.2	2.4	0	0.2	0	0.2
Eye disorders	2.2	2.4	2.6	3.0	0	2.7
Vision blurred	0.2	2.4	0.7	0.4	0	0.6

Gastrointestinal disorders	14.6	7.1	13.6	14.7	19.5	14.2
Diarrhea	3.4	0	2.7	3.3	3.4	3.0
Nausea	1.7	4.8	2.3	2.3	6.9	2.5
Constipation	1.3	0	1.2	1.4	1.1	1.3
Dyspepsia	1.7	0	1.0	1.5	1.1	1.2
Abdominal pain	0.4	0	1.2	1.2	0	1.1
Vomiting	0.9	2.4	0.8	1.4	0	1.1
Toothache	0.9	0	0.5	1.3	0	0.9
GERD	0.2	2.4	0.8	0.8	1.1	0.8
Food poisoning	0.2	0	0.2	0.2	1.1	0.3
Abdominal discomfort	0.2	0	0.1	0.2	1.1	0.2
Abdominal tenderness	0	2.4	0.2	0.1	0	0.2
Dry mouth	0.2	0	0.2	0.1	1.1	0.2
Feces hard	0	0	0	0	1.1	0.1
General disorders & admin. site conditions	7.3	7.1	7.3	9.3	11.5	8.4
Edema peripheral	2.6	0	2.5	3.5	3.4	3.0
Fatigue	1.3	0	1.1	1.5	5.7	1.5
Noncardiac chest pain	0.6	4.8	1.1	0.9	0	1.0
Pyrexia	0.7	0	0.5	1.0	0	0.7
Pain	0.6	0	0.1	0.4	2.3	0.4
Mass	0	0	0.1	0	1.1	0.1
Local swelling	0	2.4	0	0	0	0.1
Immune system disorders	0.4	2.4	1.2	1.4	1.1	1.3
Seasonal allergy	0.2	2.4	0.7	0.3	0	0.5
Hypersensitivity	0.2	0	0.2	0.4	1.1	0.4
Infection & infestation disorders	31.3	9.5	31.7	27.9	16.1	28.8
Nasopharyngitis	5.1	0	5.1	5.4	1.1	4.9
Urinary tract infection	4.7	4.8	5.1	4.1	8.0	4.7
Upper respiratory tract infection	5.2	2.4	3.9	3.5	2.3	3.6
Influenza	2.2	0	2.2	2.7	1.1	2.3
Bronchitis	2.8	0	2.4	1.5	0	1.6
Sinusitis	2.8	0	1.4	1.5	0	1.4
Pharyngitis	1.3	0	1.2	1.4	0	1.2
Gastroenteritis	0.6	0	1.0	1.3	0	1.1
Viral infection	0.6	0	1.3	0.7	0	0.9
Tinea pedis	1.3	0	0.7	1.0	0	0.8
Fungal skin infection	0.7	0	0.3	1.0	0	0.6
Rhinitis	0.2	0	1.0	0.2	1.1	0.6
Body tinea	0	0	0.3	0.1	1.1	0.3
Gastrointestinal infection	0	2.4	0	0	0	0.1
Injury, poisoning, & proced. comp. disorders	11.2	4.8	8.2	9.1	2.3	8.3
Contusion	0.6	0	1.3	1.0	0	1.1
Fall	0.4	0	1.3	0.4	1.1	0.9
Limb injury	0.4	0	0.4	0.5	1.1	0.5
Burns first degree	0	2.4	0	0	0	0.1
Investigation disorders	6.0	4.8	6.6	5.2	3.4	5.8
Weight increased	0.9	0	1.3	0.4	0	0.8
Blood triglycerides increased	0.2	0	0.8	0.4	1.1	0.6
White blood cell count increased	0	2.4	0.3	0	0	0.2
Blood alkaline phosphatase increased	0.2	0	0	0.1	1.1	0.1
Glucose urine	0	0	0.1	0	1.1	0.1
Blood potassium decreased	0	2.4	0	0	0	0.1

High density lipoprotein decreased	0	0	0	0	1.1	0.1
Protein urine present	0	0	0	0	1.1	0.1
Red blood cells urine positive	0	0	0	0	1.1	0.1
Metabolism & nutrition disorders	7.5	2.4	5.7	8.5	1.1	6.7
Hypertriglyceridemia	1.5	0	2.0	1.8	0	1.7
Dyslipidemia	0.9	0	0.8	1.2	0	0.9
Hyperlipidemia	0.7	0	0.7	1.2	0	0.9
Musculoskeletal & connective tissue disorders	13.1	4.8	14.5	13.2	12.6	13.6
Back pain	2.4	0	2.6	3.0	3.4	2.8
Arthralgia	2.6	0	2.7	2.5	0	2.4
Pain in extremity	2.2	0	1.8	2.1	2.3	1.9
Musculoskeletal pain	0.7	2.4	0.9	0.9	0	0.9
Osteoarthritis	0.7	0	1.0	0.7	0	0.8
Tendonitis	0	2.4	0.7	0.9	0	0.8
Arthritis	0.4	0	0.4	0.2	1.1	0.4
Musculoskeletal chest pain	0.4	0	0.5	0.1	1.1	0.4
Joint stiffness	0	0	0	0.1	1.1	0.1
Joint swelling	0.2	0	0	0.1	1.1	0.1
Neoplasms	2.1	0	1.6	1.4	0	1.4
Nervous system disorders	9.7	9.5	13.6	12.5	12.6	13.0
Headache	3.9	4.8	4.1	4.4	6.9	4.4
Dizziness	1.9	4.8	2.3	2.0	2.3	2.2
Sciatica	0	0	1.0	0.4	0	0.7
Tremor	0.6	0	0.4	0.5	1.1	0.5
Disturbance in attention	0	0	0	0.1	1.1	0.1
Lethargy	0.2	0	0	0.1	1.1	0.1
Psychiatric disorders	2.4	2.4	3.4	2.9	1.1	3.0
Insomnia	0.4	0	1.3	0.7	1.1	1.0
Anxiety	1.3	0	1.0	0.8	0	0.8
Depression	0.2	2.4	0.4	0.8	0	0.6
Renal & urinary disorders	1.3	2.4	2.2	2.0	1.1	2.0
Pollakiuria	0	0	0.3	0.2	1.1	0.3
Reproductive disorders	1.7	0	1.6	1.4	1.1	1.5
Prostatitis	0	0	0.2	0	1.1	0.2
Respiratory, thoracic, & mediastinal disorders	4.9	4.8	6.3	6.4	6.9	6.3
Cough	1.7	0	1.2	1.9	2.3	1.5
Pharyngolaryngeal pain	0.4	0	1.1	0.8	2.3	1.0
Epistaxis	0.6	0	0.4	0.7	1.1	0.6
Sinus congestion	0.7	2.4	0.3	0.2	1.1	0.4
Rhinorrhea	0.6	0	0.1	0.2	1.1	0.2
Skin & subcutaneous tissue disorders	10.3	4.8	11.6	12.0	8.0	11.5
Pruritis	0.4	0	1.2	2.3	0	1.6
Rash	0.7	0	1.5	1.6	2.3	1.6
Dermatitis contact disorders	0.4	0	0.5	0.8	1.1	0.7
Skin ulcer	0.9	2.4	0.4	0.3	0	0.4
Urticaria	0.4	2.4	0.2	0.3	1.1	0.4
Cold sweat	0	0	0	0	1.1	0.1
Vascular disorders	4.1	2.4	3.9	4.4	0	3.9
Hypertension	3.0	2.4	3.0	3.5	0	3.1
Hot flush	0.2	2.4	0.1	0.1	0	0.2

The incidence rates of TEAEs in fixed dose studies OPI-001 and OPI-002 were also reviewed. Events which occurred in $\geq 1\%$ of an alogliptin dose group are listed by SOC and preferred term below. The incidence of AEs in a specific SOC was similar or less frequent in the alogliptin and Alo + Pio groups when compared to pioglitazone, except for a slight increase in gastrointestinal disorders (12.6% and 13.3% vs. 10.9%, respectively). An increase in gastrointestinal AEs was not seen in the studies originally submitted to NDA 22-271 (i.e. SYR-322-003, SULF-007, MET-008, TZD-009, PLC-010, and INS-011). The incidence of AEs by PT was similar or less frequent in the alogliptin and Alo + Pio groups when compared to pioglitazone, except for a slight increase in nasopharyngitis (3.8% vs. 4.0% vs. 2.9%), upper respiratory infection (4.5% vs. 3.1% vs. 1.8%), diabetic neuropathy (1.7% vs. 1.4% vs. 0.5%), and hypertension (3.3% vs. 3.3% vs. 2.7%). However, the percentage of subjects with abnormally high systolic or diastolic blood pressure in controlled phase 2 and 3 studies of alogliptin were similar. (Please refer to section 7.4.3 Vital Signs.) The rate of cardiovascular AEs was less in the alogliptin and Alo + Pio groups when compared to pioglitazone (1.7% and 3.9% versus 5.3%, respectively).

NDA 22-426. Percent incidence of TEAEs in controlled phase 3 studies OPI-001 and OPI-002 ($\geq 1\%$ alogliptin or Alo+Pio group). Source: Integrated analysis of safety Table 8.4.2.1 (p. 386-447)			
	Alogliptin (n=421)	Pioglitazone (n=550)	Alo + Pio (n=1107)
% subjects ≥ 1 TEAE	60.3	60.5	62.7
Blood & lymphatic disorders	3.1	5.5	6.3
Anemia	0.2	1.5	2.3
Neutropenia	1.7	2.0	1.5
Eosinophilia	0.7	1.6	1.4
Cardiac disorders	1.7	5.3	3.9
Ear & labyrinth disorders	1.0	1.1	1.5
Eye disorders	1.9	2.7	2.7
Gastrointestinal disorders	12.6	10.9	13.3
Diarrhea	1.7	3.3	3.3
Abdominal pain upper	2.1	0.5	1.8
Nausea	1.0	1.6	1.8
Dyspepsia	1.0	0.2	1.2
Abdominal pain	0.7	0.9	1.1
Constipation	1.4	1.5	0.8
Toothache	1.0	0.2	0.4
General disorders & admin site conditions	5.7	7.5	7.9
Edema peripheral	1.4	3.5	2.7
Pyrexia	1.0	1.3	1.2
Hepatobiliary disorders	1.9	1.5	0.6
Infections & infestations	25.2	25.1	27.5
Nasopharyngitis	3.8	2.9	4.0
Urinary tract infection	3.8	4.9	4.0
Influenza	2.4	4.5	3.2
Upper respiratory tract infection	4.5	1.8	3.1
Pharyngitis	1.2	1.5	2.4
Bronchitis	1.2	1.1	2.1
Sinusitis	0.7	0.7	1.2
Gastroenteritis	1.2	0.9	1.0
Tinea pedis	0.5	1.1	0.7

Injury, poisoning, & procedural complications	5.5	4.7	5.1
Investigations	7.6	7.8	7.7
Weight increased	0.5	2.5	2.4
GGT increased	1.0	0.2	0.2
Metabolism & nutrition disorders	10.9	10.0	7.0
Dyslipidemia	1.9	3.1	1.9
Hypertriglyceridemia	3.8	2.9	1.5
Hypercholesterolemia	1.4	1.5	1.0
Hyperlipidemia	0.7	1.3	1.0
Musculoskeletal & connective tissue disorders	9.3	12.4	14.5
Back pain	2.1	2.7	4.4
Pain in extremity	0.7	2.4	3.1
Arthralgia	1.7	2.5	3.0
Musculoskeletal pain	0.5	1.3	1.6
Muscle spasms	1.2	0	0.8
Myalgia	1.0	0.2	0.7
Nervous system disorders	12.4	12.0	13.2
Headache	5.9	6.2	5.5
Dizziness	1.9	3.3	3.4
Diabetic neuropathy	1.7	0.5	1.4
Paresthesia	1.7	0.7	0.9
Psychiatric disorders	2.4	2.7	1.6
Renal and urinary disorders	2.1	2.9	2.5
Reproductive system & breast disorders	1.2	1.3	1.6
Respiratory, thoracic, & mediastinal disorders	4.5	4.4	3.5
Cough	1.4	1.5	1.3
Pharyngeal pain	1.7	1.3	0.4
Skin & subcutaneous tissue disorders	7.4	8.2	9.2
Pruritis	0.7	0.2	1.2
Rash	1.0	0.9	1.1
Vascular disorders	4.8	3.6	4.6
Hypertension	3.3	2.7	3.3

In the 120 day safety update, which mainly included an update on uncontrolled study OLE-012, no study treatment-emergent AEs occurred in $\geq 1\%$ of subjects in either the alogliptin 12.5 or 25 mg groups. Study drug-related AEs that occurred in $\geq 1\%$ of subjects overall in a SOC were skin and subcutaneous disorders (2.5%), gastrointestinal disorders (2.3%), infections and infestations (1.7%), investigations (1.7%), nervous system disorders (1.6%), metabolism and nutrition disorders (1.2), general disorders and administration site conditions (1.1%), and musculoskeletal and connective tissue disorders (1.0%). The lack of a control group limits conclusions in the uncontrolled period.

7.4.2 Laboratory Findings

7.4.2.1 Overview of laboratory testing in the development program

Standard safety laboratory data were obtained in all studies at baseline, during the treatment period, and at study end. The frequency of safety laboratory evaluations in pivotal phase 3

studies is shown below. Serum CPK, amylase, and lipase were not measured in the phase 3 studies.

Changes in laboratory values (or ECG) parameters were considered to be AEs if they were judged to be clinically significant (i.e. if some action or intervention was required or if the investigator judged the change to be beyond the range of physiological function). If abnormal laboratory values (or ECG) findings were the result of pathology for which there was an overall diagnosis (e.g. increased creatinine in renal failure), the diagnosis only was reported as an AE. AEs are discussed in the safety sections above.

NDA 22-271. Safety laboratory evaluations in pivotal phase 3 studies		
Hematology	Biochemistry	Urine measurements
White blood cell count	Albumin	<i>Qualitative:</i>
Autodifferential	Alkaline phosphatase	Appearance
Platelet count	Alanine aminotransferase	Color
Hemoglobin	Aspartate aminotransferase	pH
Hematocrit	Blood urea nitrogen	Specific gravity
Red blood cell count	Carbon dioxide	Ketones
Mean corpuscular (MC) volume	Calcium	Protein
MC hemoglobin	Magnesium	Glucose
MC hemoglobin concentration	Chloride	Nitrite
	Creatinine	Urobilinogen
	Glucose	Blood
	Lactate dehydrogenase	
	Phosphorus	<i>Quantitative:</i>
	Potassium	Albumin/creatinine ratio
	Sodium	
	Total bilirubin	
	Total protein	
	Uric acid	
	γ -Glutamyl-transferase	
	Lipid panel	

NDA 22-271. Frequency of safety laboratory evaluations in pivotal phase 3 studies	
Hematology and biochemistry	Screening & weeks -1, 0, 1, 2, 4, 8, 12, 16, 20, & 24 ^a
Serum TSH	Screening
Serum pregnancy test	Screening & week 26
Urinalysis	Screening & weeks 0, 12, and 26
Urine microalbumin/creatinine ratio	Screening and week 26
^a Plasma glucose only at weeks -1 & 1. No lipid panel was obtained at week 2.	

The table below summarizes the sponsor's criteria for normal and markedly abnormal ranges, which are acceptable.

NDA 22-271. Laboratory test normal and markedly abnormal ranges for phase 3 studies			
Laboratory test	Normal range	Lower markedly abnormal value	Upper markedly abnormal value
Albumin	3.5 – 5.5	< 2.5 g/dl	
Alkaline phosphatase	32 - 72		> 3x ULN

BUN	5 - 20		> 3x ULN
Basophils	0 - 3		
Bicarbonate	21 - 33		
C-reactive protein	0 - 8.4		
Calcium	8.5 - 10.5	< 0.8x LLN	> 1.2x ULN
Chloride	95 - 110		
Creatinine	0.7 - 1.4		> 1.5x baseline
Eosinophils	0 - 7		
Gamma GT	5 - 29		> 3x ULN
Hematocrit	M: 37 - 51; F: 33 - 47	< 0.8x baseline	
Hemoglobin	M: 12.5 - 17; F: 11 - 15.5	< baseline - 3 g/dl	
LDH	40 - 100		> 3x ULN
Lymphocytes	12 - 46		
MCH	27 - 34		
MCV	M: 78 - 100; F: 82 - 102		
Magnesium	1.1 - 1.9		
Monocytes	0 - 11		
Phosphorus	2.5 - 4.5		
Platelet count	125 - 375	< 50 x 10 ³ /μl	> 600 x 10 ³ /μl
Potassium	3.5 - 5.0	< 3 mEq/l	> 5.8 mEq/l
Red blood cells	M: 4 - 5.6; F: 3.7 - 5.2	< 0.8x baseline	
SGOT (AST)	8 - 22		> 3, 5, or 10x ULN
SGPT (ALT)	5 - 40		> 3, 5, or 10x ULN
Sodium	133 - 145	< 130 mEq/l	> 150 mEq/l
Specific gravity	1.002 - 1.035		
Total bilirubin	0.10 - 1.10		> 2 mg/dl
Total neutrophils	46 - 72		
Total protein	6 - 8	< 0.8x LLN	> 1.2x ULN
Uric acid	M: 4 - 8; F: 2 - 6		> 10.5 (M) or 8.5 (F) mg/dl
Urine albumin/creatinine ratio	0 - 20		
White blood cells	3.7 - 11	< 2x 10 ³ /μl	> 20x 10 ³ /μl
pH	5 - 8		

7.4.2.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This reviewer focused the review of laboratory data on the controlled phase 2 and 3 studies originally submitted to NDA 22-271 (SYR-322-003, SULF-007, MET-008, TZD-009, PLC-010, and INS-011). As other DPP-4 inhibitors have been associated with potential liver and kidney toxicity, these laboratories were also reviewed in uncontrolled study OLE-012.

7.4.2.3 Standard analyses and explorations of laboratory data

7.4.2.3.1 Analyses focused on measures of central tendency

Laboratory analyses included all subjects who received at least one dose of study medication in controlled phase 2 and 3 studies. Baseline was defined as the last value collected on or prior to the date of first dose of study medication. Endpoint was defined as the last value collected within 7 days of the last dose of study medication.

Men were required to have a hemoglobin level ≥ 12 g/dl and women ≥ 10 g/dl to enroll in the controlled phase 2 and 3 studies originally submitted to NDA 22-271. In these studies, the mean changes from baseline to endpoint in hematology results were minor and not clinically meaningful. Hematology results were similar in the alogliptin 12.5 and 25 mg groups. Small differences in change from baseline to endpoint were observed between alogliptin 12.5 and 25 mg dose groups and the placebo group for WBCs (higher), total neutrophils (higher), and lymphocytes (lower). However, these differences were not seen in the alogliptin 50/100 mg group and were not considered clinically significant.

NDA 22-271. Change from baseline to endpoint according to hematology parameter and treatment group in controlled phase 2 and 3 studies. Note: Plus-minus values are mean\pmSD; values with parentheses are median (min, max).					
	Placebo (n=534)	Alogliptin			
		6.25 (n=42)	12.5 (n=922)	25 (n=910)	>25 (n=87)
Basophils (%)	-0.3 \pm 0.73 0 (-3, 2)	-0.1 \pm 0.75 0 (-1, 1)	-0.3 \pm 0.74 0 (-3, 2)	-0.3 \pm 0.77 0 (-7, 2)	0 \pm 0.82 0 (-2, 2)
Eosinophils (%)	-0.8 \pm 2.62 -1 (-18, 11)	0.2 \pm 1.71 0 (-4, 4)	-0.9 \pm 2.59 -1 (-25, 19)	-0.8 \pm 2.57 -1 (-18, 25)	-0.4 \pm 3.12 0 (-21, 7)
Hematocrit (%)	-0.16 \pm 2.5 -0.1 (-11.7, 15.0)	0.09 \pm 2.29 -0.2 (-3.7, 8.1)	-0.16 \pm 2.58 -0.2 (-13.4, 13.7)	-0.27 \pm 2.32 -0.3 (-7.9, 8.5)	-0.12 \pm 2.29 -0.2 (-5.4, 7.9)
Hemoglobin (g/dl)	-0.03 \pm 0.74 0 (-3.1, 3.9)	-0.08 \pm 0.74 -0.15 (-1.5, 2.1)	-0.02 \pm 0.81 0 (-4.4, 4.5)	-0.06 \pm 0.7 -0.1 (-2.5, 3.0)	-0.15 \pm 0.68 -0.1 (-1.8, 2.1)
Lymphocytes (%)	0.2 \pm 7.72 0 (-35, 43)	-0.6 \pm 7.17 0.5 (-20, 14)	-1.7 \pm 8.33 -2 (-47, 53)	-1.8 \pm 8.49 -2 (-52, 49)	0.0 \pm 5.61 -0.5 (-14, 15)
Monocytes	0.1 \pm 3.13 0 (-8, 48)	0.1 \pm 2.23 0 (-7, 7)	0 \pm 3.25 0 (-20, 62)	0.1 \pm 2.55 0 (-16, 17)	0.3 \pm 2.17 0 (-7, 6)
Neutrophils (%)	0.8 \pm 9.83 1 (-53, 46)	0.5 \pm 8.63 -0.5 (-16, 26)	2.9 \pm 10.49 3 (-58, 57)	2.9 \pm 10.42 3 (-54, 58)	0.0 \pm 6.57 0 (-19, 14)
Platelet count (10 ³ /mm ³)	-1.9 \pm 31.41 -4 (-127, 132)	-2.8 \pm 32.38 -3.5 (-91, 59)	-2.4 \pm 35.56 -4 (-194, 301)	-2.8 \pm 34.39 -3.5 (-167, 243)	-8.9 \pm 29.92 -6.5 (-105, 76)
WBCs (10 ³ /mm ³)	0.00 \pm 1.40 0 (-5.9, 11.8)	0.07 \pm 1.61 -0.2 (-2.1, 7.6)	0.23 \pm 1.58 0.2 (-11.3, 13.1)	0.13 \pm 1.39 0.2 (-6.3, 5.7)	-0.26 \pm 1.26 -0.2 (-3.6, 3.3)

In the controlled phase 2 and 3 studies originally submitted to NDA 22-271, subjects with ALT levels ≤ 3 x ULN were allowed to enroll, except for study TZD-009 which had required ALT ≤ 2.5 x ULN and study SYR-322-003 which required ≤ 2 x ULN. Subjects with creatinine levels ≤ 2 mg/dl were allowed to enroll, with the exception of study MET-008 which required < 1.5 mg/dl for men and < 1.4 mg/dl for women.

The mean changes from baseline to endpoint in chemistry results were small, not clinically relevant, and were generally similar between placebo and alogliptin treatment groups. The change from baseline to endpoint in alkaline phosphatase in the placebo and alogliptin 12.5 and 25 mg groups was -0.3, -1.8, and -1.4 mU/ml respectively. The mean change in ALT in the placebo and alogliptin > 25 mg groups were -0.1 and -2.3, although the 12.5 and 25 mg groups were more similar to placebo (-0.2 and -0.6, respectively) and the median changes were zero. The mean change in AST in the placebo group was 0.2, whereas the mean change in alogliptin groups ranged from -0.9 to 0.6. The mean change from baseline in creatinine for the alogliptin 12.5 and 25 mg groups was 0 mU/ml.

NDA 22-271. Change from baseline to endpoint according to chemistry parameter and treatment group in controlled phase 2 and 3 studies. Note: Plus-minus values are mean±SD; values with parentheses are median (min, max).					
	Placebo (n=534)	Alogliptin			
		6.25 (n=42)	12.5 (n=922)	25 (n=910)	>25 (n=87)
Alkaline phosphatase (mU/ml)	-0.3±10.9 0 (-89, 56)	-2.4±9.5 0 (-32, 15)	-1.8±9.8 -2 (-83, 31)	-1.4±9.3 -1 (-63, 41)	-2.1±9.5 -3 (-24, 34)
Bicarbonate	-0.7±2.6 -1 (-11, 11)	-0.6±2.1 0 (-4, 3)	-0.6±2.7 -1 (-9, 13)	-0.6±2.5 -1 (-9, 7)	-0.2±2.6 -1 (-7, 8)
BUN (mg/dl)	0.5 ±3.9 0 (-15, 34)	0.4±3.3 0 (-6, 12)	0.5±4.0 0 (-19, 24)	0.4±4.1 0 (-15, 28)	0.8±3.8 0.5 (-8, 12)
Creatinine (mg/dl)	-0.1±0.10 0 (-0.3, 0.6)	0±0.09 0 (-0.2, 0.2)	0±0.11 0 (-0.4, 0.8)	0±0.11 0 (-0.5, 0.6)	0.02±0.10 0 (-0.2, 0.4)
Potassium	-0.02±0.50 0 (-2, 1.9)	-0.14±0.34 -0.15 (-0.8, 0.7)	-0.01±0.49 0 (-2.3, 4.2)	-0.03±0.46 0 (-2.1, 2.1)	-0.05±0.37 -0.05 (-0.9, 0.8)
SGPT (ALT; mU/ml)	-0.1±7.01 0 (-27, 50)	-0.9±7.69 -1 (-17, 23)	-0.2±9.20 0 (-68, 73)	-0.6±8.45 0 (-73, 54)	-2.3±6.39 -2 (-30, 19)
SGOT (AST; mU/ml)	0.2±5.29 0 (-39, 52)	-0.9±5.86 -1 (-15, 16)	0.6±6.34 1 (-40, 63)	0.3±6.15 0 (-65, 34)	-0.9±4.73 -0.5 (-17, 10)
Sodium	0.4±2.69 0 (-8, 9)	-0.1±3.18 0 (-6, 7)	0.6±2.66 1 (-15, 10)	0.5±2.54 1 (-12, 10)	1±3.29 1 (-7, 9)
Total bilirubin (mg/dl)	-0.01 ±0.17 -0.01 (-0.84, 0.61)	-0.01±0.16 -0.02 (-0.5, 0.29)	-0.02±0.16 -0.01 (-0.72, 0.62)	-0.01±0.16 -0.02 (-0.6, 1.14)	-0.01±0.1331 0.01 (-0.38, 0.28)
Uric acid	0.02±0.88 0 (-4.0, 2.8)	-0.3±0.919 0 (-2.7, 2.0)	0.14±0.89 0.10 (-5.4, 4.4)	0.21±0.91 0.2 (-3.3, 4.2)	0.17±0.99 0.15 (-2.3, 2.8)

Subjects with a urine albumin/creatinine ratio of > 1000 mcg/mg (>113 mg/mol) were excluded from the controlled phase 2 and 3 studies. Subjects with a history of proteinuria > 1000 mg/d were excluded from study 003.

Small increases from baseline in the alogliptin groups' urine albumin/creatinine ratios were seen when compared to placebo (30 and 15 mcg/mg versus 5 mcg/mg). The median changes were more similar (-1, -2, and -3 for the placebo and alogliptin 12.5 and 25 mg groups).

NDA 22-271. Change from baseline to endpoint according to urinalysis parameter and treatment group in controlled phase 2 and 3 studies. Note: Plus-minus values are mean±SD; values with parentheses are median (min, max).					
	Placebo (n=534)	Alogliptin			
		6.25 (n=42)	12.5 (n=922)	25 (n=910)	>25 (n=87)
Albumin/cr ratio (mcg/mg)	5.1 -1 (-2065, 616)	0	30.1 -2 (-4444, 7607)	15.2 -3 (-2586, 3718)	0
pH	0.05±0.579 0 (-2, 3)	-0.14±0.506 0 (-1.5, 1.0)	0.07±0.57 0 (-2.5, 3.0)	0.06±0.615 0 (-2.5, 3.0)	-0.04±0.496 0 (-1.5, 1.5)
Specific gravity	0.0009±0.0074 0.001 (-0.024, 0.029)	-0.0004±0.00715 0.001 (-0.025, 0.015)	0±0.00693 0 (-0.026, 0.037)	-0.0004±0.00668 0 (-0.026, 0.024)	-0.0016±0.00649 -0.001 (-0.026, 0.017)

7.4.2.3.2 Analyses focused on outliers or shifts from normal to abnormal

Few markedly abnormal hematology results were reported in the controlled phase 2 and 3 studies originally submitted to NDA 22-271. There were no clinically meaningful differences in the percentage of subjects who had markedly abnormal hematology results in placebo and alogliptin treatment groups.

NDA 22-271. Number and percentage of subjects with markedly abnormal hematology results in phase 2 and 3 controlled studies					
Variable, n (%)	Placebo (n=534)	Alogliptin			
		6.25 (n=42)	12.5 (n=922)	25 (n=910)	50/100 (n=87)
Hemoglobin					
Baseline low abnl	0	0	0	0	0
Postbaseline low abnl	2 (0.4)	0	6 (0.7)	2 (0.2)	0
Hematocrit					
Baseline low abnl	0	0	0	0	0
Postbaseline low abnl	2 (0.4)	0	6 (0.7)	4 (0.4)	0
RBCs					
Baseline low abnl	0	0	0	0	0
Postbaseline low abnl	1 (0.2)	0	5 (0.5)	5 (0.6)	0
WBCs					
Baseline high abnl	0	0	0	0	0
Baseline low abnl	0	0	1 (0.1)	0	0
Postbaseline high abnl	2 (0.4)	0	1 (0.1)	1 (0.1)	0
Postbaseline low abnl	0	0	2 (0.2)	0	0
Platelet count					
Baseline high abnl	0	0	1 (0.1)	0	0
Baseline low abnl	0	0	0	1 (0.1)	0
Postbaseline high abnl	1 (0.2)	0	3 (0.3)	1 (0.1)	0
Postbaseline low abnl	0	0	2 (0.2)	2 (0.2)	0

In the controlled phase 2 and 3 studies submitted to NDA 22-271, the percentage of subjects with postbaseline ALT > 3x ULN was similar in the placebo and alogliptin 12.5 and 25 mg groups. The percentage of subjects with postbaseline ALT > 5x ULN was 0.2, 0.2, and 0.6%, respectively, in the placebo and alogliptin 12.5 and 25 mg groups. Four of these 7 alogliptin-treated subjects had an ALT > ULN at baseline; 6 of these 7 subjects had an AE reported in association with the abnormal ALT value (2 transaminases increased, 2 liver function test abnormal, 2 hepatic enzyme increased, 1 biliary colic). Subject 307/9019 was withdrawn from study TZD-009 due to an AE of liver function test abnormal. (See narratives below.) Five of the other 6 subjects experienced transient rises in ALT that returned to baseline with continued treatment. Two alogliptin subjects (1 each 12.5 and 25 mg) who experienced ALT > 10x ULN withdrew from the study; their narratives are listed in the section below.

The percentages of subjects with postbaseline AST > 3x and 5x ULN were slightly greater in the alogliptin 12.5 and 25 mg groups when compared to placebo (> 3x: 1.0, 0.7, and 0.4%; > 5x: 0.2, 0.4, and 0%, respectively), although a similar trend was not seen with ALT. Only 1 alogliptin 12.5 mg subject experienced AST > 10x ULN.

The percentages of subjects with postbaseline markedly abnormal bilirubin were 0.4, 0.2, and 0.9% in the placebo and alogliptin 12.5 and 25 mg groups, respectively. Of the 10 alogliptin subjects with a markedly abnormal postbaseline bilirubin level, 7 had baseline levels > ULN.

More alogliptin 12.5 and 25 mg subjects experienced markedly abnormal creatinine values than placebo subjects (0.9, 1.0, and 0.4%), although case narratives were not provided.

NDA 22-271. Number and percentage of subjects with markedly abnormal chemistry results in phase 2 and 3 controlled studies					
Variable, n (%)	Placebo (n=534)	Alogliptin			
		6.25 (n=42)	12.5 (n=922)	25 (n=910)	50/100 (n=87)
SGPT (ALT) > 3x ULN					
Baseline high abnl	0	0	5 (0.5)	4 (0.4)	0
Postbaseline high abnl	6 (1.1)	0	11 (1.2)	12 (1.3)	0
SGPT (ALT) > 5x ULN					
Baseline high abnl	0	0	1 (0.1)	1 (0.1)	0
Postbaseline high abnl	1 (0.2)	0	2 (0.2)	5 (0.6)	0
SGPT (ALT) > 10x ULN					
Baseline high abnl	0	0	0	1 (0.1)	0
Postbaseline high abnl	0	0	1 (0.1)	1 (0.1)	0
SGOT (AST) > 3x ULN					
Baseline high abnl	0	0	1 (0.1)	2 (0.2)	0
Postbaseline high abnl	2 (0.4)	0	9 (1.0)	6 (0.7)	0
SGOT (AST) > 5x ULN					
Baseline high abnl	0	0	0	1 (0.1)	0
Postbaseline high abnl	0	0	2 (0.2)	4 (0.4)	0
SGOT (AST) > 10x ULN					
Baseline high abnl	0	0	0	0	0
Postbaseline high abnl	0	0	1 (0.1)	0	0
Total bilirubin					
Baseline high abnl	1 (0.2)	0	2 (0.2)	2 (0.2)	0
Postbaseline high abnl	2 (0.4)	0	2 (0.2)	8 (0.9)	0
Alkaline phosphatase					
Baseline high abnl	1 (0.2)	0	0	0	0
Postbaseline high abnl	1 (0.2)	0	0	1 (0.1)	0
Gamma GT					
Baseline high abnl	15 (2.8)	2 (4.8)	14 (1.5)	19 (2.1)	4 (4.6)
Postbaseline high abnl	22 (4.2)	2 (4.9)	22 (2.4)	49 (5.5)	4 (4.8)
BUN					
Baseline high abnl	0	0	0	0	0
Postbaseline high abnl	0	0	2 (0.2)	1 (0.1)	0
Creatinine					
Baseline high abnl	0	0	0	0	0
Postbaseline high abnl	2 (0.4)	0	8 (0.9)	9 (1.0)	0
Potassium					
Baseline high abnl	8 (1.5)	0	4 (0.4)	12 (1.3)	0
Baseline low abnl	0	0	0	2 (0.2)	0
Postbaseline high abnl	17 (3.2)	0	32 (3.5)	37 (4.1)	0
Postbaseline low abnl	1 (0.2)	0	1 (0.1)	3 (0.3)	1 (1.2)

The incidence of markedly abnormal serum chemistry values were similar in the 120-day safety update, which provided more information on uncontrolled study OLE-012.

NDA 22-271. Marked abnormalities in serum chemistry		
Serum chemistry value	Alogliptin 12.5 mg (n=1089)	Alogliptin 25 mg (n=1596)
ALT > 3x ULN	12 (1.1)	28 (1.8)
ALT > 10x ULN	0	1 (0.1)
AST > 3x ULN	6 (0.6)	19 (1.2)
Total bilirubin > 2 mg/dl	7 (0.6)	9 (0.6)
ALT > 3x ULN & bilirubin > 2 mg/dl	0	0
Creatinine > 1.5x baseline	8 (0.7)	14 (0.9)

7.4.2.3.3 Marked outliers and dropouts for laboratory abnormalities

In the controlled phase 2 and 3 studies originally submitted to NDA 22-271, 2 subjects (1 each in the placebo and alogliptin 25 mg groups) withdrew from a study because of abnormal hematology values that indicated anemia.

- 315/8016 (MET-008; placebo): 65 year old male with a history of iron deficiency anemia and lower gastrointestinal bleed withdrew from the study on day 106 due to an AE of anemia that started on day 29. The subject's baseline hemoglobin was 12.5 g/dl (normal 12.5 – 17.0) and on day 29 it was 11.6 g/dl. On day 106, hemoglobin was 10.1 g/dl and the subject was withdrawn.
- 404/5006 (Study INS-011; alogliptin 25 mg): 56 year old woman with a history of anemia and thrombocytopenia withdrew from the study due to worsening anemia on day 168. On day 1, hemoglobin, hematocrit, and platelet counts were 12.0 g/dl, 36.3%, and $109 \times 10^3 /\mu\text{l}$ respectively. A posttreatment markedly abnormal platelet count was $47 \times 10^3 /\mu\text{l}$. After study discontinuation, she was diagnosed with myelofibrosis.

The percentages of subjects with abnormal liver enzymes > 3x, 5x, or 10x ULN were generally similar between groups. Review of subjects' narratives with ALT/AST > 3x ULN, identified 7 alogliptin-treated subjects with liver enzymes > 5x ULN but < 10x ULN. (Please refer to narratives below.) No action was taken with the study drug in these 7 cases. Liver enzymes returned to normal in all subjects except 363/4003, who had elevated transaminases at baseline and a history of alcohol use. Five of the 7 reports described alternative etiologies for the elevations. No subject met Hy's law criteria (i.e. AST/ALT > 3x ULN, Alk Phos < 2 ULN, and Total Bili > 2 x ULN).

- 412/7007 (alogliptin 25 mg; SULF-007): A 61 year old male with no relevant medical history had ALT 213 mU/ml and AST 144 mU/mL on day 56. Relevant concomitant medications included paracetamol, chlorpheniramine, and pseudoephedrine. The subject also experienced the flu on day 52. Transaminases normalized on day 64. No action was taken with the study drug as a result of this event. Transaminases remained normal in study OLE-012.
- 449/7007 (alogliptin 25 mg; SULF-007): A 35 year old male with no relevant medical history had ALT 192 mU/ml and AST 75 mU/ml on day 113. There were no relevant

concomitant medications. The event resolved on day 141. No action was taken with study drug. Transaminases remained normal in study OLE-012.

- 464/8006 (alogliptin 25 mg; MET-008): A 75 year old female experienced elevated liver function tests with a relevant history of aortocoronary bypass, coronary heart disease, fatty liver, biliary colic, polyarthritis, arterial hypertension, and hyperlipoproteinemia, experienced biliary colic on day 147 with associated transaminase elevation (ALT 199 mU/ml and AST 104 mU/ml). Transaminases normalized on day 153. No action was taken with study drug. The subject did not continue into OLE-012.
- 452/9003 (alogliptin 25 mg; TZD-009): A 40 year old female with a relevant history of hyperlipidemia, hypertension, and hypothyroidism experienced elevated liver enzymes on day 82 (ALT 247 mU/ml and AST 215 mU/ml). Relevant concomitant medications included atorvastatin, metronidazole, ketorolac, metoclopramide, ciprofloxacin, and diclofenac sodium. No action was taken with the study drug. Transaminases normalized on day 113 and remained normal in OLE-012. Other etiologies considered were the antibiotic or anesthetic used at the time of her appendectomy.
- 452/009009 (alogliptin 12.5 mg; TZD-009): A 62 year old female with a history of hypothyroidism and hypertension experienced increased hepatic enzymes on day 113 (ALT 138 mU/ml and AST 128 mU/ml). Weekly laboratories showed a decrease in hepatic enzyme elevation. The values normalized on day 188. No action was taken with the study drug. Transaminases remained normal in study OLE-012.
- 363/4003 (alogliptin 12.5 mg; PLC-010): A 27 year old female with a history of elevated transaminases and total bilirubin experienced elevated ALT (and AST) on day 1 (ALT 139 mU/ml and AST 65 mU/ml). Baseline transaminases were elevated (ALT 73 mU/ml and AST 33 mU/ml). There were no concomitant medications. The subject admitted to consumption of alcoholic beverages since November 2006. On day 15, transaminases improved (ALT 85 mU/ml and AST 44 mU/ml). On days 113 and 208, transaminases were also elevated (ALT 122 and 99 mU/ml; AST 49 and 46 mU/ml, respectively). No action was taken with the study drug. The subject voluntarily withdrew for personal reasons with last dose of study drug on day 147.
 - **COMMENT: Transaminases were elevated at baseline. The subject also has a history of alcohol use.**
- 452/5007 (alogliptin 25 mg; INS-011): A 58 year old male with a history of hypertension, hyperuricemia, gallstones, and microalbuminuria experienced elevated ALT and AST on day 15 (78 and 127 mU/ml, respectively). Concomitant medications included acetaminophen, atenolol, disprin, puricos, ramipril, Cosopt, and felodipine. No action was taken with study drug. Transaminases normalized on day 24. The subject discontinued from INS-011 due to lack of efficacy and rolled over to study OLE-012. The investigator reported that the elevated liver function tests were possibly due to excessive alcohol consumption.

Two alogliptin subjects (1 each 12.5 mg and 25 mg) experienced ALT or AST > 10x ULN in controlled phase 2 or 3 studies. Neither met Hy's law criteria. Both withdrew from the study. Their narratives are as follows:

- 311/9003 (alogliptin 12.5 mg; TZD-009): 49 year old male with a history of T2D, hyperlipidemia, depression, and anxiety who experienced ALT > 10x ULN which was reported as an AE of transaminase increased. His ALT and AST were abnormal at baseline (66 and 32 mU/ml, respectively). On day 32, ALT and ALT were 646 and 585 mU/ml, respectively. On day 42, ALT and AST were 46 and 22 mU/ml, respectively. On day 49, ALT and AST were 25 and 22 mU/ml, respectively. Study drug was interrupted on nonspecified days. The subject withdrew voluntarily from the study at week 8. At the end of study visit, ALT was 15 mU/ml and AST 27 mU/ml. The investigator attributed the abnormal liver tests to alcohol. Concomitant medications included fluoxetine HCl, buspirone, trazadone, and ezetimibe; trazadone is associated with hepatitis. The narrative did not specify the quantify of alcohol imbibed nor if the patient was tested for viral hepatitis.
 - **COMMENT: This case of increased transaminases may not be due to alcohol, as alcoholic hepatitis usually presents with an AST:ALT ratio > 2.**
- 307/9019 (alogliptin 25 mg; TZD-009): 47 year old male with a relevant medical history of T2D, hypertriglyceridemia, hypercholesterolemia, diabetic neuropathy, hypertension, and obesity who had an ALT > 10x ULN at baseline (ALT 430 mU/ml and AST 190 mU/ml). On day 5, the study drug was discontinued due to the abnormal liver enzyme tests. On day 8, the values had improved to 357 and 125 mU/ml, respectively. However, he discontinued from the study on day 22 due to an AE of liver function test abnormal.
 - **COMMENT: This patient should probably not have been enrolled due to elevated ALT at baseline.**

There were no markedly abnormal criteria for urinalysis test results in the controlled phase 2 and 3 study groups.

7.4.2.4 Special assessments: Renal toxicity and hepatotoxicity

Very large exposures (≥ 200 fold excess vs. clinical exposure) were required to identify target organs in animals, which included kidney, lung, liver, and male reproductive organs. The kidney is the major route of excretion. As kidney toxicity occurred at very high concentrations in animals (≥ 200 x MRHD), the risk of kidney toxicity in humans is minimal. The liver findings at the LOAEL in chronic studies was also > 200x the MRHD.

Marketed sitagliptin requires dose adjustment for subjects with moderate, severe, or ESRD. Because there is a need for dosage adjustment based upon renal function, assessment of renal function is recommended prior to the initiation of sitagliptin and periodically thereafter. In a 12-week study of sitagliptin in 91 patients with chronic, renal impairment, 37 patients with moderate renal impairment were randomized to sitagliptin 50 mg daily while 14 patients with moderate renal impairment were randomized to placebo. Mean (SE) increases in serum creatinine were observed in patients treated with sitagliptin (0.12 mg/dl [0.04]) and in patients treated with placebo (0.07 mg/dl [0.07]). The clinical significance of this increase in serum creatinine relative to placebo is unknown.

In alogliptin NDA 22-271, the mean change in serum creatinine in the alogliptin treatment groups from baseline to endpoint was 0 mg/dl. Small increases from baseline in the alogliptin groups' mean urine albumin/creatinine ratios were seen when compared to placebo (30 and 15 mcg/mg versus 5 mcg/mg). The median changes were more similar (-1, -2, and -3 for the placebo and alogliptin 12.5 and 25 mg groups). A greater percentage of alogliptin 12.5 and 25 mg subjects experienced markedly abnormal creatinine values when compared to placebo (0.9% and 1.0% vs. 0.4%), although narratives were not provided for subjects with increased creatinine. Thus, a small percentage of subjects may be at increased risk for markedly abnormal serum creatinine values when taking alogliptin 12.5 or 25 mg.

Although marketed sitagliptin is not associated with hepatotoxicity, the nonmarketed DPP-4 inhibitor vildagliptin may be. Mean ALT values improved more in subjects on alogliptin 12.5 and 25 mg when compared to placebo (-0.2 and -0.6 vs. -0.1 mU/ml), whereas mean AST increased slightly more in the alogliptin treatment groups when compared to placebo (0.6 and 0.3 vs. 0.2 mU/ml). Thus, no consistent pattern was seen in the effect of alogliptin 12.5 and 25 mg in the change in liver enzymes from baseline to endpoint.

The percentage of subjects with markedly abnormal ALT > 3x or 10x ULN were similar between the alogliptin 12.5 and 25 mg and placebo groups. However, the alogliptin 25 mg group had a greater percentage of subjects with ALT > 5x ULN when compared to placebo or alogliptin 12.5 mg (0.6% vs. 0.2% and 0.2%). As discussed above, liver enzymes generally returned to normal in these subjects without study drug interruption. Five of the 7 reports described alternative etiologies for the elevations. No subject met Hy's law criteria

AST was more likely than ALT to be markedly abnormal. Both alogliptin 12.5 and 25 mg groups had a higher percentage of subjects with AST > 3x or 5x ULN, when compared to placebo (> 3x ULN: 1.0% and 0.7% vs. 0.4%; > 5x ULN: 0.2% and 0.4% vs. 0%). A similar percentage of subjects in each treatment group had AST > 10x ULN (0-0.1%).

Of the 2 subjects (1 each 12.5 mg and 25 mg) who experienced ALT or AST > 10x ULN which resulted in withdrawal from controlled phase 2 or 3 studies, both had elevated liver enzymes at baseline (1 subject > 10x ULN) and 1 had reported alcohol use.

Although a consistent effect of alogliptin on liver enzymes was not seen, subjects may be a slightly higher risk for markedly abnormal transaminases, particularly AST, although transaminase elevation > 5x ULN usually resolved without study drug interruption and may have been due to alternative etiologies. In addition, there is less concern with AST because this measurement is less specific than ALT for the liver.

The incidence of markedly abnormal serum chemistry values were similar in the 120-day safety update, which provided more information on uncontrolled study OLE-012.

7.4.3 Vital Signs

The sponsor's vital sign abnormality criteria are shown below. As the American Diabetes Association recommends diabetics maintain blood pressure (BP) < 130/80 mmHg, the high abnormal systolic and diastolic blood pressure values should have been more rigorously set.

NDA 22-271. Criteria for abnormal vital signs		
Vital sign	Low abnormal value	High abnormal value
Heart rate	<50 bpm & CFB decrease \geq 15 bpm	>120 bpm & CF B increase \geq 15 bpm
Systolic blood pressure	<90 mmHg & CFB decrease \geq 20 mmHg	>160 mmHg & CFB increase \geq 20 mmHg
Diastolic blood pressure	<50 mmHg & CFB decrease \geq 15 mmHg	>95 mmHg & CFB increase \geq 15 mmHg
CFB=Change from baseline		

The changes from baseline to endpoint in blood pressure and heart rate were similar between treatment groups. Alogliptin has neutral effects on blood pressure and heart rate.

NDA 22-271. Change from baseline to endpoint according to vital sign parameter and treatment group in controlled phase 2 and 3 studies. Note: Plus-minus values are mean\pmSD; values with parentheses are median (min, max).					
	Placebo (n=534)	Alogliptin			
		6.25 (n=42)	12.5 (n=922)	25 (n=910)	>25 (n=87)
Systolic BP (mmHg)	0 \pm 14.7 0 (-54, 49)	-1.5 \pm 14.7 -2 (-32, 32)	0.3 \pm 13.9 0 (-62, 50)	0.8 \pm 13.9 0 (-50, 57)	0.7 \pm 13.9 1 (-44, 42)
Diastolic BP (mmHg)	-0.9 \pm 9.2 0 (-28, 30)	-0.7 \pm 7.6 0 (-20, 10)	0 \pm 9.0 0 (-30, 55)	0.3 \pm 9.3 0 (-40, 34)	-1.1 \pm 8.3 0 (-20, 18)
Heart rate (bpm)	-0.6 \pm 9.3 0 (-36, 30)	-0.2 \pm 8.0 0.5 (-18, 16)	0.1 \pm 8.6 0 (-40, 40)	0.5 \pm 8.5 0 (-30, 41)	-1.2 \pm 9.4 0 (-27, 20)

The percentage of subjects with abnormal vital sign measurements postbaseline were similar between the placebo and alogliptin treatment groups.

NDA 22-271. Number and percentage of subjects with abnormal vital signs in the controlled phase 2 and 3 study groups postbaseline					
	Placebo (n=533)	Alogliptin			
		6.25 (n=42)	12.5 (n=916)	25 (n=906)	>25 (n=87)
Systolic BP					
High abnl	24 (4.5)	0	28 (3.1)	46 (5.1)	2 (2.3)
Low abnl	1 (0.2)	0	2 (0.2)	1 (0.1)	0
Diastolic BP					
High abnl	18 (3.4)	1 (2.4)	27 (2.9)	42 (4.6)	3 (3.4)
Low abnl	4 (0.8)	0	2 (0.2)	3 (0.3)	0
Heart rate					
High abnl	0	0	2 (0.2)	0	0
Low abnl	3 (0.6)	0	2 (0.2)	1 (0.1)	2 (2.3)

7.4.4 Electrocardiograms (ECGs)

A standard 12-lead ECG was obtained at screening, baseline, week 12, and the end of treatment visit in the controlled phase 2 and 3 studies originally submitted to NDA 22-271. Additional ECGs were performed at the discretion of the investigator. The investigator or designee was

responsible for reviewing the ECG and determining the clinical significance of the results which were recorded on the CRF.

The table below summarizes the mean change from baseline in ECG parameters. The mean change in ECG intervals was always < 5 msec and there did not appear to be any relationship to alogliptin dose. Therefore, alogliptin has minor effects, if any, on ECG parameters using central tendency analysis.

NDA 22-271. Change from baseline to endpoint in ECG parameters in the controlled phase 2 and 3 study group					
Parameter	Placebo (n=534)	Alogliptin (mg)			
		6.25 (n=42)	12.5 (n=922)	25 (n=910)	50/100 (n=87)
Ventricular rate (bpm)					
Baseline mean (SD)	71.2 (11.66)	71.7 (10.81)	71.0 (11.84)	71.5 (11.28)	68.6 (11.16)
Mean CFB (SD)	0.1 (9.41)	-1.2 (10.94)	0.9 (9.25)	0.2 (9.39)	-1.0 (8.16)
PR interval (msec)					
Baseline mean (SD)	161.8 (27.36)	157.8 (23.93)	161.5 (29.20)	160.7 (25.27)	162.1 (22.29)
Mean CFB (SD)	-1.9 (17.83)	1.8 (12.32)	-0.2 (18.54)	0.6 (16.29)	2.3 (13.64)
QRS duration (msec)					
Baseline mean (SD)	88.1 (15.56)	89.9 (14.01)	87.9 (18.62)	87.9 (15.69)	90.5 (15.45)
Mean CFB (SD)	1.1 (13.82)	1.2 (4.93)	1.3 (11.57)	1.6 (12.54)	-0.1 (6.40)
QT interval (msec)					
Baseline mean (SD)	388.0 (34.02)	390.6 (31.31)	388.5 (37.48)	386.4 (33.08)	393.6 (30.17)
Mean CFB (SD)	0.8 (28.68)	3.4 (23.40)	-2.7 (29.22)	-0.3 (27.63)	3.1 (25.66)
QTcF interval (msec)					
Baseline mean (SD)	408.2 (26.47)	412.4 (25.42)	408.2 (30.46)	407.4 (27.18)	409.3 (22.85)
Mean CFB (SD)	1.2 (25.31)	1.1 (16.15)	-1.0 (26.31)	0.1 (24.48)	1.0 (18.96)
CFB = Change from baseline					
The QTc interval was calculated using the Fridericia correction (QTcF = QT/((60/Ventricular Heart Rate)**(1/3)).					

The sponsor's ECG abnormality criteria were appropriate and are shown below. The percentage of subjects with abnormal ventricular rate, PR interval, QRS complex, QRS complex, and QTcF were similar at endpoint across treatment groups in the controlled phase 2 and 3 study group.

NDA 22-271. Abnormality criteria for ECGs		
Parameter	Low abnormal	High abnormal
Heart rate	<50 bpm & decrease from baseline ≥15 bpm	>120 bpm & increase from baseline ≥15 bpm
PR interval	<120 msec	>200 msec
QRS interval	<40 msec	>120 msec
QTcF interval	N/A	>450 to 480 msec; >480 to 500 msec; >500 msec; Increase from baseline ≥30 to <60 msec; Increase from baseline ≥60 msec

NDA 22-271. Number and percentage of subjects with abnormal ECG parameters at endpoint in the controlled phase 2 and 3 study group					
Parameter	Placebo (n=534)	Alogliptin (mg)			
		6.25 (n=42)	12.5 (n=922)	25 (n=910)	50/100 (n=87)

Ventricular rate					
Endpoint n	513	39	882	870	81
Endpoint high abnl	0	0	0	0	0
Endpoint low abnl	0	0	1 (0.1)	0	0
PR interval (msec)					
Endpoint n	507	39	869	862	81
Endpoint high abnl	28 (5.5)	2 (5.1)	51 (5.9)	46 (5.3)	6 (7.4)
Endpoint low abnl	17 (3.4)	0	38 (4.4)	26 (3.0)	1 (1.2)
QRS duration (msec)					
Endpoint n	513	39	882	870	81
Endpoint high abnl	21 (4.1)	1 (2.6)	46 (5.2)	34 (3.9)	3 (3.7)
Endpoint low abnl	1 (0.2)	0	2 (0.2)	0	0
QTcF interval (msec)					
Endpoint n	513	39	882	869	81
Endpoint high abnl	34 (6.6)	2 (5.1)	57 (6.5)	44 (5.1)	4 (4.9)
CFB = Change from baseline					
The QTc interval was calculated using the Fridericia correction ($QTcF = QT / ((60 / \text{Ventricular Heart Rate})^{1/3})$).					

Two SULF-007 subjects withdrew from a study due to AEs associated with ECG changes. Only 1 event (415/7001) may have been related to study drug.

- 415/7011 (alogliptin 25 mg): 71 year old female with a history of T2D, hypertension, and anxiety disorder was withdrawn due to T wave inversions on day 85. Diagnostic tests on day 85 showed alterations in ventricular repolarization with negative T waves in leads V1-V6 of mild intensity. The last dose was on day 99. The event was reported to be ongoing.
- 424/7008 (alogliptin 12.5 mg): 57 year old male with a history of T2D and mild ischemic heart disease was withdrawn due to ECG changes. Prior to day 1, the subject was hospitalized for angina pectoris, which resolved. On day 1, the subject developed ECG changes suggestive of ischemia which was reported as “ECG abnormal.” The subject was referred to a cardiologist and, on day 3, he was admitted to the hospital for elective coronary angiography which was reported as normal. During the procedure, an ECG showed minimal ischemic changes in V2-V5 and a diagnosis of stable angina was made. The subject was discharged on day 5. Study drug was discontinued on day 2 due to the planned procedure. The subject was withdrawn from the study and came to the clinic for an early termination visit on day 3.
 - **COMMENT: It is not clear if the subject received 1 dose of study drug on day 1 prior to the ischemic ECG being recorded. It is unlikely that 0-2 days’ exposure to alogliptin resulted in the ECG changes described.**

7.4.5 Special Safety Studies

According to the sponsor, there was no clinically significant affect of age, gender, or race on the metabolism of alogliptin. Elderly subjects had 28% higher AUC₀₋₂₄ than those of young subjects and C_{max} in the elderly subjects was not significantly different to that of young subjects.

Women had 19% and 22% higher AUC₀₋₂₄ and C_{max} than those of men. White subjects had 28% and 20% higher AUC₀₋₂₄ and C_{max} than those of black subjects, respectively. Exposure to alogliptin metabolites were less than 4% of alogliptin.

However, according to Drs. Sang Chung and Luke Bi's clinical pharmacology review, the sponsor pooled subgroups to assess the effect of age, sex, and race on alogliptin exposure (e.g. young black men, young white men, young black women, and young white women). There was a significant interaction between age and sex on alogliptin exposure. Elderly white women had a 97% increase in exposure compared to young white men. The creatinine clearance in elderly white women was approximately half that of young white men, suggesting the renal function decrease resulted in the increased exposure in elderly white women.

The effects of renal impairment on alogliptin PK were evaluated in study SYR-322-006, an open label, parallel group, comparison, single dose (50 mg) alogliptin in 48 subjects (24 healthy subjects and 6 subjects in each of the mild, moderate, severe, and ESRD categories). Alogliptin's AUC increased by 69%, 108%, 219%, and 281% in subjects with mild, moderate, severe renal impairment and ESRD when compared to control subjects. C_{max} also increased by 13%, 42%, 27%, and 32% in subjects with mild, moderate, severe, and ESRD. Metabolite (M1) exposure significantly increased with renal impairment, although it may not be clinically meaningful because the exposures were significantly lower (< 4%) than that of alogliptin.

Although the sponsor proposed the following dose adjustment for subjects with moderate, severe, or ESRD, the clinical pharmacology reviewers also recommended dose adjustment to 12.5 mg for subjects with mild renal impairment because 1) the mean exposure increased by 69% in these subjects and 2) efficacy should not be compromised with this adjustment because the HbA1c lowering effect of 12.5 mg (-0.54% in monotherapy) is comparable to that of 25 mg (-0.57% in monotherapy).

NDA 22-271. The sponsor's recommended dosing. NOTE: Clinical pharmacology also recommends 12.5 mg for subjects with mild renal impairment.			
Degree of renal insufficiency	Serum creatinine levels (mg/dl)	Creatinine clearance (ml/min)	Recommended dosing
Moderate	Men > 1.7 to ≤ 3.0 Women > 1.5 to ≤ 2.5	≥ 30 to < 50	12.5 mg once daily
Severe/ESRD	Men > 3.0 Women > 2.5	< 30	6.25 mg once daily*
*Without regard to timing of dialysis in patients with ESRD			

The sponsor believes the 69% increase in mild renal impairment patients is mostly influenced by 1 subject who had a CrCl of 53 ml/min (Cockcroft-Gault calculation) and that exposure in that subject was higher than all subjects with moderate renal impairment. Clinical pharmacology, however, does not view the subject in question as an outlier because renal PK study SYR-322-006 only included 6 subjects with mild renal impairment.

When the controlled phase 3 trials were reviewed however, as shown below, a significant number of subjects with mild renal impairment were exposed to alogliptin 12.5 or 25 mg for 26 weeks. Among men and women with elevated baseline serum creatinine, the percentage of subjects with TEAEs was similar in the alogliptin 12.5 and 25 mg groups.

The incidence rates of TEAEs were generally similar between the alogliptin and placebo groups when analyzed by sex and baseline serum creatinine, although the small number of subjects with abnormal baseline creatinine in the placebo group limits one's ability to make meaningful comparisons.

One subject (383/7027) was discontinued from study SULF-007 on day 93 due to an AE of chronic renal failure. However, this 68 year old male had a history of chronic renal failure and nephritic syndrome; serum creatinine and BUN values were near baseline at the time of study termination.

NDA 22-271. Number of subjects exposed to alogliptin (12.5 or 25 mg) for at least 6 months by baseline category of renal impairment (Cockcroft-Gault and MDRD formulas) in 26-week, controlled studies 007 – 011, OPI-001, and OPI-002		
Renal impairment	Cockcroft-Gault	MDRD
Normal	2,009	1,110
Mild	560	1,415
Moderate	44	87
Severe	1	2

NDA 22-271. Number of any treatment-emergent adverse event by sex and serum creatinine at baseline in studies 003 and 007 – 011				
	Placebo	All alogliptin	Alogliptin (mg)	
			12.5	25
Male < 1.7 mg/dl, N	264	987	456	476
Any AE, n (%)	165 (62.5)	601 (60.9)	294 (64.5)	283 (59.5)
Male ≥ 1.7 mg/dl, N	1	18	8	9
Any AE, n (%)	0	16 (88.9)	7 (87.5)	8 (88.9)
Female < 1.7 mg/dl, N	267	944	450	422
Any AE, n (%)	180 (67.4)	632 (66.9)	301 (66.9)	292 (69.2)
Female ≥ 1.7 mg/dl, N	2	12	8	3
Any AE, n (%)	2 (100)	11 (91.7)	7 (87.5)	3 (100.0)

NDA 22-271. Serum creatinine and BUN measurements for subject 383/7027, a 68 year old male with history of chronic renal failure and nephritic syndrome who was discontinued from study SULF-007 due to chronic renal failure		
	Creatinine (mg/dl)	BUN (mg/dl)
Baseline	1.9	49
Day 2	2.0	
Study termination (day 93)	2.2	53

In conclusion, this review agrees with the sponsor's recommendation to reduce the alogliptin dose to 12.5 mg for subjects with moderate, but not mild, renal impairment for the following reasons:

- When the 1 subject with mild renal impairment who had greater exposures than all moderately renally impaired subjects was excluded, the increase in exposure in the remaining 5 subjects with mild renal impairment was 47% relative to control indicating no need for dose adjustment in subjects with mild renal impairment.

- The controlled phase 3 program studied 560 - 1,415 subjects with mild renal impairment, depending on the formula used to calculate creatinine clearance.
- No significant difference in the incidence of AEs was seen between the alogliptin 12.5 and 25 mg groups when analyzed by sex and baseline serum creatinine in controlled studies, although the small number of subjects limits one's ability to make meaningful comparisons.

Study SYR-322-023 assessed the single dose PK of alogliptin 25 mg in subjects with and without hepatic impairment. Alogliptin exposure was decreased by 10% and 9% for AUC_{0-t} and C_{max} , respectively, in subjects with moderate hepatic impairment, as defined by the Child-Pugh system, compared to those of healthy control subjects. Thus, moderate hepatic impairment did not significantly affect alogliptin exposure. The PK of alogliptin was not evaluated in subjects with mild or severe hepatic impairment.

NOTE: Clinical Pharmacology recommends evaluating the impact of mild, moderate, and severe hepatic impairment on exposure. However, these studies are not required. The sponsor can elect studies based on the drug's properties and its business plans. Liver metabolism is not a major elimination pathway for alogliptin. Thus, liver functionality is not critical for alogliptin's disposition. Since moderate hepatic impairment did not affect alogliptin's exposure, the sponsor can label mild hepatic impairment like that of moderate hepatic impairment. However, the label will need to explicitly state that the PK of alogliptin has not been studied, and is not known, in patients with severe hepatic impairment.

7.4.6 Immunogenicity

No immunogenicity studies were completed. Alogliptin is a small molecule and is, therefore, not expected to be immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Adverse events potentially associated with alogliptin include MACE events, angioedema, PCDRs, and renal and hepatotoxicity. Each of these potential AEs is discussed in more detail in the sections 7.3.5 Submission Specific Primary Safety Concerns, 7.3.4 Significant AEs, and 7.4.2.4 Special Assessments, respectively.

Of the 35 MACE events reviewed, 10 occurred in placebo, 11 in alogliptin 12.5 mg subjects, and 14 in alogliptin 25 mg subjects. When the 1 placebo: 3.7 alogliptin subject randomization ratio is considered, there does not appear to be a dose-dependent effect on MACE events.

No clear dose dependency was seen for AEs in the angioedema cluster when the percentage of subjects experiencing events was reviewed. However, there was a dose related trend when the

number of events per 100 subject-years of exposure was reviewed (placebo 9.8; 12.5 mg alogliptin 11.4; 25 mg alogliptin 13.3).

A slight dose-related trend in AEs (up to the 25 mg dose but not with the 50/100 mg doses) in the PCDR cluster was seen when both the percentage of subjects and number of events per 100 subject-years of exposure were reviewed.

NDA 22-271. Treatment-emergent PCDR cluster events in controlled phase 2 and 3 studies						
Cluster, n (%) (a)	Placebo (n=534)	All Alo (n=1961)	Alogliptin			
			6.25 (n=42)	12.5 (n=922)	25 (n=910)	50/100 (n=87)
PCDR	37 (6.9) [24.9]	188 (9.6) [28.4]	1 (2.4) [13.8]	81 (8.8) [26.4]	100 (11.0) [30.1]	6 (6.9) [44.4]

(a) Number of events per 100 subject-years of exposure

No clear dose-related trend was seen in the changes in serum creatinine.

NDA 22-271. Baseline and mean±SD change from baseline (CFB) in creatinine (mg/dl) in controlled phase 2 and 3 studies			
	Placebo (n=534)	Alo 12.5 (n=922)	Alo 25 (n=910)
Baseline	0.97±0.20	0.95±0.22	0.97±0.21
CFB Week 1	0.01±0.08	-0.02±0.06	-0.01±0.10
CFB Week 2	0±0.1	0.01±0.10	0.01±0.10
CFB Week 4	-0.01±0.10	0.01±0.10	0±0.11
CFB Week 8	-0.01±0.11	0.01±0.11	0±0.11
CFB Week 12	-0.01±0.11	0±0.10	0.01±0.10
CFB Week 16	-0.02±0.11	0±0.12	-0.01±0.11
CFB Week 20	-0.02±0.11	-0.01±0.10	-0.01±0.11
CFB Week 26	-0.02±0.10	0±0.11	0±0.11
CFB Week 28	-0.04±0.07	0.02±0.11	0.05±0.07
CFB Week 30*	-0.10	0.10	-0.10
CFB Endpoint	-0.01±0.10	0±0.11	0±0.11

The alogliptin 25 mg group had a greater percentage of subjects with ALT > 5x ULN when compared to placebo or alogliptin 12.5 mg (0.6% vs. 0.2% and 0.2%). The clinical significance of this difference is unclear, as the percentage of subjects with markedly abnormal ALT > 3x or 10x ULN were similar between the alogliptin 12.5 and 25 mg and placebo groups

AST was more likely than ALT to be markedly abnormal. Both alogliptin 12.5 and 25 mg groups had a higher percentage of subjects with AST > 3x or 5x ULN, when compared to placebo (> 3x ULN: 1.0% and 0.7% vs. 0.4%; > 5x ULN: 0.2% and 0.4% vs. 0%). A similar percentage of subjects in each treatment group had AST > 10x ULN (0-0.1%).

The change from baseline to each visit and endpoint was calculated by the sponsor for controlled phase 2 and 3 trials. Study 003 had a 12 week treatment period, whereas studies 007 through 011 had 26 week treatment periods. For each visit, the value closest to the scheduled visit day was summarized. Endpoint was defined as the last value collected within 7 days of the last dose

of study medication. The alogliptin 25 mg subjects who completed the 30 week trials, experienced a minor dose-related increase in transaminases (ALT > AST) that is not clinically meaningful. This change was not seen when endpoint values were reviewed, possibly due to hyperglycemic rescue criteria and resulting dropout rate which resulted in fewer subjects completing the study.

NDA 22-271. Baseline and mean±SD change from baseline (CFB) in ALT and AST in controlled phase 2 and 3 studies						
	ALT (mU/mL)			AST (mU/mL)		
	Placebo (n=534)	Alo 12.5 (n=922)	Alo 25 (n=910)	Placebo (n=534)	Alo 12.5 (n=922)	Alo 25 (n=910)
Baseline	18.6±10.0	19.1±11.5	19.4±17.0	16.6±6.7	16.7±7.0	16.8±8.6
CFB Week 1	-2.1±4.7	-2.4±6.8	-1.0±14.6	-0.4±4.0	-0.6±3.8	0.5±14.1
CFB Week 2	-0.5±5.2	-1.1±6.1	-1.0±5.6	-0.6±4.4	-0.2±5.2	-0.3±5.9
CFB Week 4	-0.8±5.1	-0.4±20.4	-1.1±5.6	-0.5±4.7	0.3±19.2	-0.3±4.7
CFB Week 8	-0.7±6.4	-0.9±8.0	-0.7±9.6	-0.6±5.2	-0.2±5.4	-0.2±6.8
CFB Week 12	0.2±8.4	-0.8±7.8	-0.4±10.9	0±5.5	-0.1±5.8	0.1±8.9
CFB Week 16	0.6±8.05	-0.7±8.4	-0.4±9.5	0.2±5.7	0.2±6.8	0.2±5.4
CFB Week 20	0.1±7.9	-0.4±7.7	-0.3±10.4	0.2±5.7	0.4±5.7	0.4±6.2
CFB Week 26	-0.1±7.1	-0.5±8.4	-0.8±7.6	0.2±5.3	0.6±5.8	0.4±5.5
CFB Week 28	3.4±10.9	-0.6±5.3	0.5±9.8	2.8±7.6	0.6±3.7	0.7±4.1
CFB Week 30*	3.0	4.0	10.5±10.6	2.0	3.0	6.5±3.5
CFB Endpoint	-0.1±7.0	-0.2±9.2	-0.6±8.5	0.2±5.3	0.6±6.34	0.3±6.15
*SD not provided by the sponsor.						

7.5.2 Time Dependency for Adverse Events

The 25 MACE events which occurred in alogliptin 12.5 or 25 mg subjects occurred on days 26 – 186, with a mean of 94 days.

The 3 subjects, who experienced AEs in the angioedema cluster which lead to discontinuation, had been exposed to alogliptin for 99-184 days.

Of the 3 subjects who experienced SAEs in the PDCR cluster in phase 2 and phase 3 studies of alogliptin, one subject had an anaphylactic reaction after a wasp bite on day 79. The other 2 subjects had been exposed to alogliptin for 4 and 32 days. Subject 226/9002, who was exposed for 32 days, discontinued due to serum sickness.

No clear time-related trend was seen in the changes in serum creatinine.

While mean ALT showed a slight decrease in alogliptin treatment groups at most time points, mean AST was slightly increased in both alogliptin and placebo groups. The quantity of change at most time point was, likely, clinically insignificant. However, the alogliptin 25 mg subjects

who completed the 30 week trial, experienced an increase in transaminases (ALT > AST). This change was not seen when endpoint values were reviewed.

7.5.3 Drug-Demographic Interactions

Elderly white women had a 97% increase in exposure compared to young white men. The creatinine clearance in elderly white women was approximately half that of young white men, suggesting the renal function decrease resulted in the increased exposure in elderly white women. Sex and race, however, did not affect alogliptin exposure.

7.5.4 Drug-Disease Interactions

In subjects with mild, moderate, and severe renal impairment and end stage renal disease (ESRD), the AUC_{0-t} increased by 69%, 108%, 219%, and 281%, respectively. Although the sponsor recommends dosage adjustment in moderate, severe, and ESRD, clinical pharmacology also recommends dose adjustment for subjects with mild renal impairment. Moderate hepatic impairment did not significantly alter alogliptin exposure. The PK of alogliptin was not evaluated in subjects with mild or severe hepatic impairment.

7.5.5 Drug-Drug Interactions

Thirteen drug- and drug-drug interaction studies were conducted to determine the effect of alogliptin on other drugs and the effect of other drugs on alogliptin. Drugs used in these studies included CYP and Pgp markers substrates. No clinical meaningful interactions with alogliptin were observed. Please also refer to section 4.4.3 Pharmacokinetics and Drs. Sang Chung and Like Bi's clinical pharmacology review.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

As described in section 4.3 Preclinical Pharmacology/Toxicology, alogliptin poses minimal carcinogenic risk to humans based on high exposure multiples at the NOAEL (32x) for rat thyroid C-cell tumors, very high exposure multiples ($\geq 288x$) at doses that caused increased combined thyroid C-cell adenomas and carcinomas in male rats, and absence of any other drug-related tumors in rats ($> 400x$ female MRHD) or mice (60x MRHD). Of note, two glucagon-like peptide 1 (GLP-1) analogues (exenatide and liraglutide) increase thyroid C-cell adenomas in rats, but there is no evidence to suggest the finding with alogliptin (which increases GLP-1) is due to a common mechanism. There is no evidence of increased C-cell tumors with 3 other DDP4 inhibitors, sitagliptin, (b) (4) and saxagliptin.

7.6.2 Human Reproduction and Pregnancy Data

According to pharmacology/toxicology reviewer Dr. David Carlson, fetal growth and developmental effects occur at maternally toxic doses. In rats, the concentration of alogliptin in milk is 2x maternal plasma concentration, thus fetal exposure with breastfeeding is expected in humans.

Two pregnancies were reported in the phase 1 program. Both subjects had completed study drug administration at the time of their first positive pregnancy test and both subjects terminated their pregnancies via induced abortion.

- Study 015 subject 0001/004 received alogliptin 100 mg daily for 7 days in a drug-interaction study.
- Study 019 subject 1093 received alogliptin 50 mg daily for 7 days.

The following pregnancies were also reported in the phase 2 and 3 program in subjects who received alogliptin.

- 390/4001: 32 year old female withdrew from study SULF-007 due to lack of efficacy and received alogliptin 12.5 mg daily for 8 days in study OLE-012. Study drug was discontinued upon confirmation of pregnancy on day 9. The subject had no complications during her pregnancy and delivered a 39 week healthy infant by Cesarean-section on (b) (6).
- 258/7005: 41 year old female completed study SULF-007 and received alogliptin 25 mg for 166 days in study OLE-012. Study drug was discontinued upon confirmation of pregnancy on day 166. The subject, who had gestational diabetes, vaginally delivered a full-term healthy infant on (b) (6).
- 412/3119: 32 year old female with a history of T2D, spontaneous abortion, 2 Cesarean-sections, and vaginal mycosis experienced a spontaneous abortion on day 80. The subject had vaginal bleeding and pain in the hypogastrium from day 80-81. A serum pregnancy test on day 85 was positive, suggesting < 1 week gestation. A transvaginal ultrasound, however, showed a normal uterus and no signs of pregnancy. Another pregnancy test on day 92 confirmed that the subject was not pregnant. It was determined that she aborted on day 80. Study drug was discontinued on day 84 and not resumed.
- 830/3002: 46 year old female with a history of T2D and 4 pregnancies (1 live birth, 3 spontaneous abortions) experienced an abortion spontaneous on day 197 of study OPI-001, in which she received alogliptin 25 mg + pioglitazone 45 mg. The subject had a positive serum pregnancy test on day 183 and positive urine and serum pregnancy tests on day 188. β HCG was 390.7 mIU/ml. On day 199, the subject presented with 2 days of vaginal bleeding. A transvaginal ultrasound confirmed a spontaneous abortion, and the event resolved. Previous spontaneous abortions were due to fall, lack of glycemic control, and premature rupture of membranes. The subject took her last dose of study medication on day 180.

7.6.3 Pediatrics and Effect on Growth

Alogliptin has not been studied in the pediatric population to date. The sponsor requested a waiver of the requirement to conduct studies evaluating alogliptin in subjects 0-9 years, due to the lack of T2D subjects under 10 years of age requiring pharmacologic intervention. The sponsor requested a deferral of the requirement in subjects ≥ 10 years of age, due to the need to characterize the safety and efficacy of alogliptin in the adult population prior to conducting pediatric studies.

The Pediatric Review Committee (PeRC) met on September 24, 2008 and decided that alogliptin studies would be deferred in ages 10-16 years and waived in ages 0-9 years.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of alogliptin overdose were reported during clinical development.

The highest doses of alogliptin that were administered in clinical trials were single doses of 800 mg to healthy subjects and multiple doses of 400 mg daily for 14 days to subjects with T2D. No dose-limiting AEs were observed at these doses.

Alogliptin is modestly dialyzable. Over a 3 hour hemodialysis session, approximately 7% of the drug was removed. Therefore, hemodialysis is unlikely to benefit an overdose situation. It is not known if alogliptin is dialyzable by peritoneal dialysis.

No clinical studies were conducted to evaluate the abuse potential of alogliptin since its drug class is not associated with abuse. No pattern of events was observed during the clinical program to suggest abuse potential.

7.7 Additional Submissions

Not applicable.

8 Postmarketing Experience

Alogliptin is not currently marketed in the United States or elsewhere in the world.

9 Appendices

9.1 Literature Review/References

Not applicable.

9.2 Labeling Recommendations

Review of the labeling was deferred as alogliptin will not be approved at this time.

9.3 Advisory Committee Meeting

Not applicable.

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/s/

Valerie Pratt
5/13/2009 02:31:33 PM
MEDICAL OFFICER

Hylton Joffe
5/13/2009 03:21:01 PM
MEDICAL OFFICER
Please see CDTL memorandum.