CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA Complete Response
Application Number(s)	22-271 and 22-426
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Division / Office	DMEP/ODEII/OND
Reviewer Name(s)	Valerie S.W. Pratt, M.D.
Review Completion Date	01-17-13
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
Cmax	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 insulinotropic polypeptide
GLP-1	Glucagon-like polypeptide-1
HCl	Hydrochloride
Hct	Hematocrit
HDL	High-density lipoproteins
HEV	Hepatitis E virus
Hgb	Hemaglobin
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 ≤3x ULN at baseline and shifted to >10x 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 >10x 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 includes 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 PPARγ 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 withDPP4 inhibitors or any other anti-diabetic drug

Additional safety concerns with DDP4 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 DDP4 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 (≥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 DDP4 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 Kajiyama 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, 2021: 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)

Hoewever, 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) 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 PPARγ agonist. Activation of PPARγ 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

	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

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 thee 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 (≥1000mg/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 75years 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 ≥10g/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 ≥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:

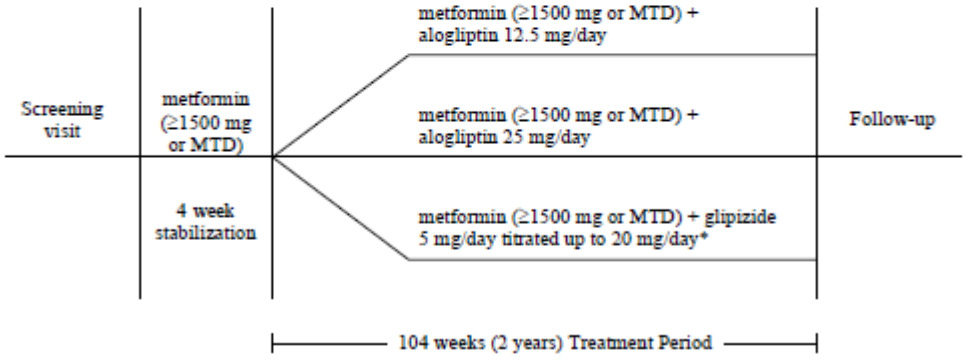
- To evaluate other measures of glycemic control after treatment with alogliptin plus metformin as compared with glipizide plus metformin, including HbA1c change from Baseline in other visit and FPG change from Baseline in all visits.
- To evaluate clinically meaningful levels of response in HbA1c after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

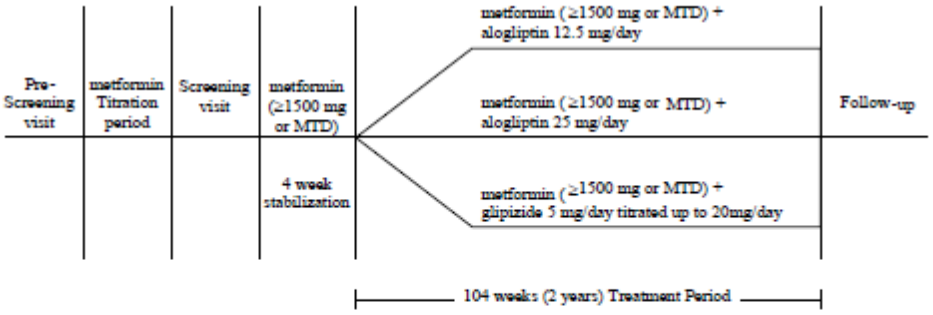


*: titration of glipizide from 5mg to 20 mg total daily dose only for subjects who demonstrate persistent hyperglycemia after at least 2 weeks but prior to Week 20.

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 ≤6.5% and ≤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 ± SE	Change from baseline Adj. mean ± SE	Difference in adjusted mean change 95% CI	p-value
Study 010 (monotherapy)					
Alo 25 mg	131	172±4	-16±4	-28 (-40, -15)	<0.001
Alo 12.5 mg	133	174±4	-10±4	-22 (-34, -9)	<0.001
Placebo	64	173±7	11±5		
Study 007 (add-on to sulfonylurea)					
Alo 25 mg	198	174±4	-8±3	-11 (-22, 1)	0.07
Alo 12.5 mg	201	172±4	-5±3	-7 (-18, 5)	0.24
Placebo	99	177±5	2±5		
Study 008 (add-on to metformin)					
Alo 25 mg	204	172±3	-17±3	-17 (-26, -9)	<0.001
Alo 12.5 mg	211	168±3	-19±3	-19 (-27, -10)	<0.001
Placebo	104	180±5	0±4		
Study 009 (add-on to pioglitazone)					
Alo 25 mg	197	170±3	-20±3	-14 (-23, -5)	0.003
Alo 12.5 mg	196	173±3	-20±3	-14 (-23, -5)	0.003
Placebo	97	171±5	-6±4		
Study 011 (add-on to insulin)					
Alo 25 mg	128	186±6	-12±6	-18 (-33, -2)	0.03
Alo 12.5 mg	131	190±5	2±6	-4 (-19, 12)	0.66
Placebo	127	196±7	6±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 in 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 ≤3x ULN at baseline and shifted to >10x 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 >10x 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 includes hepatic enzyme elevations in the labeling section 6.2 Postmarketing

Experience. I agree with this proposal and also recommend adding related text to Sectin 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 ~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)

	n/N (%) of Subjects		
Disposition Category	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 2.4Important 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)

	Number (%) of Subjects		
SOC	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 ≥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

	Number (%) of Subjects					
	2011 NDA Resubmission			2012 NDA Resubmission		
SOC Preferred Term	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

	Number (%) of Subjects					
	2011 NDA Resubmission			2012 NDA Resubmission		
SOC Preferred Term	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 (pruritits, 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 2.4Important 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 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 pruritits. 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)

	Number (%) of Subjects		
Preferred Term	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.l

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 consistant 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 cutanous 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)

	Number (%) of Subjects		
Criteria Met (a)	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)

	Number (%) of Subjects		
Preferred Term	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)

	Number (%) of Subjects		
Preferred Term	All Comparators (a) N=5987	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)

	Number (%) of Subjects		
Event Category	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)

	Number (%) of Subjects		
Preferred Term	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 alveiolitis 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)

	Number (%) of Subjects With Markedly Abnormal Result					
	Baseline (a)		During Treatment (b)		Last Assessment (c)	
Parameter	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	>10×ULN Elevation	Peak Elevation	Last Assessment (a)			
8260-010/402 Alogliptin 25 mg 58-year-old female	≤1×ULN	Day 92 >10×ULN	Day 92 >10×ULN	Day 358 ≤1×ULN	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	>10×ULN	Day 9 >10×ULN	Day 9 >10×ULN	Day 372 ≤1×ULN	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	>3×ULN	Day 42 >10×ULN	Day 42 >10×ULN	Day 42 >10×ULN	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	>1×ULN	Day 112 >10×ULN	Day 112 >10×ULN	Day 141 >1×ULN	No	Hepatic steatosis Hepatitis A	None reported
831-2508/OPI-002 Alogliptin 25 mg 49-year-old male	>1×ULN	Day 86 >20×ULN	Day 91 >20×ULN	Day 86 >20×ULN	No	Hepatitis B	Concurrent use of acetylsalicylic acid
307-9019/009 (b) Alogliptin 25 mg 47-year-old male	>10×ULN	Day 1 >10×ULN	Day 8 >10×ULN	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	>1×ULN	Day 32 >20×ULN	Day 32 >20×ULN	Day 57 ≤1×ULN	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	>5×ULN	Day 15 >10×ULN	Day 15 >10×ULN	Day 20 >5×ULN	No	Bile duct stone	Fatty liver, concurrent use of fluconazole
5039-003/305 Alogliptin 12.5 mg 56-year-old male	>1×ULN	Day 113 >10×ULN	Day 113 >10×ULN	Day 113 >10×ULN	No	Hemochromatosis	None reported
5304-055/305 Alogliptin 12.5 mg 45-year-old male	≤1×ULN	Day 45 >10×ULN	Day 51 >20×ULN	Day 48 >20×ULN	Yes	Hepatitis E	Concurrent use of atorvastatin
5505-016/305 Alogliptin 25 mg 46-year-old male	≤1×ULN	Day 274 >10×ULN	Day 274 >10×ULN	Day 555 ≤1×ULN	No	Alcohol	Obesity
8664-005/402 (b) Alogliptin 25 mg 59-year-old male	≤1×ULN	Day 263 >10×ULN	Day 263 >10×ULN	Day 351 ≤1×ULN	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

	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.

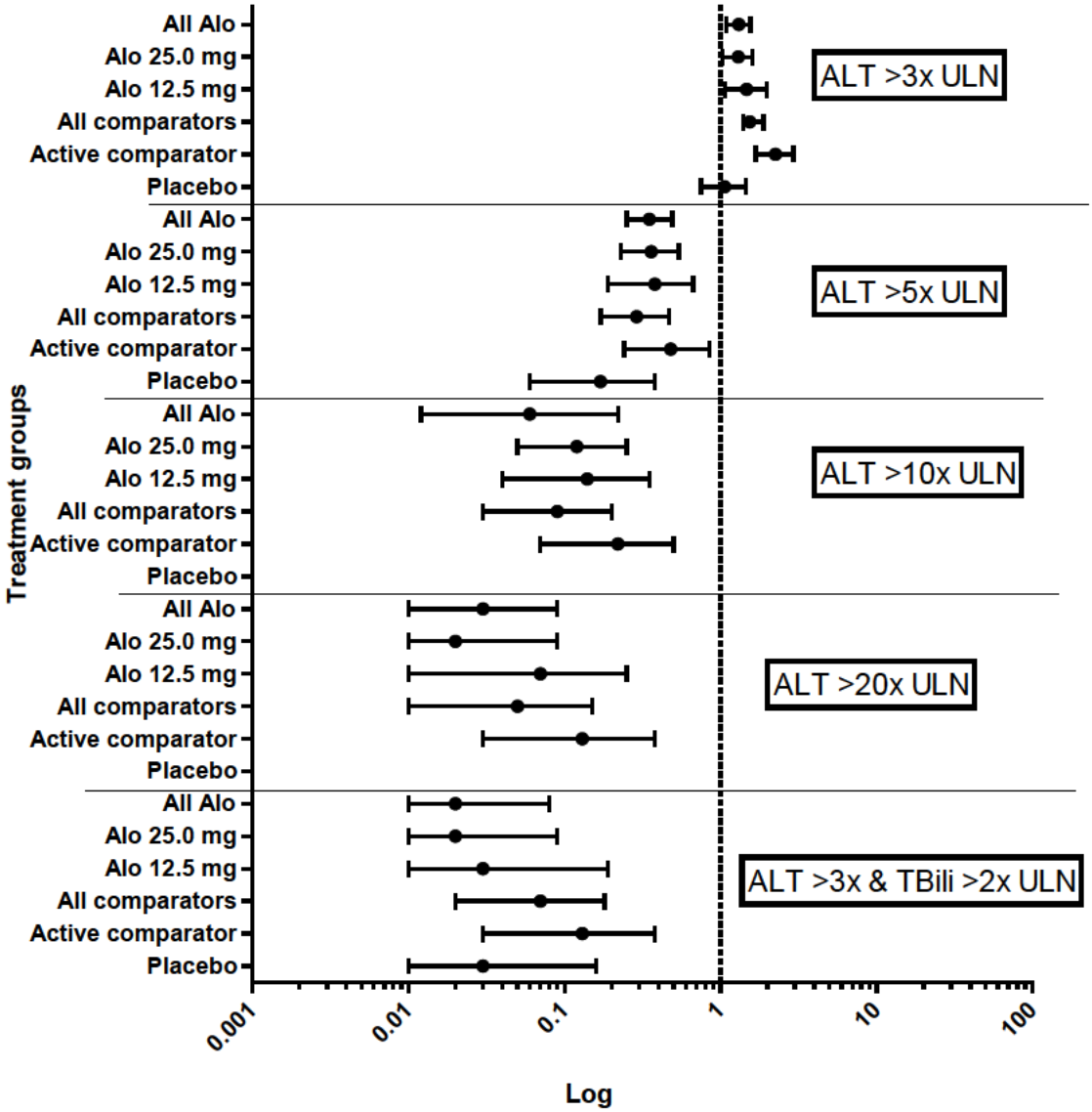


Figure 3. Percentage of subjects with markedly abnormal ALT including values observed up to seven days after last dose (Controlled phase 2 and 3 studies)

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	Choledocholithiasis	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

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

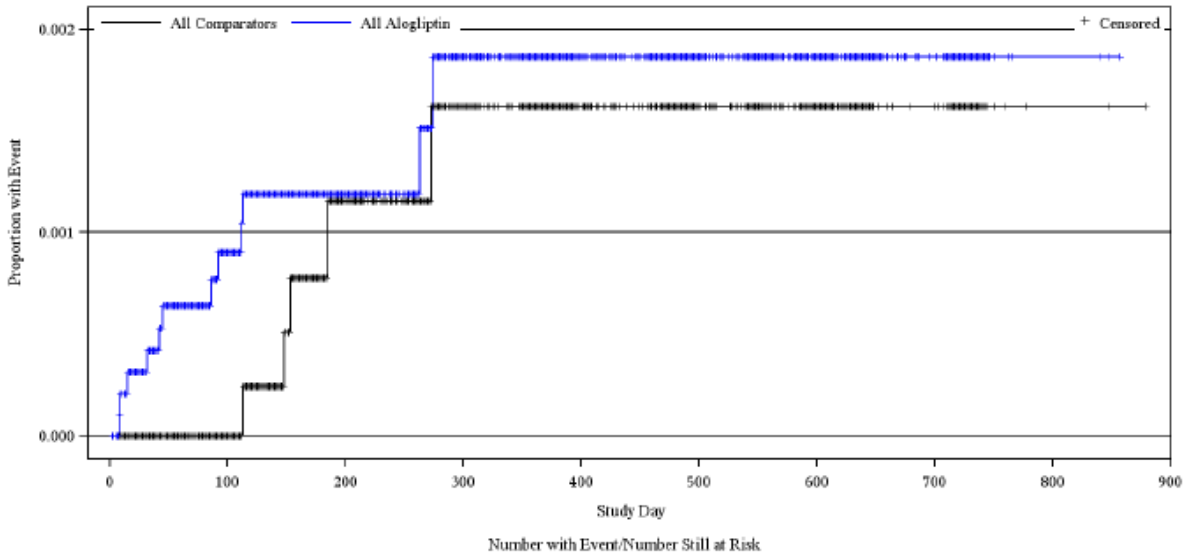
Table 26. Shifts in ALT from baseline including values observed up to the day of last dose (Controlled phase 2 and 3 studies)

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.



Number with Event/Number Still at Risk

Study Day	1	166	335	518	701
All Alogliptin	0/9608	10/6445	12/2632	12/1304	12/ 511
All Comparators	0/5786	3/3689	5/1868	5/ 706	5/ 249

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.

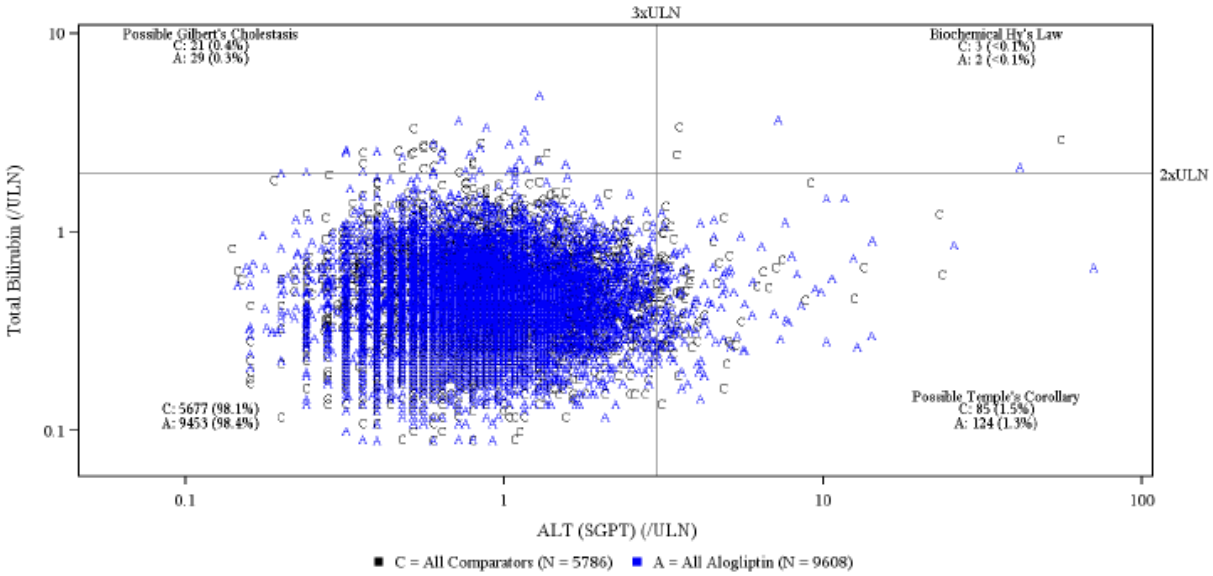


Figure 5. eDISH plot (Most extreme observation per subject) (Controlled phase 2 and 3 studies)

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)

	Number (%) of Subjects		
Preferred Term	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)
Hypertransaminaseamia	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 TCI2012A01229 is a 70 year old male who experienced a MI on [redacted] (b) (6) On [redacted] (b) (6) an inpatient laboratory test showed hepatic function abnormality. On [redacted] (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.

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.*

- TCI2011A06837: 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 gualenate, 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.*
- TCI201106892: 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.*
- TCI2011A01179: 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.*

- TCI2012A01573: 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: doneprezil 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.*
- TCI2011A02923: 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 nonsserious 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 aobut 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 ≤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 ≤3x ULN at baseline and shifted to >10x 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 >10x 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 includes 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 ≥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

	Number (%) of Subjects					
	2011 NDA Resubmission			2012 NDA Resubmission		
SOC Preferred Term	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	n=4161	n=7361
	-0.02 (0.271)	-0.03 (0.264)	-0.02 (0.264)
BUN (mg/dL)	n=5786	n=6408	n=9608
	0.4 (5.10)	0.6 (5.23)	0.5 (4.84)
Serum creatinine (mg/dL)	n=5786	n=6408	n=9608
	0.00 (0.193)	0.01 (0.220)	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 m^2; mild = eGFR ≥60 - <90 mL/min/1.73m^2; moderate = eGFR ≥30 - <60 mL/min/1.73m^2; severe = eGFR <30 mL/min/1.73m^2.
(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)

	Number (%) of Subjects With ≥1 Markedly Abnormal Result During Treatment		
Parameter (Criterion)	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". [redacted] (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 ≥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: Octber 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:

- TCI2012A03395: 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, 201; 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 forth 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, [redacted] 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

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 8 November 2012

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmacovigilance and Epidemiology (OPE)
Leonard B. Seeff, M.D., Hepatology Consultant (Hill Group), OPE

TO: Mary Parks, M.D., Director, Division of Metabolic and Endocrine Products (DMEP), Office of New Drugs (OND)
Amy Egan, M.D., Medical Team Leader, DMEP
Valerie Pratt, M.D., Medical Reviewer, DMEP

VIA: Gerald Dal Pan, M.D. M.H.P., Director, OSE; Acting Director OPE

SUBJECT: Hepatic safety of alogliptin (NDA 022271), alogliptin/pioglitazone (NDA 022426), and alogliptin/metformin (NDA 203414), Takeda

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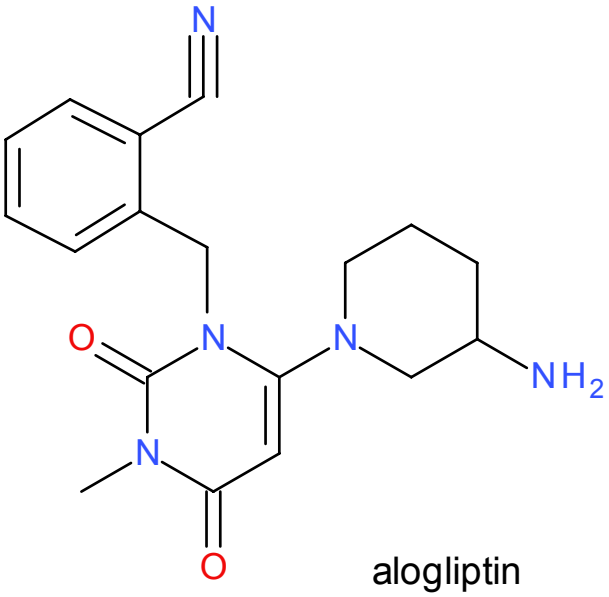
Documents reviewed:
1) Consultation request dated 15 October 2012 from Dr. Pratt via Mr. Rich Whitehead and Ms. Margarita Tossa, with requested response date 9 November, OSE tracking #2012-2411.
2) Takeda summary dated 4 October 2012, provided clinical details on cases showing either ALT >10xULN or {ALT/AST >3xULN & BILI >2xULN}
3) Previous consultation reports by Dr. Leonard Seeff of 21 February and 8 May 2012
4) Summary minutes of end-of-review meeting 29 June 2012; Takeda and FDA/ODE II/DMEP

Alogliptin, a dipeptidyl peptidase-4 compound (SYR-322) was approved in Japan in April 2010 and marketed by Takeda as an oral drug with brand name NESINA® for treatment of patients with type 2 diabetes mellitus. The original new drug application (NDA 022271) in the United States submitted in December 2007 was not approved 29 June 2009, citing inadequate information. A resubmission 25 July 2011, along with NDA 022426 for an alogliptin/pioglitazone combination, was also not approved 25 April 2012 because of residual concerns about rare hepatotoxicity and differing opinions of consultants on whether or not caused by alogliptin hypersusceptibility. The sponsor assembled a group of well known hepatologists (b) (4) as a Liver Safety Evaluation Committee (LSEC) to review cases of special interest and concern as to whether alogliptin was the probable cause of liver injury or dysfunction observed. As has been noted by other sets of reknowned experts in hepatology serving in the drug-induced liver injury network (DILIN) of the National Institutes of Health, experts do not always agree on the likelihood of causation by administered drugs, in cases for which there may be other possible causes such as several types of acute viral hepatitis, autoimmune hepatitis, alcohol-induced hepatitis, from other drugs or substances also taken concurrently, genetic and metabolic liver diseases, and others.

The dipeptidyl peptidase-type 4 inhibitors reduce inactivation of glucagon-like peptide-1, which lowers blood glucose and decreases gastric emptying. Three other agents of this class have been approved for use in the United States, including sitagliptin (JANUVIA®, Merck Sharp Dohme; 16 October 2006), saxagliptin (ONGLYZA®, Squibb; 31 July 2009), and linagliptin (TRADJENTA®, Boehringer Ingelheim; 2 May 2011), and others are under development.

Among these agents, alogliptin has perhaps the simplest structure:



alogliptin

With respect to the stated concerns about possible hepatotoxicity of alogliptin in some people, as mentioned above, there have been no published reports (byPubMed search) of significant or serious liver injury from the considerable experience in Japan since it was approved there in 2010. That does not mean that there actually have been no cases, just none published. We should evaluate the data carefully, however, concerning this issue, in light of some of the rather serious post-marketing cases reviewed by Dr. Seeff in his previous consultations of February and May. We recognize that experts don't always agree on the likelihood of causal association, and that opinions are highly dependent on adequate clinical information to exclude other possible causes of findings observed or reported. Such information is often or usually missing from spontaneous reports from busy practicing physicians, but lack of information is nor reassuring.

We shall not repeat here the findings and conclusions reached by Dr. Leonard Seeff in February and May of this year that considered those mainly post-marketing cases from Japan. Review of the same cases by the sponsor's consultants (b) (4) showed that they did not always concur with each other, nor did Dr. Seeff when he looked at presumably the same information as they had done. In this consultation, we shall focus on cases forwarded to us in the consultation request of 15 October 2012, which included 11 cases from clinical trials who showed ALT peak elevations >10xULN, and 5 cases with {ALT>3xULN & BILI>2xULN}. 1 of which was the same (305/5304-055). In citing the cases by number, we shall try to be more consistent than was the sponsor, using the convention of Study/Site-Subject to identify the person of interest.

Dr. Seeff took the lead in reviewing the 11 cases with ALT elevations >10xULN, and I focused on the 5 potential "Hy's Law" cases. We emphasize the point that there really is no such thing as a "biochemical Hy's Law" case, as suggested by the sponsor and reiterated in your consultation request. The intent of setting low threshold limits of {ALT>3xULN & BILI>2xULN}.was not for making diagnosis, but simply as conservative levels for screening possible cases to follow by investigating them further by medical process to estimate the most likely or probable cause of the findings observed or reported. As Dr. Hyman Zimmerman repeatedly stated and wrote, "drug-induced hepatocelluar jaundice is a serious lesion," with substantial mortality. The very first idea of that advice was that there had to be evidence to support the cause of the finding as from a drug administered, which requires ruling out or excluding other possible causes, including diseases such as acute viral hepatitis of several types, alcoholic and autoimmune hepatitis, diseases of iron or copper deposition, other drugs, biologics, generics, or dietary supplements also taken. There is no known pathognomonic biomarker or indicator of drug-induced liver injury, even biopsy, and certainly not by imaging. The process of investigating a patient for what caused a problem is a medical exercise in differential diagnosis, and cannot be done by statistical approaches.

First, the 11 cases from Studies 303, 305, 307, 311, 395. 402, and 831:

Peak ALT Values >10 x ULN

303/3128-003 (*Study/Site-Subject*)

This 73 year old man with a history of cholelithiasis, cholecystectomy, malaria and onychomycosis who was receiving treatment with fluconazole and ranitidine, was started on (ALT 144 IU/L; AST 103 IU/L, ALP 150 IU/L, total serum bilirubin 0.74 mg/dl), with values returning to normal when re-tested 6 days later. On day 8, he apparently developed acute abdominal pain and 7 days later, all 3 serum enzymes, ALP in particular, were found again to be abnormal. He was diagnosed as having a bile duct stone and, indeed, 5 days later, had a total serum bilirubin value of 4.07 mg/dl. with continuing elevation of the ALP level. A day later,alogliptin treatment was permanently discontinued and values returned to normal thereafter. Also noted was fatty liver disease on US.

Comment (LBS): This was not an instance of alogliptin hepatotoxicity, but rather transient gall stone obstruction. Noteworthy is that the term "Hy's law" was mentioned which is of course incorrect until a diagnosis of dili is reached. Raised aminotransferases and serum bilirubin caused by other conditions should not be called Hy's law.

303/5505-016

This 46 year old obese male being treated with metformin was started on treatment with alogliptin on September 6, 2010. Liver-related chemistries were normal at baseline and remained normal until day 274 when he had an ALT of 356 IU/L, and an AST of 260 IU/L with a normal serum bilirubin value. At this point, the drug was withdrawn and 8 days later, all values had returned to normal (even unusually low). As best as can be determine, treatment was re-started without evidence of further enzyme elevation. No information is supplied regarding an effort to seek cause for the abnormality other than to say that he had had "alcohol use," whatever that means. Accordingly, the cause for the single set of biochemical abnormality remains unknown.

Comment (LBS): This is yet another instance in which there is a single set of moderately increased aminotransferase levels for which no cause was identified. That this is almost certainly not alogliptin dili is evident from the prolonged latency after starting treatment of approximately 9 months and the lack of recurrence after re-starting treatment. However, what the actual cause is cannot be determined from the information presented.

305/5039-003

This 56 year old male with a history of cataracts, diarrhea, headaches and increased GGT levels, who was receiving metformin and ibuprofen, was started on treatment with alogliptin on July 27, 2009. Both prior to starting treatment, and continuing thereafter until day 57, he had very mild elevations in his ALT levels, all other routine liver-related chemistries being normal. On day 113, he suddenly developed an ALT level of 321 IU/L and an AST of 166 IU/L. Treatment apparently continued until day 134 when he voluntarily withdrew from treatment. By day 141, his ALT level had fallen to 54 IU/L. It is then stated that he had hemochromatosis which might, according to the narrative, have been responsible for the abnormal serum enzymes This seems hardly likely.

Comment (LBS): We are faced once again with a single set of aminotransferase abnormalities consistent with mild hepatocellular injury. The cause is entirely unclear. Since the drug was withdrawn and the chemistries fell thereafter to almost normal values, dili cannot be absolutely ruled out. However, no information is presented to show that other potential causes for the liver abnormality were sought. Regardless, this represents only minimal and transient, indeed trivial liver dysfunction. In the absence of any other explanation, it is conceivable that alogliptin might have led to the single set of enzyme elevations but this is not really drug-induced liver injury.

305/5304-055 (*see also below as potentially more serious)*

A 54 year old man with a history of anxiety who was taking metformin, atorvastatin, ursodeoxycholic acid, aspirin, vitcofol and multivitamins was started on treatment with alogliptin on March 29, 2010. His baseline liver chemistries were normal, but they became slightly abnormal (ALT 85 IU/L, AST 51 IU/L) on day 29. He was apparently worked up for etiology, and was diagnosed to have developed acute hepatitis E based on a positive test for IgM anti-HEV. The aminotransferase level increased 9 days later and treatment was discontinued on day 48 when the values had increased even further. The values peaked 3 days after discontinuing alogliptin (ALT 1036 IU/L, AST 578 IU/L), the bilirubin level rising to 2.37 mg/dl. By day 79, all values had returned to normal.

Comment (LBS): Very nice case. The diagnosis could easily have been dili until work up revealed acute HEV infection.

307/9019-009

This 47 year old man with a history of hypertriglyceridemia, hypercholesterolemia, diabetic neuropathy, gout and obesity who had been receiving treatment with pioglitazone, began treatment with alogliptin on November 13, 2006. He was also being treated with metformin, paracetamol, pseudoephedrine, fenofibrate, and nutria min C resist(?). His baseline liver chemistries were abnormal (ALT 430 IU/L; AST 190 IU/L, t. bilirubin 1.3 mg/dl). On day 5, alogliptin was discontinued and on day 8, the last time he was seen in this study, both serum enzymes were still moderately elevated. The subject was referred to his primary care physician and apparently was lost to follow-up thereafter.

Comment (LBS): This is clearly not alogliptin dili since enzyme elevations were already present at baseline. The diagnosis is not known even though the patient was referred to his PCP for further evaluation, none of which was forthcoming. Alogliptin was discontinued 5 days after starting treatment.

311/9003-009 (*previously reviewed*)

This 49 year old male with a history of hyperlipidemia, drug hypersensitivity (?) and anxiety, who was being treated with pioglitazone, fluoxetine, buspirone, trazidone, and ezetimibe, was started on treatment with alogliptin on June 16, 2006. He had an unexplained slight elevation in his ALT and GGT levels at baseline which had returned to normal 2 weeks later. On day 32, he was suddenly found to have an ALT level of 646 IU/L, an AST level of 585 IU/L, and slight increases in the levels of total serum bilirubin and ALP but still in the normal range. Alogliptin was withdrawn and 10 days later, the values were back to normal. It is implied that alogliptin treatment was re-started without giving a date, without further elevation of the serum enzymes and that he voluntarily withdrew from the study on day 91. Inexplicably, there is reference to a set of values obtained on day 208, all of which were normal. The single set of abnormal values is ascribed to "alcohol intake" without further explanation.

Comment (LBS): I do not know the cause for the single set of moderately abnormal aminotransferase values but cannot consider them to be due to alcohol intake. First, there is no information given as to how much alcohol was taken and for how long, and the pattern of enzyme elevation is decidedly unlike that seen in alcoholic liver disease. Moreover, the values had returned to normal 10 days later. It is also unlikely that alogliptin was responsible since, as best as I can glean from the skimpy information given, the patient was started back on alogliptin without re-emergence of enzyme abnormalities. I'm not sure what the cause of the single spike in enzymes is and wonder whether the sample tested was actually from someone else.

395/3054-001

This was a 67 year old female with a medical history of dyslipidemia and cholecystectomy who was begun on treatment with alogliptin on April 10, 2007. Her baseline ALT level was a smidgen above normal, but the ALT and other liver chemistries reported were all normal until day 112. At this time, the ALT increased to 257 IU/L and the AST to 118 IU/L with normal total serum bilirubin and ALP values. One week later, the ALT had decreased to 128 IU/L and the AST to 70 IU/L. Alogliptim was apparently not discontinued yet the aminotransferase levels became normal on day 141 and remained normal through day 183. The reason for the transient slight elevation in aminotransferase levels without concomitant hyperbilirubinemia remains unclear although it is stated that an ultrasound revealed fatty liver (which must have spontaneously disappeared if the raised enzymes were a result of this occurrence). Also, there is mention of hepatitis A infection reported on day 169 (well after the first enzyme obtained from the sponsor be obtained regarding whether a follow-up ultrasound was performed and what the specific serologic findings were that led to a diagnosis of hepatitis A.

Comment (LBS): The sponsor attributes the short-lived increases in serum enzymes 112 days after starting alogliptin treatment to fatty liver disease and/or hepatitis A. The data made available are insufficient to confirm either of these two diagnoses. Although I cannot absolutely rule out a role for alogliptin, I think it extremely unlikely. In any case, the "liver disease" was trivial.

402/8070-002
This 60 year old man with a history of atherectomy (?), peripheral artery angioplasty, myocardial infarction, coronary artery bypass and multiple other medical problems including chronic hepatitis C, was started on treatment with alogliptin on June 24, 2010. Throughout the entire 610 days of follow-up, and even prior to starting treatment, he had persistently abnormal aminotransferase levels, the ALT always exceeding the AST, with normal serum bilirubin and alkaline phosphatase levels. The patient was also receiving multiple other medications, several with a known history of having caused dili in the past. No information is given regarding hepatitis C (or other forms of viral hepatitis) serologic markers, but almost certainly the persistently elevated serum enzyme levels are a consequence of chronic hepatitis C. Of note is that on day 42, his ALT level peaked at 267 IU/L with an AST value of 277 IU/L at which time, alogliptin was discontinued. Nevertheless, the serum enzymes levels remained abnormal throughout his follow-up although at a lower level.
Comment (LBS): Without question, the observed aminotransferase abnormalities in this patient were not a consequence of alogliptin treatment but presumably rather of chronic hepatitis C. Moreover, even after alogliptin treatment was withdrawn, serum enzymes remained abnormal showing an absence of dechallenge.

402/8260-010 This 58 year old female with a history of dyslipidemia, myocardial infarction, unstable angina, and hypertension was begun on treatment with alogliptin on February 22, 2011. Starting with completely normal liver-related chemistries, she was found to have a single set of abnormalities 92 days later (ALT 293 IU/L; AST 149 IU/L; ALP 129 IU/L, and T. Bilirubin 1.65 mg/dL). At the tiome, she was also receiving multiple other medications (cloipidogrel, metformin, simvastatin, carvedilol, spironolactone, gliclazide, isosorbide dinitrate and mononitrate, and aspirin). Alogliptin was withdrawn. Just prior to the elevated values, she was diagnosed with unstable angina and she had cardiac catheterization, revealing coronary obstruction, followed by successful coronary artery angioplasty. Ten days later, the aminotransferase levels returned to normal and she was started back on alogliptin treatment without developing abnormal chemistries. Continued follow-up values while on alogliptin treatment remained normal.
Comment (LBS): This was clearly not a case of alogliptin hepatotoxicity but the single set of abnormal values resulted presumably from her cardiac disease. Moreover, re-challenge with the drug did not result in repeat liver dysfunction.

402/8521-002
An 81 year old female with a history of chololithiasis, cardiac failure, and myocardial infarction presenting with hypertension, angina pectoris, osteochondrosis, the post-cholecystectomy syndrome, and presbyopia was started on treatment with alogliptin on January 25, 2011. At the time of starting treatment she had abnormal baseline liver-related abnormal chemistries (ALT 349 IU/l; AST 259 IU/L, and ALP 134 IU/L. These tests were abnormal also 12 days before starting treatment (why was she treated?). The values remained persistently abnormal through day 36, falling gradually to normal by day 94. On day 85, she was diagnosed to have acute pancreatitis. There is also notation that the patient had underlying hepatitis C but without supporting serologic evidence presented. Moreover, she continued to be treated with alogliptin until day 372 but the liver chemistries remained normal from day 197 onward.

Comment (LBS): Clearly, with abnormal liver chemistries noted even prior to starting treatment, and with normal values noted for several months even after re-starting treatment, the abnormalities cannot be attributed to treatment with alogliptin. The cause for the abnormalities remains unclear, although it is suggested that it might be a result of chronic hepatitis C (no serologic results given), chronic pancreatitis, or underlying cardiac disease.

402/8664-005

This 59 year old male with multiple medical problems (angina pectoris, mitral valve prolapse, diabetic nephropathy, dyslipidemia and an enlarged prostate) who was receiving treatment with aspirin, captopril, clopidogrel, isosorbide, metoprolol, atorvastatin, and, trimetazadine, was begun on treatment with alogliptin on April 29, 2011. Prior to baseline, he had a slightly elevated ALT value, 78 IU/L, but it was normal at baseline and remained normal until day 263 when he was found to have an ALT of 256 IU/L, an AST value of 57 IU/L, a serum bilirubin value of 1.65 mg/dl and a ALP of 213 IU/L. Both alogliptin and atorvastatin were discontinued and the values decreased slightly by day 267 and were almost back to normal by day 277. Alogliptin appears to have been re-started (but the information on this is obtuse and no re-start date is mentioned). Serum enzymes thereafter remained normal. The sponsor attributed the abnormalities to atorvastatin based on evidence of dechallenge. As usual, no mention is made of efforts to identify cause.

Comment (LBS): Yet another instance of delayed hepatocellular injury without a specific cause being identified. Although attributed to atorvastatin dili, there is no information on how long that drug had been in use, it would have been less likely if atorvastatin was being received for a prolonged period. I am uncertain what the cause was for the raised aminotransferases, and although the likelihood is low, alogliptin cannot be completely ruled out although I am skeptical of this diagnosis. Unfortunately, other causes were not sought. As usual, this was a trivial finding.

831/2508-002

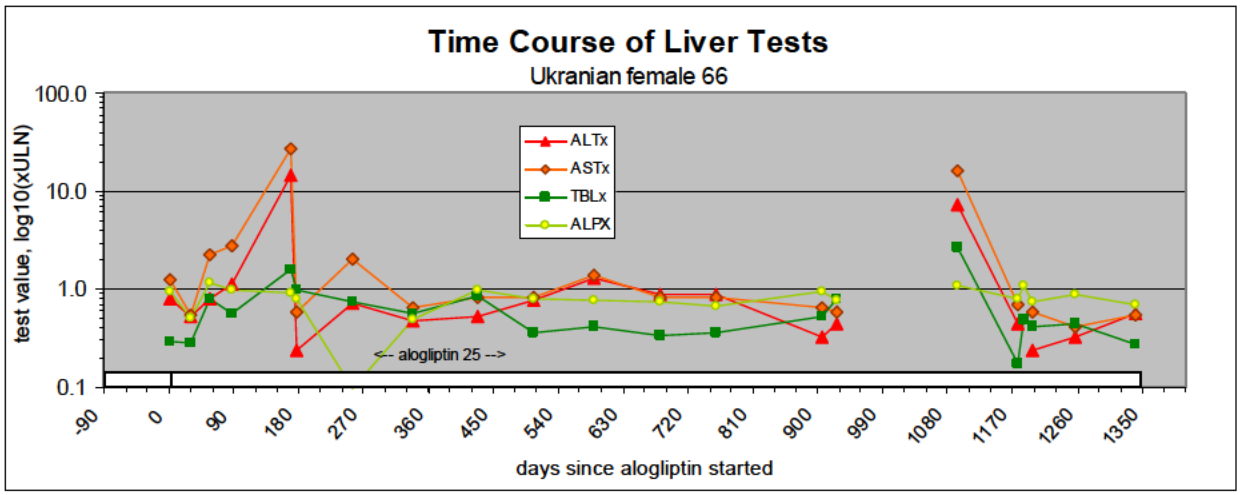
This 49 year old male with hypoacusis and an umbilical hernia began treatment with alogliptin on July 31, 2007. The ALT and AST values preceding treatment and at baseline were mildly abnormal but returned to normal between days 15 and 68. On day 64, he was diagnosed serologically with acute hepatitis B (serologic results not reported), and on day 86, was found to have an ALT value of 689 IU/L and an AST of 515 IU/L. Five days later (day 91), his ALT value had risen to 1771 IU/L and his AST to 1345 IU/L with normal ALP and serum bilirubin values. Alogliptin treatment was discontinued on day 107, and one month later, his serum enzymes had returned to normal. It is unfortunate that the hepatitis B serology defining acute hepatitis B is not made available in this obviously shortened report. It would be worth knowing how the acute HBV infection was acquired.

Comment (LBS): This is presumably an instance of short-lived acute hepatitis B without available confirmatory serologic evidence, but still this diagnosis seems likely.

Possibly More Serious Cases: ALT/AST >3x ULN; Total Bilirubin >2x ULN

012/961-2501 (*Study/Site-Subject*)

This is a somewhat complicated narrative of a 66 year old woman with a history of cardiac disease, hypertension and obesity who had previously been enrolled in another trial in which she had received alogliptin; during treatment, she was found to have very mild increases in his ALT, LDH, and GGT, but treatment continued. In the present study, she received alogliptin and nifedipine and her liver-related chemistries remained normal until day 169 when she was found to have a single set of abnormal values (ALT 360 IU/L, AST 602 IU/L, total bilirubin 1.73 IU/L) after which the values returned to normal remaining normal until month 39 when, once again, a single set of abnormal values was found (ALT 180 IU/L, AST 356 IU/L, total bilirubin 2.91 mg/dl). Treatment continued and the enzyme and bilirubin values returned to normal. The patient was entirely asymptomatic. The attending physician considered the abnormalities as laboratory errors.



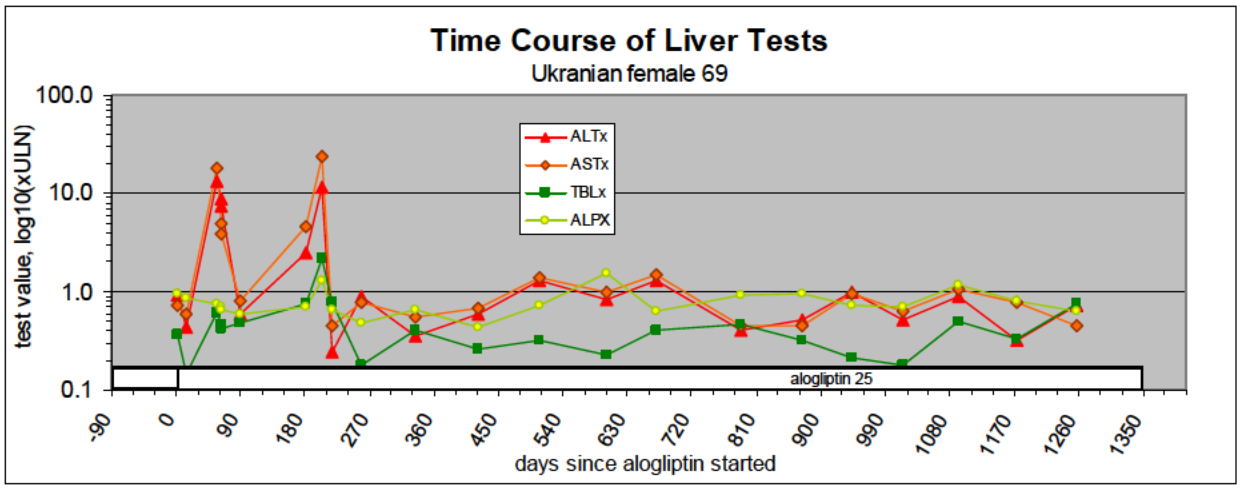
Comment (JRS): Inspection of the data and graphic display shows that this woman tolerated alogliptin very well, but had periodic abnormalities AST > ALT with no cholestasis. She had known heart disease and congestive failure, and the enzyme elevations corresponded to episodes of congestive failure (with centrilobular liver congestion). Probably cardiac, not drug-induced.

Comment (LBS): Single abnormal sets of values 6 and 39 months after starting treatment considered to be a laboratory error by the attending physician. The cause is otherwise unclear and could represent laboratory error or perhaps bouts of congestive heart failure. This is not drug hepatotoxicity.

012/961-3006

This was a 69 year old female with a history of hypertension and cerebral atherosclerosis who had participated in an earlier study using pioglitazone but because of apparent lack of efficacy, was rolled into a new open-label study receiving alogliptin on November 16, 2007. In the first study, she had had low level GGT elevations throughout. She was also receiving an ACE

inhibitor. Baseline and 2 week follow-up laboratory values were normal, but on day 56 (Week 8), she was found to have an ALT of 333 IU/L and an AST value of 396 IU/L with normal ALP and total serum bilirubin values. Similar abnormalities were noted on day 62 and day 63 repeated because the specimen was said to be unsatisfactory. Thereafter, the values dropped back to normal despite continuing treatment with the drug.. Then on day 182 (month 60), the enzymes increased again (ALT 62 IU/L, AST 100 IU/L) increasing further on day 203 (ALT 290 IU/L, AST 530 IU/L, total bilirubin 2.35 IU/L.). Apparently, drug treatment continued, and the bilirubin and aminotransferase values returned to normal and remained normal until day 1337. The narrative suggests that the first abnormality was a result of alcohol use over the holidays and the second bout to exposure to an insecticide. No other etiologies were sought.



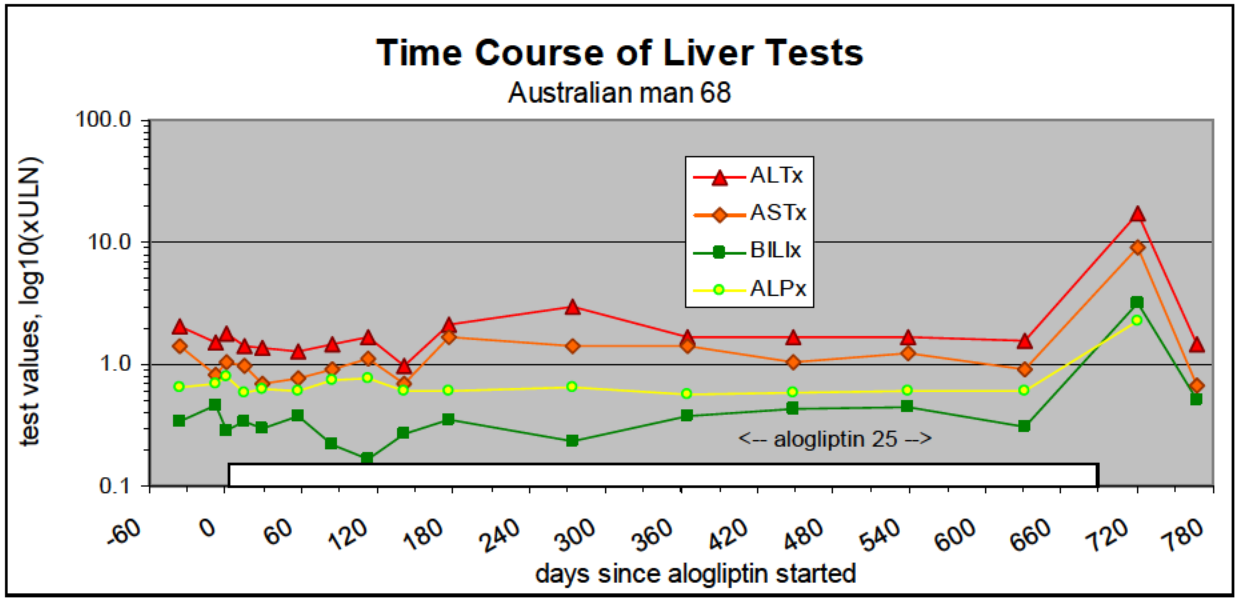
Comment (JRS): The two rather sharp increases in AST and ALT in January and May 2008, were attributed to preceding alcohol and insecticide exposure, but not convincingly. Alogliptin administration continued, and did not appear causative. The pattern of AST > ALT is seen in recurrent alcoholic hepatitis but usually at lower levels of activity, suggesting heart insufficiency as a factor (not mentioned in the narrative). The case was not well worked up or explained.

Comment (LBS): There were two episodes of fairly prominent liver abnormalities, one associated with jaundice. I cannot say what the causes were. The type of abnormality first seen is quite unlike that caused by alcohol. I cannot speak to the second episode that conceivably might have been due to toxic exposure to an insecticide, as is suggested in the narrative. Were it not for the fact that alogliptin treatment continued throughout, I would have been suspicious that it might have played a role. However, the second episode was quite late and liver abnormalities did not re-occur with continued use of alogliptin so therefore I will eliminate alogliptin as the cause for the observed biochemical abnormalities.

305/5312-001

This 68 year old male with a history of hypertension, hyperlipidemia and bruising of his arms started on the study drug on June 30, 2010. The patient was also receiving celecoxib, esomeprorozole, atorvastatin, telmisartan, oxycodone, paracetamol and metformin. Beginning prior to starting the study drug and continuing throughout follow-up until day 631, he had minimal elevations in his ALT levels, the other chemistries remaining normal [redacted] (b) (6) he was found to have an ALT value of 429 IU/L, an AST value of 198 IU/L, an ALP value of 160

IU/L (4 x higher than the previous values), and a total serum bilirubin value of 3.49 mg/dl. He was hospitalized and worked up for gall stone obstruction which seemed confirmed by an US examination. Magnetic resonance evaluation revealed choledocholithiasis, following which he underwent an ERCP with sphincterotomy and gallstone removal. Screening for hepatitis A, B, and C were all negative.

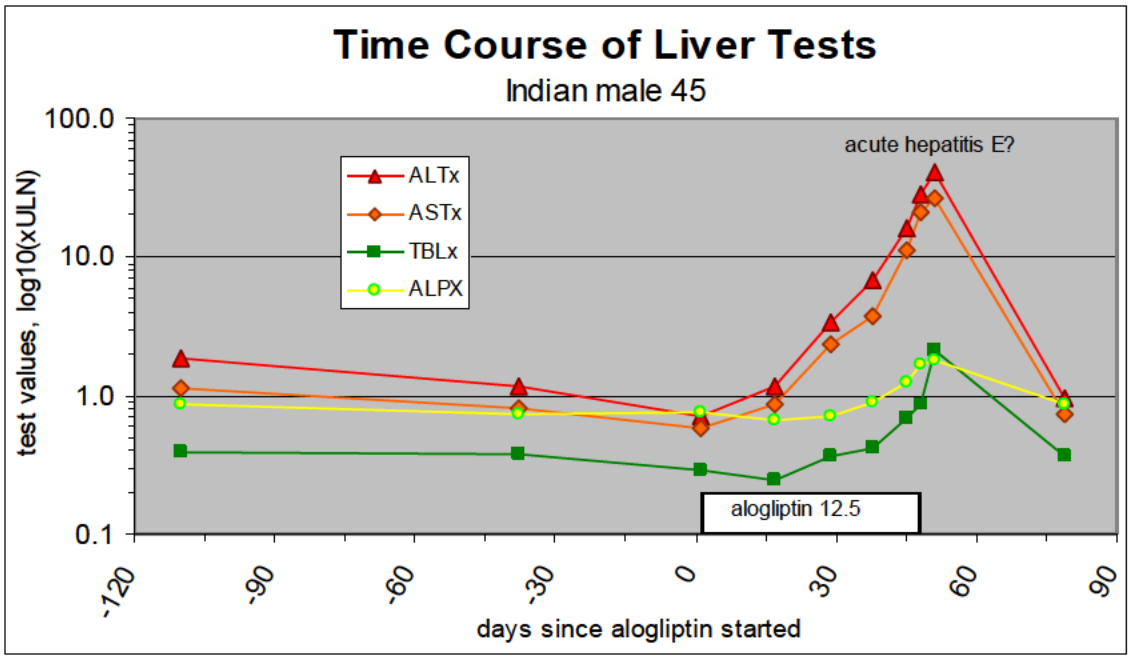


Comment (JRS): The slight but persistent ALT elevations were never investigated or explained, but the patient tolerated alogliptin well for two years. At that point a common duct stone was confirmed, then removed, with resolution. The aminotransferases elevations were relatively greater then the rise in alkaline phosphatase, so there may may have been some hepatocellular injury in addition to the cholestasis caused by the gallstone.

Comment (LBS): This is clearly an instance of obstructive jaundice caused by a gall stone. That finding and the fact that liver dysfunction occurred (b) (6) *completely eliminates a diagnosis of alogliptin hepatotoxicity.*

305/5304-055 (*see also above)*

A 54 year old man with a history of anxiety who was taking metformin, atorvastatin, aspirin, ursodeoxycholic acid, vitcofol and multivitamins with minerals, was started on treatment with alogliptin 12.5 mg/kg/day on March 29, 2010. His baseline liver chemistries were normal, but his ALT had been modestly elevated 4 months before. On alogliptin treatment, they became slightly abnormal (ALT 85 IU/L, AST 51 IU/L) on day 29, then markedly so on day 38 but his serum bilirubin had not yet risen. Because of the rising aminotransferase levels, alogliptin was stopped on day 48. The aminotransferaes contined to rise for three days more and serum bilirubin then reached 2.15xULN. He was worked up for etiology, and was diagnosed to have developed acute hepatitis E based on a positive test for IgM anti-HEV. By day 79, all liver test values returned to the normal range.



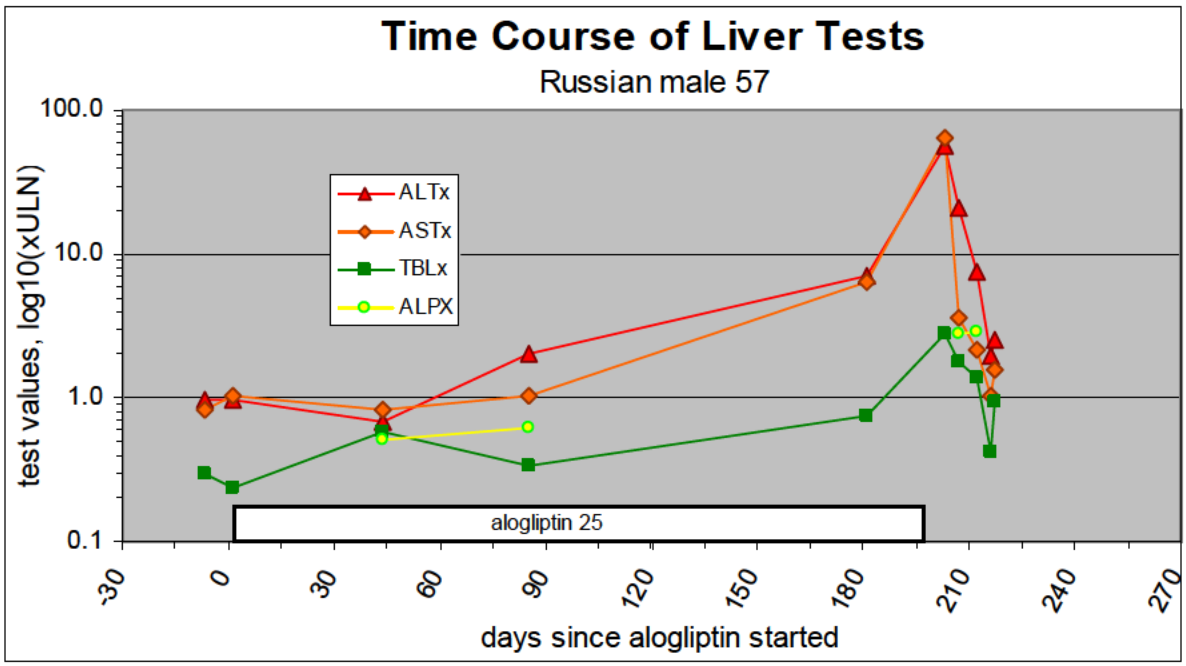
Comment (JRS): This subject showed aminotransferase activity rises about four weeks after starting alogliptin, with sharp subsequent increases that led to stopping the drug three weeks later. The investigator found acute-phase IgM antibodies against acute viral hepatitis E, which subsided within four weeks. Although this case was investigated alertly, it was not reported to the sponsor until September 2010 and norto the FDA by the sponsor until April 2011.

Comment (LBS): Very nice case. The diagnosis could easily have been dili until work up revealed acute HEV infection.

402/8413-006

A 57 year old male with a history of unstable angina, myocardial infarction, congestive cardiac failure, associated with hyperlipidemia, peptic ulcer, and hypertension was started on study drug on November 16, 2011. He was also receiving atorvastatin, clopidogrel, metoprolol, perindopril, and glibenclamide. At baseline and follow-up to day 85, all liver-related chemistries were normal. On day 85 (February 8), his ALT had risen from the previous 17 IU/L to 50 IU//L. No comment is made of this slight abnormality. On the next-reported testing day (day 181, May 14, almost 3 months following the first abnormality) his ALT was 176 IU/L, AST was 142 IU/L without elevation of his serum bilirubin. By day 203 (May 14, about 3 weeks later), the next value shown, he had undoubtedly developed an acute hepatitis as indicated by an ALT of 1410, an AST of 1390, and a raised serum bilirubin of 3.03 mg/dl. There is a comment in the narrative that the patient had drunk "200 ml of vodka 2 days prior to this visit" displaying the first set of abnormalities inferring that this event had something to do with the observed biochemical abnormalities that is almost certainly not correct as indicated by the high ALT/AST ratio and the subsequent marked increase in both serum enzymes. Serologic work-up failed to implicate hepatitis A, B, and C, he is reported to be positive for IgG anti-HAV; no testing for hepatitis E

was reported. The study drug was discontinued on day 207, as was atorvastatin, following which the chemistries improved, falling eventually to normal.



Comment (JRS): This pattern is not typical of acute alcoholic hepatitis because of the very high peak values of the transaminases at 56 and 63 xULN for ALT and AST, but more likely an acute viral infection that was not diagnosed, such as acute hepatitis A or E with no chronicity. A weak attempt was made to rule out other causes but no explanation was found. Alogliptin causation cannot be excluded.

Comment (LBS): This patient developed an acute hepatitis beginning apparently almost 3 months after starting the study drug. The serum bilirubin was transiently increased. There is a paucity of reported testing with a gap of almost 3 months between the first identified ALT value and the next reported test showing a quadrupling of the A LT value. About 3 weeks later, the enzyme elevations indicate clearly that the patient had developed an acute hepatitis that subsided thereafter, concomitantly with the withdrawal of both alogliptin and atorvastatin, although this may have been coincidental. An important question is whether the sequence, beginning 3 months after starting treatment and terminating about 4 months later was a result of the same insult. If so, although strangely protracted, it would be within the latency period of potential alogliptin dili. On the other hand, if there were in fact two insults, it is possible that the high enzymes occurring later were a result of some other etiology than dili. Serologic data excluded a diagnosis of acute hepatitis A, B, and C, but testing for hepatitis E was not reported, so this cannot be entirely excluded. This case was poorly reported or poorly worked up by the involved physician. . I doubt that atorvastatin accounted for the liver injury. IT IS IMPORTANT IN THIS CASE TO LEARN WHETHER THE STUDY MEDICATION WAS ALOGLIPTIN. IF SO, IT CANNOT BE RULED OUT AS A CAUSE FOR THE ACUTE HEPATITIS. UNLESS ACUTE HEPATITIS E OR SOME OTHER UNDEFINED ETIOLOGY IS IDENTIFIED, I WOULD GRADE ALOGLIPTIN DILI AS AT LEAST POSSIBLE, VERGING ON PROBABLE.

Two more Japanese post-marketing cases:

TCI12012A05586

This 64 year old male (referred to as 'she' in the narrative), was started on treatment with lansoprazole on August 4, 2012, and then on sulfamethoxazole/trimethoprim on August 20, 2012. He had apparently been receiving oral prednisolone for transverse myelitis following which he was found to have an elevated HbA1c. He was therefore started on treatment with alogliptin on August 27, 2012 (b) (6) the patient developed a fever and by the next day, was seen in the outpatient department to have a rash on his limbs and trunk; he also had oral mucosal eruption. On the same day, his ALT was 134 IU/L, his AST 83 IU/L, his ALP 195 IU/L, and his total bilirubin, 0.2 mg/dl. By the next day, the rash had spread even more and now his ALT value was 1057 IU/L, his AST was 640 IU/L, his ALP was 188 IU/L, and his bilirubin remained normal. All three dugs – alogliptin, sulfamethoxazole/trimethoprim, and lansoprazole - were then discontinued. He was seen by dermatology who recommended increasing his dose of prednisolone and also placed him on an anti-allergy drug. Over the following 5 days, his abnormal liver chemistries began to improve although they were still abnormal when he was reported to have been seen last (b) (6) He showed peripheral eosinophilia, and his skin biopsy was quite abnormal.

Comment (LBS): In my view, this is an impressive case of drug-induced liver injury but I would attribute the liver injury first to sulfamethoxazole/trimethoprim and second to lansoprazole, the latter less likely than the former. I am not aware that alogliptin cause an immunoallergic form of drug induced liver injury and therefore would place it third in likelihood, swamped I believe by the greater likelihood that one of the other two drugs was responsible for the liver injury. It would be interesting to have additional follow-up on this case.

TCI2012A05429

This 80 year old man with a suspected diagnosis of hemophagocytic syndrome (?) started treatment with alogliptin on May 8, 2012; no further information regarding this event is provided. It is then stated that he was started on ursodeoxycholoc acid at another hospital without indicating the reason; perhaps it was because he was found to have jaundice and an increase in his aminotransferase levels apparently on July 11, 2012 (the dates reported are confusing). It appears that he stopped treatment with alogliptin on that date. No laboratory values are provided and no information given on what evaluation was done to determine the cause of the liver dysfunction, other than to repeat a presumptive diagnosis of hemophagocytic syndrome. He was apparently also receiving azosemide, allopurinol, and furosemide. His jaundice is then reported to have deepened but again, no values are mentioned. He was given pulsed steroid therapy, but his blood pressure began to decline, becoming "stable." As later reported. He was then reported to have died (b) (6) without ant description of his medical problem, his treatment, the course of the disease, and the circumstances surrounding his death. Importantly, there is absolutely no information regarding the cause of his liver disease.

Comment: This is a glaringly inadequate report surrounding the cause for the liver injury in this patient, the course of the illness, and the basis for his death. There is absolutely no way of establishing even a presumptive diagnosis to identify a cause for the liver disease and of his death. In my view, it is mandatory for the sponsor to provide the needed information, especially since the patient died without being able to determine whether the death was liver-related.

Summary

This consultation involved a review of 17 cases, 15 of which were pre-marketing cases and 2, post-marketing cases. In the former group, 11 were selected based on ALT values of greater than 10 times the upper limit of normal, and 4 based on what is referred to as "biochemical Hy's law cases." It must be emphasized and re-emphasized that the term "Hy's law cases" should be utilized only for persons found to have increased ALT and bilirubin levels with some confidence (at least probably) caused by drug-induced liver injury. We should not use the term "biochemical Hy's Law," and should discourage sponsors from using it. Hy's law **requires** assessment of the probable cause as drug-induced, which is a medical process of differential diagnosis, and cannot be concluded just by statistical methods.

Among 10 cases with only raised aminotransferase values, most had only single sets of abnormal values that were difficult to pinpoint as to cause, some had other causes likely to be responsible for the abnormalities (cardiac disease, perhaps acute hepatitis B, C, or E, gallstone obstruction). Unfortunately, the data provided were regularly quite limited, creating difficulty in reaching a reasonable diagnosis. Indeed, even when the abnormalities were attributed to an acute viral hepatitis infection, the diagnosis had to be taken on good faith because the actual serologic confirmation was not provided.

Among the 5 cases of both ALT and bilirubin elevation, 3 appeared to have other causes for the abnormalities (cardiac disease or gallstone obstruction), whereas one of them (**402/8413-006**) represents, in our view, a possible/probable case of alogliptin hepatotoxicity, or at least in which that cannot be excluded. This patient developed an acute hepatitis presentation approximately 3 months after starting treatment. Serologic testing for hepatitis A, B, C were reported negative (hepatitis E was not evaluated), and the abnormal values subsided after discontinuation of the study drug. Unfortunately, there were important prolonged gaps between testing of the liver panel making it difficult to determine what the sequence of abnormalities really was.

One of the two post-marketing cases was almost certainly a result of drug-induced liver disease but not necessarily a result of alogliptin. The clinical manifestations suggested strongly that it might have been the result of one of two additional drugs received, either sulfamethoxazole/ trimethoprim or lansoprazole. The second case in which the patient developed liver disease together with jaundice was so poorly reported that it is impossible to determine what the cause was for the reported liver disease. Moreover, the patient died without being able to determine whether the liver disease accounted for the death.

Finally, a comment about implicating alcohol as a cause for observed liver abnormalities. It is unusual for an occasional drinker to develop more than a mild increase in AST levels if they happen to have a "weekend binge." Alcoholic hepatitis generally occurs in chronic alcoholism, with recurrent episodes following binges. Moreover, almost always, the AST value exceeds that of the ALT, and the ALT value extremely rarely exceeds 100 U/L. Only a minor fraction of advanced alcoholics, about 15-20%, ever develop serious liver disease, despite drinking maximal amounts of alcohol humanly possible. There is indeed a major factor of dose-related toxicity of alcohol, but also a very important factor of individual susceptibility that is still "idiosyncratic."

Recommendations

1. The recently provided information on cases reported in clinical trials shows that most of the serious liver injury or dysfunction has some other causative explanation than alogliptin-induced, but there still remain cases in which no satisfactory or convincing alternative causative diagnosis was found or could be determined by review of the clinical informationj supplied.

2. We are still concerned about the inadequate investigation or reporting of patients receiving alogliptin after approval (so far, Japan only, but there will be many more if alogliptin is approved in the United States). This is a general problem all over the world, and we realize it will not be solved just by labeling. The sponsor should assume more responsibility for safe use of this drug and advise prescribers to be somewhat cautious in its use, to check liver tests (serum ALT, AST, ALP, BILI) twice before starting it, then monitor ALT at least monthly for six months, and to repeat testing for elevations above 2xULN or 2xB (B, average of pre-treatment baseline values) within a week to confirm. If still elevated or worse, consider temporary interruption of alogliptin therapy and investigate for probable cause using full liver set (ALT, AST, ALP, BILI) and other tests as needed for diagnosis, with prompt reporting of the cases and details about them.

3. That said, we concur with the DMEP reviewers that alogliptin is approvable.

4. It is in the best interest of the sponsor, as well as of patients to be treated, to be cautious and vigilant about the hepatic safety of alogliptin until much more experience with it can be gained worldwide. It not sufficient to call cases “confounded” because there may be some other possible cause of the findings, and certainly no service to the patient.

John R. Senior, M.D. & Leonard B. Seeff, M.D.

cc: V. Pratt, DMEP
A. Egan, DMEP
M. Parks, DMEP
G. Dal Pan, OSE

REFERENCES

Feng J, Zhang Z, Wallace MB, Stafford JA, Kaldor SW, Kassel DB, Navre M, Shi L, Skene RJ, Asakawa T, Takeuchi K, Xu R, Webb DR, Gwaltney SL2nd. J Med Chem. 2007 May 17; 50(10: 2297-3000. [PMID17441705]

Goossen K, Gräber S. Longer term safty of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes: systematic review and meta-analysis. Diabetes Obes Metab. 2012 Apr20;Epub. [PMID 22519906]

Monami M, Dicembrini I, Martelli D, Mannucci E. Safety oof dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. Curr Med Res Opin. 2011 Nov;27 Suppl 3:57-84. [PMID 22016978]

Pratley RE. Alogliptin: a new, highly selective dipeptidyl peptidase-4 inhibiotr for the treatment of type 2 diabetes. Expert Opin Pharmacother. 2009 Feb;10(3):503-12. [PMID19191685]

Seino Y, Miyate Y, Hiroi S, Hirayama M, Kaku K. Efficacy and safety of alogliuptin added to metformin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label, long-term extensión study. Diabetes Obes Metab. 2012 Oct; 14(10):927-36/ [PMID 22583679]

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/s/

JOHN R SENIOR
11/10/2012
Major contribution by Dr. Leonard Seeff

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 # **Supp #**	NDA 22-271 (alogliptin) 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:	*Complete Response*

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 insulinotropic 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**

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ALT > 3 xULN ALT > 5x ULN ALT > 10x ULN	6 (1.1%) 1 (0.2%) 0	23 (1.2%) 7 (0.4%) 2 (0.1%)
Resubmission	**N=4074**	**N=7011**
ALT > 3 xULN ALT > 5x ULN ALT > 10x ULN ALT > 20x ULN	39 (1%) 6 (0.1%) 0 0	71 (1%) 21 (0.3%) 8 (0.1%) 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 N1467	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)

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 hepatocelluar/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 demonstrated 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 postmarking 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).

(b) (4)

Reference ID: 3121835

(b) (4)

(b) (4)

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 (b) (4) major adverse cardiovascular events (MACE) events were reported of which Study 402 contributed (b) (4) 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

(b) (4)

(b) (4)

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 # **Supplement #**	22271 (alogliptin) 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:	*Complete Response*

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.

Reference ID: 3121541

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.

Reference ID: 3121541

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: Septebmer 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 Bourcer: 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:

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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).

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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.

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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/m2	30.5	30.9	29.3	29.6
Mean duration of DM, yrs	7.5	6.9	9.2	9.1
Renal function, MDRD				
Normal	17.2%	18.9%	11.9%	10.7%
Mild	62.5%	65.5%	52.6%	58.0%
Moderate	18.3%	14.4%	28.4%	26.5%
Severe	1.0%	0.6%	2.9%	2.6%
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

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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. (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.

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

(b) (4)

(b) (4)

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

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> 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

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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 hepatoxicity 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

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		or urine about 4 days, abnl labs 3wks	pattern predominating ALT869,AST625, AP1169 bilirubin normal no viral hepatitis reports				
TCI2010A05612	no	2 months	mixed hepatocelluar/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

TC12011A4573 – Narrative as provided by Dr. Seeff

Case TC12011A04573 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

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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.

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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*

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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

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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.

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On [redacted] (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]
- [redacted] (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. [redacted] (b) (4) being the more dismissive of alogliptin causality in most cases, including one patient who had fulimant 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

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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)

[redacted]

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

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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 [redacted] (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 hepatoxicity, (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.

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.

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/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 # Supplement#	NDA 22271 and NDA 22426
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:	*Complete Response*

Reference ID: 3120098

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

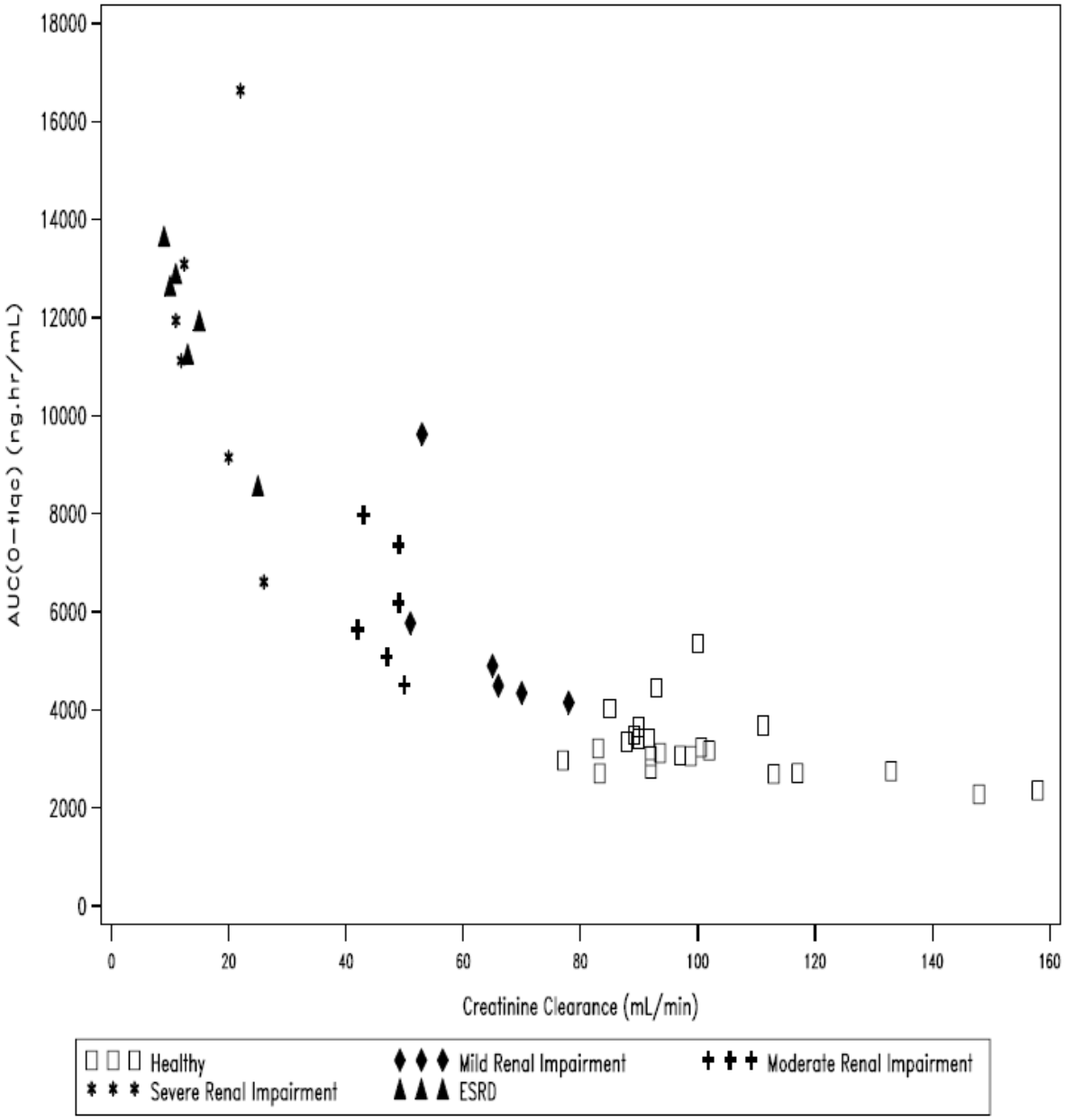
The clinical pharmacology reviewers recommend approval. See the reviews by Drs. Sang Chung and Ritesh Jain for details.

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) ≥3x 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 ≥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. ≥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 ≥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 ≥8.0%. Although the mean baseline HbA1c was only 7.5%, about one-fourth of patients had baseline HbA1c ≥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).

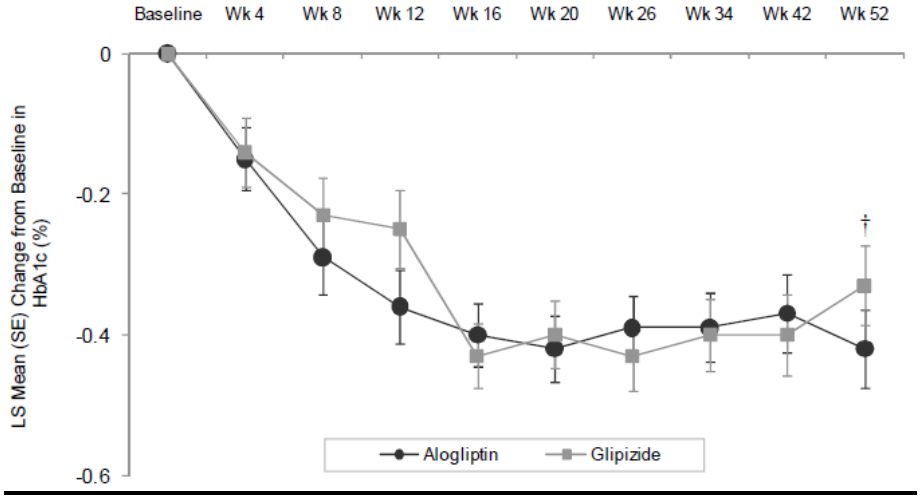
The percentage of patients achieving HbA1c ≤7.0% at Week 52 was comparable in the two treatment groups (49% for alogliptin and 45% for glipizide; p=0.59).

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



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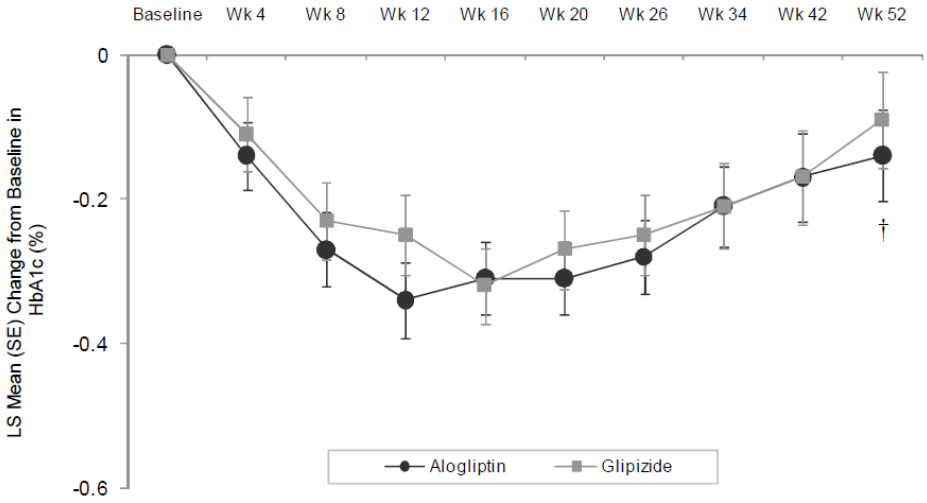
(b) per-protocol population with last-observation-carried-forward



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 ≥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 >2.5x 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 ≥8.5% with ≤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 ≥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 ≥8.5% with ≤0.5% reduction from baseline. In contrast, patients in Study 303 were withdrawn after Week 12 if the HbA1c was ≥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.

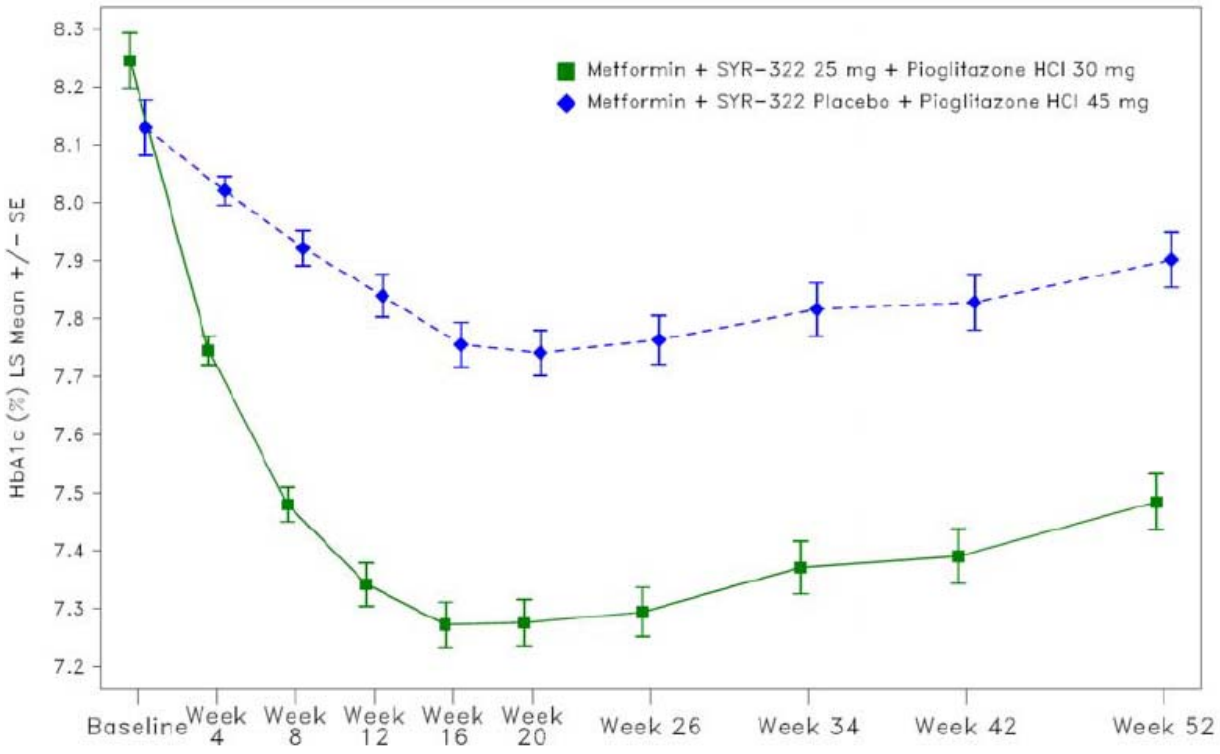
Table 2. HbA1c change from baseline for Study OPI-004 (Adapted from Table 9 in Dr. Janice Derr's biostatistics review)

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.

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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.

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

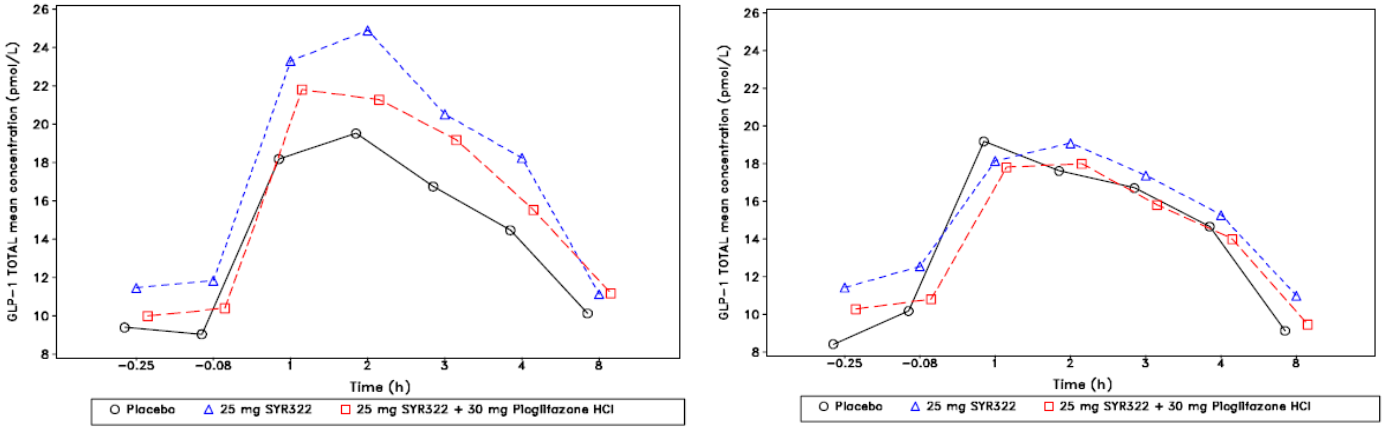


Figure 5. Postprandial active GLP-1 concentrations at baseline (left) and Week 16 (right)

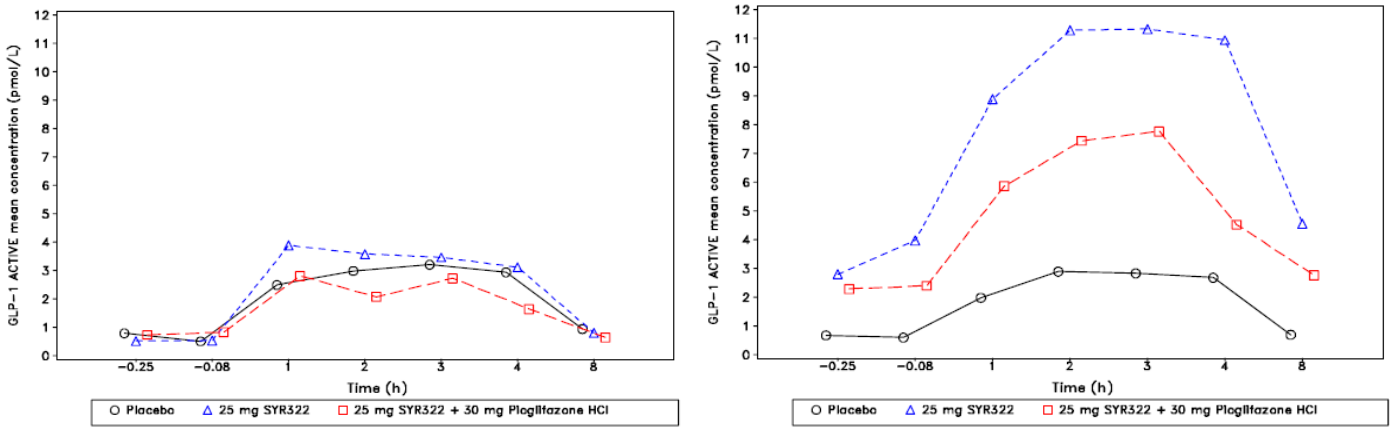
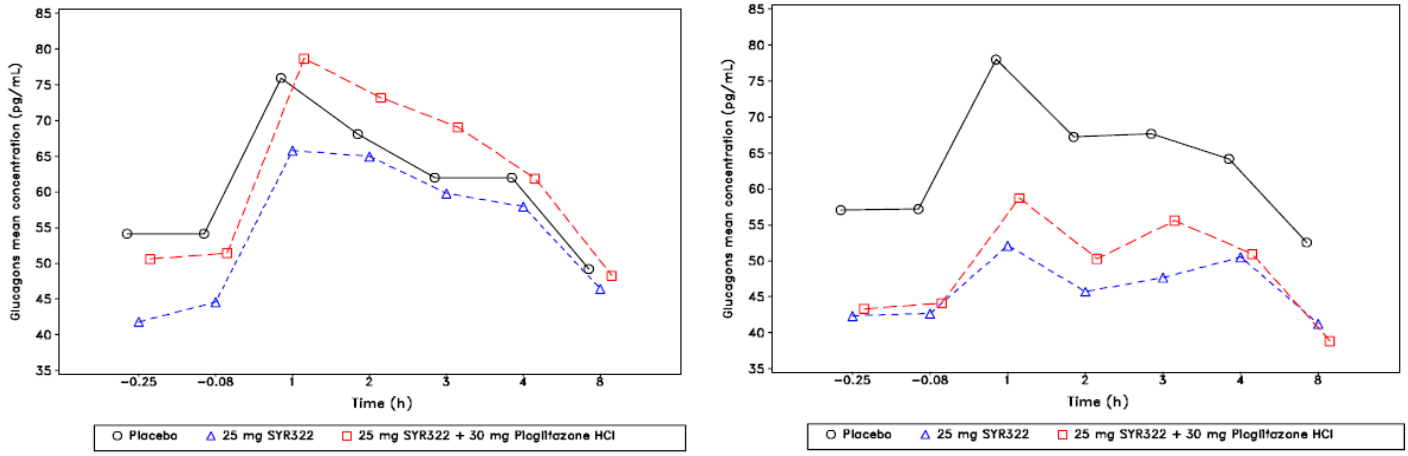


Figure 6. Postprandial glucagon at baseline (left) and Week 16 (right)



Reference ID: 3120098

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).

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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 H_2-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.

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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 ≥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 ≥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 ≥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)

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Table 5. Common adverse events (incidence ≥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 (eGFR ≥60 mL/min), 12.5 mg for patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), and 6.25 mg for patients with severe renal impairment (eGFR <30 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 ≥3x ULN with total bilirubin >2x ULN or if the serum ALT or AST is >8x 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 >5x ULN for more than two weeks or the serum ALT or AST is ≥3x 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)

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(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 (25^{th}-75^{th} 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)

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(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 ≥3x ULN and total bilirubin >2x 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 is 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 (≤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).

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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.**

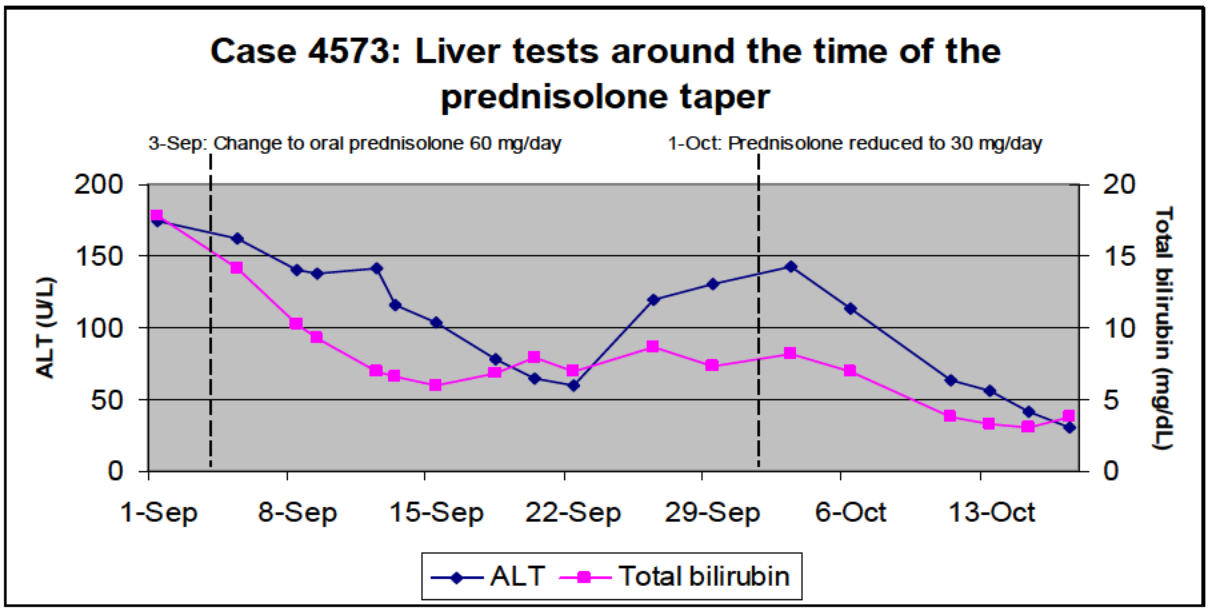
305/5304-055: This 45 year-old man from India had mild pre-treatment serum ALT elevations (up to 46 U/L). The ALT was 85 U/L at Week 4 and continued to increase thereafter, reaching 714 U/L about 2.5 weeks later at which point the patient tested positive for hepatitis E and alogliptin was discontinued. 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.

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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 (b) (6) However, (b) (6) the ALT was 1030 U/L (23x ULN) with a total bilirubin of 1.3 mg/dL. On (b) (6) the ALT was 1025 U/L with a total bilirubin of 2.1 mg/dL (peaking at 2.2 mg/dL on (b) (6)) and a normal alkaline phosphatase. On (b) (6) 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 (b) (6) the ALT was 264 U/L (5.9x ULN) and total bilirubin was 1.2 mg/dL. The serum ALT had normalized on (b) (6) The narrative states that based on subsequent increases in liver tests (the narrative shows a serum ALT of 138 U/L on (b) (6) and 101 U/L on (b) (6)), 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. Dr. (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) **n: 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.

(b) (4)

(b) (4)

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.

(b) (4)

(b) (4)

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 (b) (4) 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.

Reference ID: 3120098

- 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

Reference ID: 3120098

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 glycrrhizin/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)

*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

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

Reference ID: 3120098

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

	MDRD		Cockcroft-Gault	
Shift	**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 >1.5x 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 >1.5x 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 ≥2x 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 ≥3x criterion instead of a ≥2x 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) [redacted]

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) [redacted] he 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) [redacted]

(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) (4)

had isolated violations pertaining to the alogliptin NDA [redacted (b) (4)] 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.

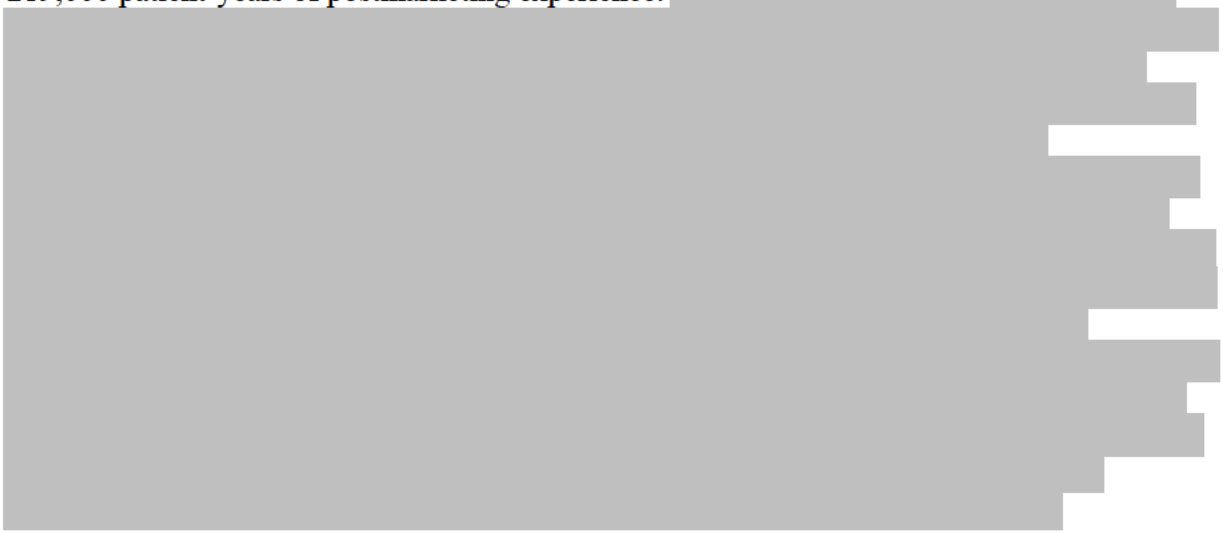
As mentioned previously, Takeda estimates that there are ~219,000 patient-years of postmarketing exposure to alogliptin. This estimate was obtained by dividing the total number of tablets shipped by 365 (365 tablets represent one-patient year of exposure because alogliptin is dosed once-daily). Therefore, 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)

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

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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 TCI2011A04573 and TCI2011A06837 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 [PPARγ] 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 DDP4 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 DDP4 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 Kajiyama 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. Pedtro 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 form 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 ± SE1	Difference in adjusted mean change (95% CI)[1]	P-value
1. HbA1c change from baseline at week 52					
A. FAS/LOCF					
Alogliptin Glipizide	204 201	7.48 (0.686) 7.43 (0.633)	-0.13 (0.055) -0.10 (0.056)	-0.02 (-0.18, 0.13)	–
B. PPS/LOCF					
Alogliptin Glipizide	171 149	7.52 (0.679) 7.44 (0.648)	-0.13 (0.064) -0.07 (0.068)	-0.06 (-0.24, 0.13)	–
2. HbA1c ≤7.0; Week 52; FAS/LOCF					
	N	n (%)	Odds Ratio[2] (95% CI)		P-value
Alogliptin Glipizide	204 201	103 (50.5%) 91 (45.3%)	1.447 (0.898, 2.331)		0.129

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 ≤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 stud (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 PPARγ agonist. Activation of PPARγ 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

	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,

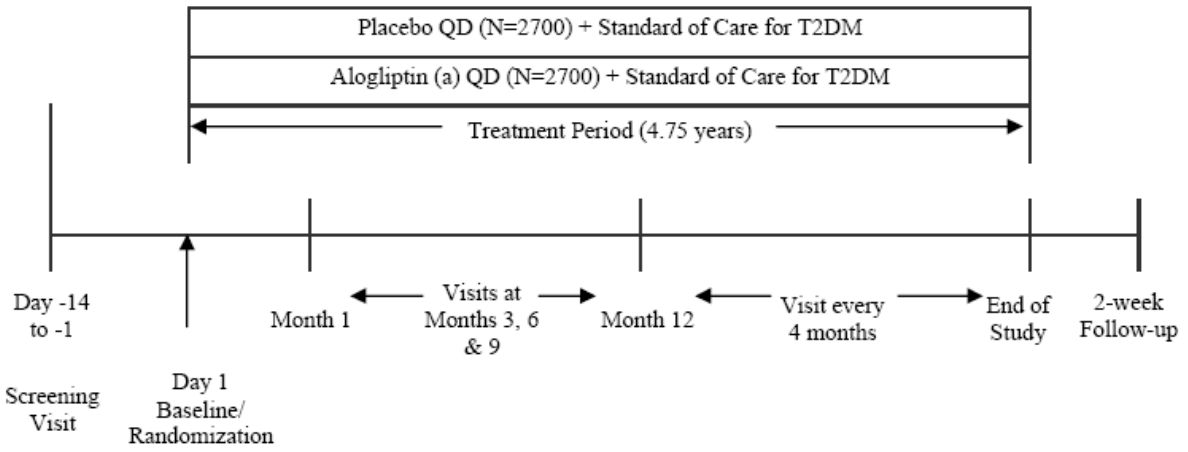
2010, the agency recommended that stent thrombosis be adjudicated using the Academic Research Consortium definitions and that the timing of the events in each treatment group be specified. Although I did not find evidence that the sponsor heeded this particular advice, in the context of the lengthy definitions 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 mg/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)
Procedure	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)
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							
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	

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 ≥2x compared to baseline
- eGFR decreases >50% compared to baseline

Study drug should also be interrupted if pancreatitis is suspected or amylase/lipase are ≥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.

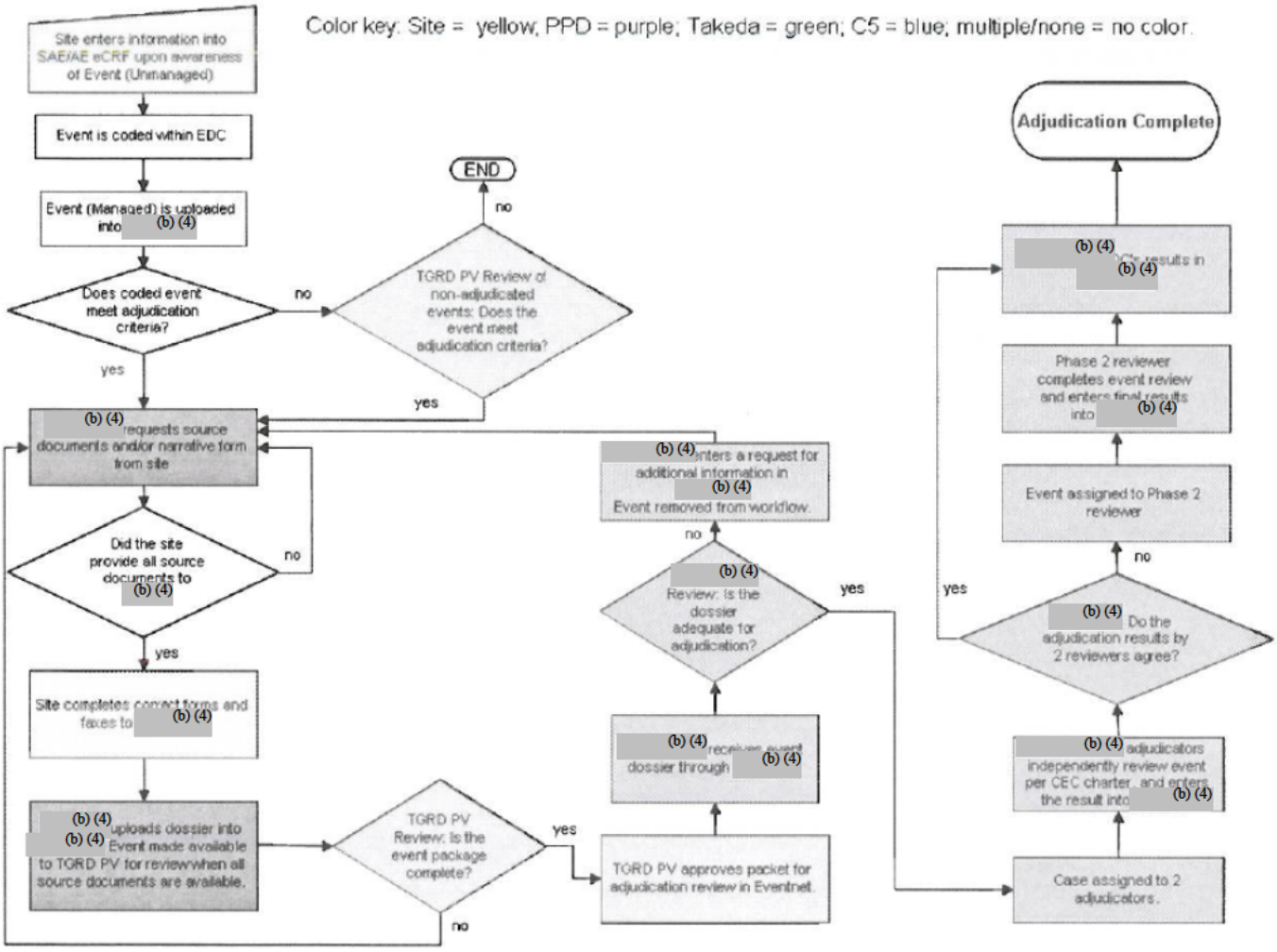


Figure 2. Study 402: CV event adjudication process
Source: CEC charter Appendix 3
Abbreviations: (b) (4)
eCRF=Electronic case report form; EDC=Electronic data capture; (b) (4) (CRO); (b) (4); TGRD=Takeda Global Research & Development

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 ≥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 ≤6.5% or 7.0% and decrease from baseline ≥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) ß-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.

Assessments	Screening Period (Up to 2 weeks)	Washout Period 4 weeks			Treatment Period										Follow-up Period
Week	-6 to -5	-4	-3	-1	Baseline Visit (Day 1)	2	4	8	12	16	20	26	34	42	52 (or ET)	54 (or 2 weeks after ET visit)

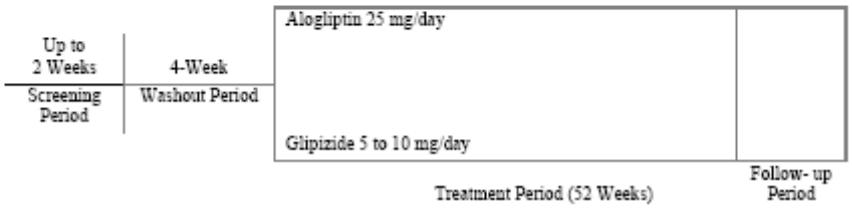


Figure 3. Study 303: Design (Note: There is no washout period for patients who failed only diet and exercise.)

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
Week	(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
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		
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
Week	(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
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)		
Dispense alogliptin 25 mg or matching placebo					X	X (j)	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		
Document drug accountability						X	X	X	X	X	X	X	X	X	X	

Source: CSR 303 Table 9.b

Inclusion criteria:

1. 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 ≥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 ≤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 ≤6.5% or 7.0% and decrease from baseline ≥0.5%, 1.0%, 1.5%, 2.0% at week 52), 2-hour PPG, marked hyperglycemia (FPG ≥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, adioponectin, 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 (≥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 (≥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 ≥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

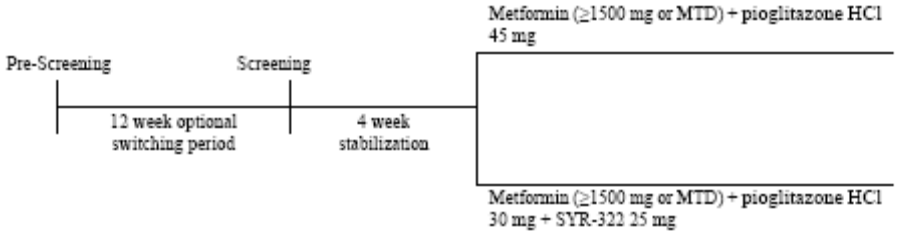


Figure 4. Study OPI-004 design (Note: The pre-screening and switching periods apply only to patients in Schedule B.)

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																

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 ≥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.*

Comment: Subjects with fairly low HbA1c's were enrolled in this non-inferiority trial. This may make it easier to demonstrate non-inferiority. This will be further discussed in the context of the efficacy results.

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 ≤ 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 µg/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 ≥8.5% AND ≤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, adioponectin, 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 interested 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, nataglinide, 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 ≤7.0% or ≤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 ≤7.0% and ≤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.

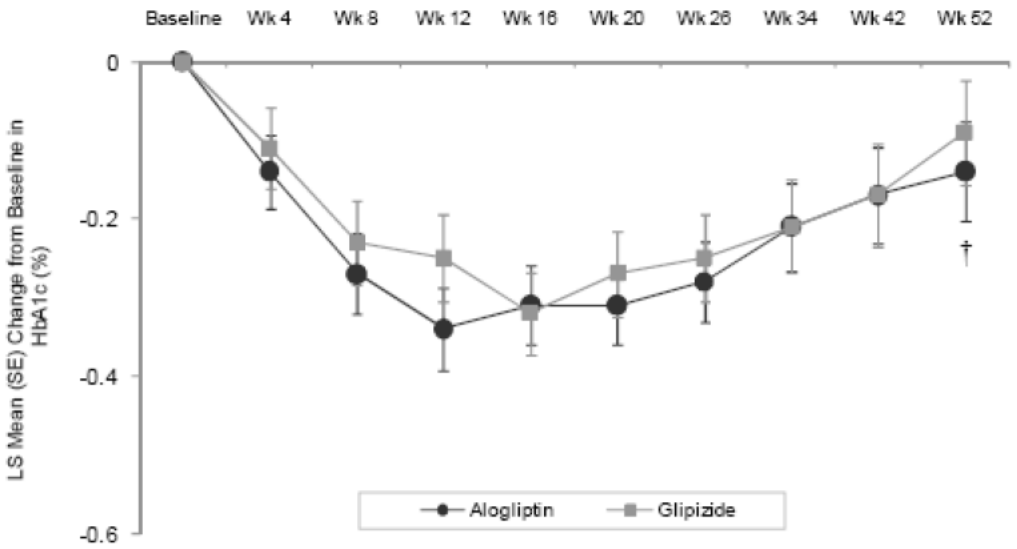


Figure 5. Study 303: LS mean change from baseline in HbA1c (%) (PPS, LOCF)

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. Pedtro 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

			Week 26			Week 52		
Treatment	**N**	**Mean Baseline HbA1c (SD)**	**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

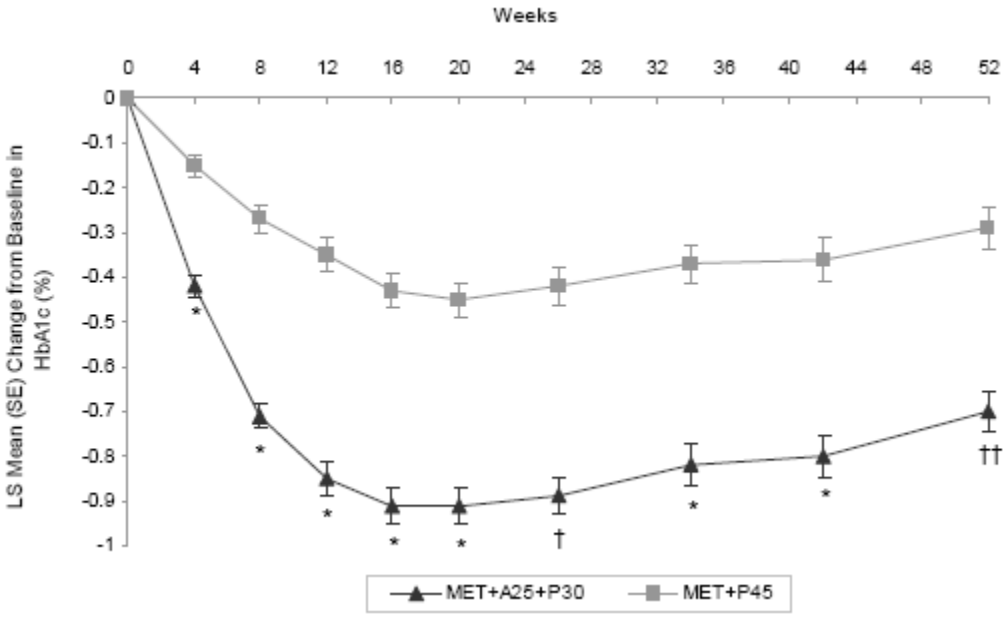


Figure 6. Study OPI-004: LS mean (SE) change from baseline in HbA1c (%) (PPS, LOCF)

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) as the Agency has not included similar language in other labels.
- Removal of the discussion of (b) (4) Lately, we have no longer been permitting such language in diabetes labels
- Removal of the statement about a (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 (mghr/dl) from baseline to week 4 and 16 (FAS)

		Week 4				Week 16			
Treatment	**Baseline mean (SD)**	**N**	**LS Mean Change (SE)**	**LS Mean Diff v Plb (95% CI)**	**LS mean diff v Alo (95% CI)**	**N**	**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 (mghr/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 ≤7.0% and ≤6.5% at endpoint: A greater percentage of alogliptin subjects achieved HbA1c ≤7.0% or 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 ≤7.0% or ≤6.5% at week 52 (FAS)

Clinical Response Measure Statistics	Alogliptin N=222	Glipizide N=219	P-Value
HbA1c ≤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 ≤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 ≤7.0% or ≤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).

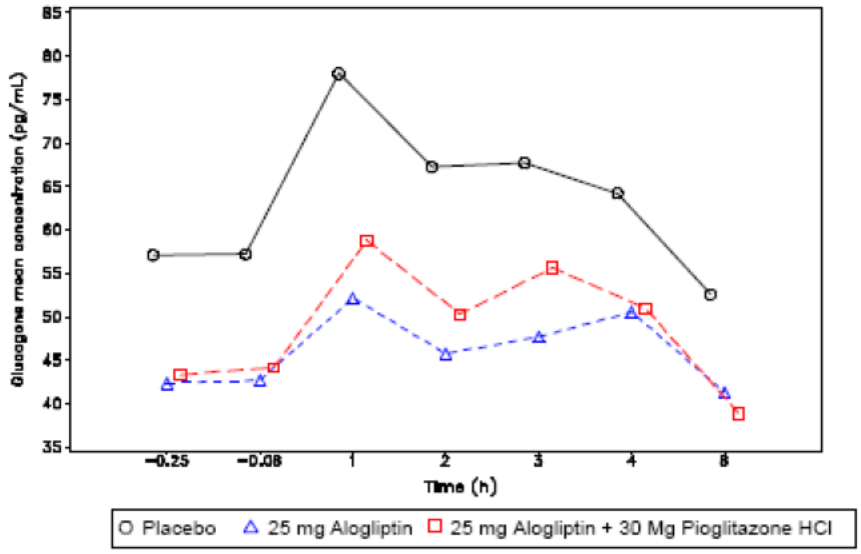


Figure 7. Study 301: Glucagon (pg/ml) postprandial concentrations by week 16 time point (FAS, LOCF)

Source: CSR 301 Figure 11.c

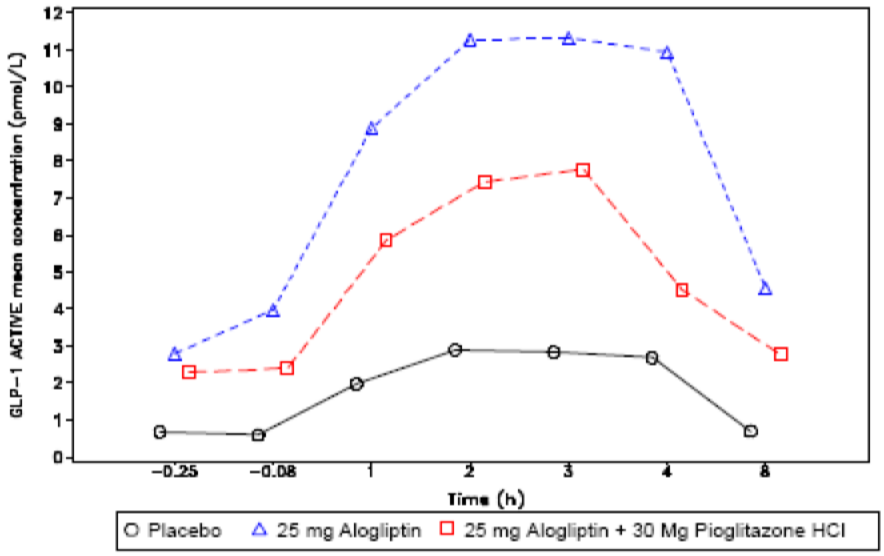


Figure 8. Study 301: Active GLP-1 (pmol/l) postprandial concentrations by week 16 time point (FAS, LOCF)

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).

(b) (4)

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)

	Alogliptin N=222	Glipizide N=219
Subgroup	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 ± SE	Change from baseline Adj. mean ± SE	Difference in adjusted mean change 95% CI	p-value
Study 003 (dose-ranging) – 12-week trial				
42	8.0±0.2	-0.2±0.1	Not reported	
42	7.9±0.2	-0.5±0.1	Not reported	
45	8.0±0.2	-0.6±0.1	Not reported	
43	8.1±0.2	-0.4±0.1	Not reported	
44	8.0±0.2	-0.5±0.1	Not reported	
41	8.2±0.2	0.0±0.1	Not reported	
Study 010 (monotherapy) – 26-week trial				
128	7.9±0.1	-0.6±0.1	-0.6 (-0.8, -0.4)	<0.001
131	7.9±0.1	-0.6±0.1	-0.5 (-0.8, -0.3)	<0.001
63	8.0±0.1	0.0±0.1		
Study 007 (add-on to sulfonylurea) – 26-week trial				
197	8.1±0.1	-0.5±0.1	-0.5 (-0.7, -0.3)	<0.001
201	8.1±0.1	-0.4±0.1	-0.4 (-0.6, -0.2)	<0.001
97	8.2±0.1	0.0±0.1		
Study 008 (add-on to metformin) – 26-week trial				
203	7.9±0.1	-0.6±0.1	-0.5 (-0.7, -0.3)	<0.001
210	7.9±0.1	-0.6±0.1	-0.5 (-0.7, -0.3)	<0.001
103	8.0±0.1	-0.1±0.1		
Study 009 (add-on to pioglitazone) – 26-week trial				
195	8.0±0.1	-0.8±0.1	-0.6 (-0.8, -0.4)	<0.001
195	8.1±0.1	-0.7±0.1	-0.5 (-0.7, -0.3)	<0.001
95	8.0±0.1	-0.2±0.1		
Study 011 (add-on to insulin) – 26-week trial				
126	9.3±0.1	-0.7±0.1	-0.6 (-0.8, -0.4)	<0.001
130	9.3±0.1	-0.6±0.1	-0.5 (-0.7, -0.3)	<0.001
126	9.3±0.1	-0.1±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.

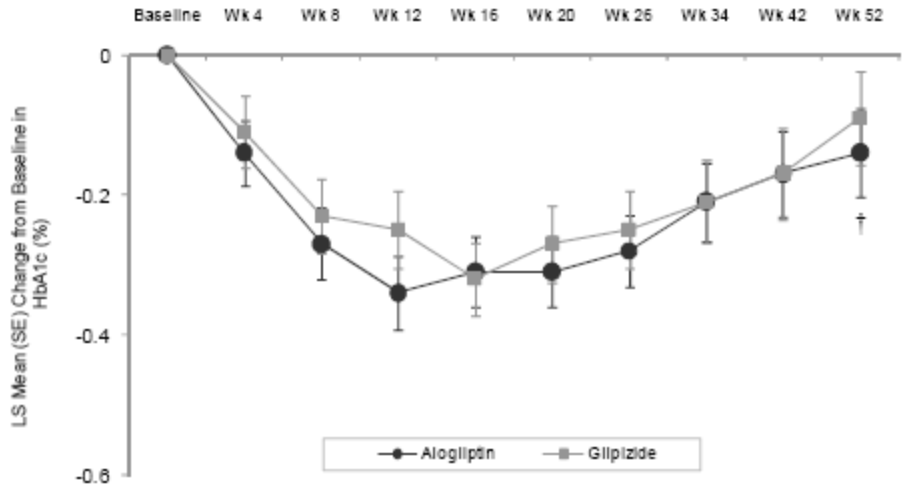


Figure 10. Study 303: Change in HbA1c from baseline (PPS)

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 form 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

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. 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 interested 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 TCI2011A04573 and TCI2011A06837 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 form 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)

	n/N (%) of Subjects		
Disposition Category	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	Number (%) of Subjects: 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	Number (%) of Subjects: 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.

Reference ID: 3095059

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

As described in section 2.4Important 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

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

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

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.

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=principle 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

	Number (%) of Subjects					
	Original NDA			NDA Resubmission		
SOC Preferred Term	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

	Number (%) of Subjects					
	Original NDA			NDA Resubmission		
SOC Preferred Term	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)

	Number (%) of Subjects [Events per 100 Subject-Years]			
MedDRA SMQ	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 [redacted] red wheals, itching, and urticaria developed in the lumbar region. On [redacted] 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 37.7º 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 [redacted] when she was discharged.
- TCI2011A05420: 74 year old Japanese female started alogliptin on September 16, 2011. On [redacted] she had a generalized rash (urticaria) and alogliptin was discontinued. On [redacted] she visited the hospital. On [redacted] the event was resolving and a drug-induced lymphocyte stimulation test (DLST) was to be performed.
- TCI2011A04779: 63 year old male started alogliptin around [redacted] 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 (b) (6) 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 ≥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)

- TCI2011A05092: A middle-aged female was switched from vildagliptin to alogliptin. Ten days later, erythema exudativum mutiforme developed on her whole body. Alogliptin was discontinued. The event resolved. Vildagliptin was restarted without any problems. Lymphocyte transformation test was positive for alogliptin.
- TCI2011A05698: 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.
- TCI2011A06360: 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)

	Number (%) of Subjects		
Preferred Term	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)
Seborrhoeic dermatitis	3 (0.1)	2 (0.1)	4 (0.1)
Acarodermatitis	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, pruritis, 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. Gastroscopy 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 1st 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)

	Number (%) of Subjects		
Preferred Term	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.

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)

	Number (%) of Subjects		
Preferred Term	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)

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)

	Number (%) of Subjects		
Preferred Term	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 facture AEs (Alogliptin/pioglitazone controlled phase 3 studies)

	Number of Subjects (%)		
Preferred Term (a)	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)

	Number (%) of Subjects		
Event Category	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

	Alogliptin N=222		Glipizide N=219	
Hypoglycemia Episodes	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) 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.

(b) (4)

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)

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)

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 ≥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

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: [redacted] (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 ≥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)

	Number (%) of Subjects					
	Original NDA			NDA Resubmission		
SOC Preferred Term	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		>3 xULN
	Other studies: 32.0 – 72.0		
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		>3 xULN
	Other studies: 5.0 – 29.0		
Hematocrit/PCV (%)	M: 37.0 – 51.0	<0.8 x baseline	
	F: 33.0 – 47.0		
Hemoglobin (g/dl)	M: 12.5-17.0	<Baseline – 3 g/dl	
	F: 11.0-15.5		
Lactic dehydrogenase (mu/ml)	10.0 – 100.0		>3 xULN
Lymphocytes (%)	12-46		
Microablumin/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	<0.8 x baseline	
	F: 3.7 – 5.2		
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		>10.5
	F: 2.0 – 6.0		>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	$<2 \times 10^3/mm^3$	$>20 \times 10^3/mm^3$

*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 TCI2011A04573 (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)

	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline			During Treatment		
Parameter (Criterion)	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 (>20×ULN)	0	0	0	0	1 (<0.1%) [0.0]	2 (<0.1%) [0.1]
ALT (>10×ULN)	2 (<0.1%)	3 (0.1%)	3 (<0.1%)	0	6 (0.1%) [0.2]	8 (0.1%) [0.2]
ALT (>8×ULN)	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 (>5×ULN)	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 (>3×ULN)	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

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 in 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. [redacted] 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. [redacted] Unblinded Assessment	Dr. [redacted] 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

Biochemical Hy's Law Postmaketing 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 glimepride 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. Rabeprozole 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×ULN)	16 (0.6)	15 (0.5)	17 (0.3)
Albumin (<2.5 g/dL)	0	0	0
Serum creatinine			
>1.5×Baseline	32 (1.2)	46 (1.4)	57 (1.1)
>1.5×Baseline and >ULN	20 (0.7)	22 (0.7)	27 (0.5)
>ULN with >0.3 mg/dL increase from Baseline	59 (2.1)	73 (2.2)	88 (1.8)
≥2× 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×baseline	5 (1.2)	9 (1.0)	20 (1.3)
>1.5×baseline and >ULN	0	4 (0.4)	6 (0.4)
>ULN with >0.3 mg/dL increase from baseline	3 (0.7)	6 (0.6)	16 (1.1)
≥2× 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)
≥1.25×Baseline	53 (31.0)	133 (33.9)	175 (28.7)
≥1.5×Baseline	41 (24.0)	100 (25.5)	133 (21.8)
≥2×Baseline	23 (13.5)	65 (16.6)	88 (14.4)
≥3×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)

	Number (%) of Subjects		
Preferred Term	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)

	Number (%) of Subjects With ≥1 Markedly Abnormal Result					
	Baseline			During Treatment		
Parameter (Criterion)	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×LLN)	0	0	0	2 (0.1)	2 (0.1)	2 (<0.1)
Calcium high (>1.2×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×LLN)	2 (0.1)	0	0	0	2 (0.1)	3 (0.1)
Protein, total (>1.2×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)

	Number (%) of Subjects		
Preferred Term	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)

	Number (%) of Subjects With ≥1 Markedly Abnormal Result					
	Baseline			During Treatment		
Parameter (Criterion)	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; $<50\times10^3/mm^3$)	0	2 (0.1)	2 (<0.1)	1 (<0.1)	7 (0.2)	9 (0.2)
Platelet count (high; $>600\times10^3/mm^3$)	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; $<2\times10^3/mm^3$)	0	1 (<0.1)	2 (<0.1)	1 (<0.1)	4 (0.1)	6 (0.1)
White blood cell count (high; $>20\times10^3/mm^3$)	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)

	Number (%) of Subjects		
Preferred Term	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)

	Number (%) of Subjects		
Preferred Term	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).

Reference ID: 3095059

(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)

	n/N		
Variable	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)

	n/N (%) of Subjects With ≥1 Abnormal Measurement					
	Baseline			During Treatment		
Variable (Criteria)	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 Previous Study 010	Alogliptin 12.5 mg (8 days) Alogliptin 25 mg (182 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.
012/258-7005(a) 40/White Previous Study 007	Alogliptin 25 mg (165 days) Alogliptin 25 mg (182 days)	Barrier method	Positive pregnancy test on 02 March 2007 (Day 166 of Study 012). Pregnancy outcome unknown.
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 ≥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". (b) (4) I agree with the requested waiver. 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 hepatotoxocity, 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

	n/N (%) Subjects With AEs Leading to Study Drug Discontinuation					
		Alogliptin				
Study	Placebo	6.25 mg	12.5 mg	25 mg	50 mg	Comparator (a)
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)

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

metformin	efficacy, safety study with metformin				

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.

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/s/

VALERIE S PRATT
02/29/2012

HYLTON V JOFFE
02/29/2012
Please see CDTL memorandum.

Medical Officer Review
Division of Metabolism and Endocrinology Products

NDAs 22-271 & 22-426
Name of drugs: Alogliptin & alogliptin/pioglitazone FDC
Sponsor: Takeda
Relevant INDs: 69,707 & 73,193
Indication: Type 2 diabetes mellitus (T2DM)

Type of Meeting: Type B, End of Review (EOR)
Date of Submission: January 21, 2010
Date of Meeting: February 23, 2010

Medical Reviewer: Valerie Pratt, M.D.
Medical Team Leader: Hylton Joffe, M.D.

Background: The sponsor submitted NDAs 22-271 and 22-426 for alogliptin and alogliptin/poiglitazone (A/P) FDC, respectively, for the treatment of T2DM. On June 26 and September 2, 2009, respectively, the applications received a complete response for the following clinical reasons:

- A numerical imbalance in serious cardiovascular (CV) adverse events (AEs), not favoring alogliptin therapy
- The lack of controlled data beyond week 26
- A 70% increase in the mean area under the time-alogliptin concentration (AUC) curve in subjects with mild renal impairment compared to subjects with normal renal function in study SYR-322-006
- In NDA 22-426, greater incidences of elevation in BUN, serum creatinine, and urinary albumin/creatinine ratios and greater shifts to mild or moderate renal impairment

The purpose of this EOR meeting is to obtain agreement on the following:

- Content of each NDA resubmission
- CV analyses of
    - CV outcomes study, SYR-322_402 (402)
    - A pooled study of all controlled phase 2 and 3 studies
- Safety updates for alogliptin and A/P FDC tablets

Notes:

- The sponsor is in the process of amending CV protocol 402 and the case report form based on our January 4, 2010 comments. Comments that affect the statistical analysis plan (SAP) for study 402 or safety updates are not reflected in this submission, although applicable changes will be made prior to finalizing the SAPs.

- In February 2010, the sponsor emailed an additional draft table shell (153342_13Jan2010 for study 402) and rationale to be reviewed in conjunction with question 6. They are reviewed below.

Meeting Package Summary: The sponsor plans to resubmit the alogliptin and A/P NDAs in parallel. Since the submission of the original NDAs, 4 controlled clinical studies (3 of which are 52 weeks or longer in duration) have been completed or initiated and 1 open label extension study remains ongoing.

- SYR-322_301: Ongoing, randomized, double blind, placebo controlled, 16 week study evaluating alogliptin and alogliptin coadministered with pioglitazone versus placebo on postprandial lipids in subjects with T2DM. A total of 71 subjects were randomized to either alogliptin 25 mg daily, coadministration of alogliptin 25 mg and pioglitazone 30 mg daily, or placebo. This study should be completed this year. Data from this study will be included in the alogliptin and A/P NDA resubmissions.
- SYR-322_303: Ongoing, randomized, double blind, active controlled, 52 week study evaluating alogliptin versus glipizide in elderly subjects (65-90 years) with T2DM. A total of 441 subjects were randomized to receive 25 mg alogliptin daily or 5 mg glipizide daily (titrated for inadequate control to 10 mg daily). This study should be completed this year. Data from this study will be included in the alogliptin NDA resubmission.
- 01-06-TL-322OPI-004: Recently completed, phase 3, double blind, 52 week study that evaluated the addition of alogliptin versus the titration of pioglitazone in T2DM subjects receiving metformin/pioglitazone combination therapy. A total of 404 subjects received alogliptin 25 mg in addition to pioglitazone 30 mg and metformin ≥1500 mg or maximum tolerated dose (MTD) and 399 subjects received pioglitazone 45 mg and metformin ≥1500 mg or MTD. Data from this study will be included in the alogliptin and A/P NDA resubmissions.
- SYR-322_402 (402): Long term CV outcomes study that was recently initiated to satisfy the requirements of the CV guidance. This is a randomized, double blind, placebo controlled study evaluating the incidence of major adverse CV events (MACE) following treatment with alogliptin compared with placebo in subjects with T2DM and acute coronary syndrome. Approximately 2700 subjects will receive alogliptin (6.25, 12.5 or 25 mg QD based on renal function) and 2700 subjects will receive placebo, in addition to standard of care. The overall duration of this study is dependent on reaching the predefined number of MACE vents, although the maximum length of follow up is expected to be approximately 4.75 years. The median length of study participation for each subject is estimated to be 2 years. A maximum of 4 interim analyses will be conducted in sequential order after approximately 80, 100, 125, and 150 adjudicated events within the primary MACE composite have occurred. Interim data from this study will be included to support the safety of alogliptin.
- SYR-322-OLE-012: Ongoing, 4 year, open label extension study. Interim data from this study was included in the original NDA and 120-day safety update for alogliptin. This study will not be completed at the time of the resubmission, however, serious adverse event (SAE) summary tables and corresponding

narratives for deaths and SAEs for all subjects who had a serious adverse event since the time of the 120-day safety update will be provided in the alogliptin NDA resubmission.

At the time of resubmission, the sponsor proposes that the safety and efficacy of alogliptin and A/P will be supported by 12 phase 2 and 3 controlled studies (including the 4 described above). The clinical overview and summary sections of the NDA resubmission will be updated with results from these new clinical studies. A safety update will summarize safety results from the 4 new studies (301, 303, 402, OPI-004) combined with the phase 2 and 3 controlled studies previously included in the integrated analysis of safety (IAS) (003, 007, 008, 009, 010, and 011), OPI-001, and -002. Data from phase 1 and the ongoing open-label extension study will not be included.

Please refer to Appendices 2 and 3 for the proposed structure of the alogliptin and A/P NDA resubmissions.

Safety Analyses: In the alogliptin NDA resubmission integrated analysis of safety (IAS), study treatment groups will be described as placebo, active comparator, alogliptin 12.5 mg, and alogliptin 25 mg, as well as all alogliptin (6.25, 12.5, 25, 50, and 100 g) and all comparators (i.e. placebo and active). Analyses will be similar to those in the original filing with the following exceptions:

- Cumulative exposure will be summarized for the phase 2 and 3 controlled studies overall and by study
    - *Internal comment: You should summarize exposure for subjects with mild, moderate, and, severe renal impairment.*
    - According to our meeting minutes of the April 27, 2009 Type A meeting, the sponsor estimated that 400-500 patients with moderate renal impairment will have 1 year of exposure to study medication and 80-100 patients with severe renal impairment will have 1 year of exposure to study medication. These numbers represent all exposure, not just alogliptin-exposed patients. We later requested that at least 100 subjects with severe renal impairment have at least 1 year of exposure to alogliptin. However, according to the meeting package, the sponsor anticipates that 400-500 subjects with moderate renal impairment and 80-100 subjects with severe renal impairment will be enrolled in study 402 and exposed for at least 1 year. In the event that this study does not evaluate a sufficient number of subjects with severe renal impairment to satisfy our request, the sponsor plans to conduct a supplementary postmarketing safety study in subjects with severe renal impairment.
        - *Internal comment: According to the April 27, 2009 meeting minutes which were finalized on August 26, 2009, the sponsor stated that at the time of the intermediate analysis that satisfies 1.8, there will not be 1 year of exposure data for all renal impairment patients. However, when study 402 is completed, the sponsor estimated that 200-250 subjects with moderate renal impairment should be exposed to alogliptin for 1 year and at least*

100 subjects with severe renal impairment should be exposed to alogliptin for at least 1 year. The sponsor now states that there may not be 1-year data for 100 patients with severe renal impairment from the pre-approval studies and is proposing a supplemental postmarketing study, if needed (see Question 18 and the associated discussion in the meeting minutes).

- Summary tables will be generated for medical history and concurrent conditions, including subsets of CV history, conditions, and medications
- AEs of special interest: potential cutaneous drug reactions (PCDR, previously used definition), angioedema standardized MedDRA Query (SMQ), acute pancreatitis SMQ, and malignancies SMQ. (The CV-related AE cluster will be replaced by the MACE analyses.)
    - *Internal comment: Cutaneous toxicity, including ulceration, necrosis, mixed cell inflammation, hemorrhage, edema and granulation tissue, has been observed with some other DDP4 inhibitors. However, it 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.*

      Your definition of PCDR events includes high level group terms in the immune system disorders SOC and skin and subcutaneous disorders SOC from MedDRA. However, the only ulcer term included is "venous ulcer pain." Although alogliptin does not appear to be associated with cutaneous toxicity in humans, you should include this PCDR events as AEs of special interest and broaden its search criteria to include terms related to ulceration, necrosis, mixed cell inflammation, hemorrhage, edema and granulation tissue.
    - *Internal comment: In addition to describing events of acute pancreatitis as AEs of special interest, please also provide data on serum amylase and lipase and imaging results obtained in patients with suspected or confirmed pancreatitis.*
- Serious special interest AEs and special interest AEs leading to discontinuation will be summarized in addition to the summaries of treatment-emergent adverse events by groupings that were included in the original filing.
- AEs will also be summarized by Baseline and Endpoint renal status.
- In the original submission, the long-term safety of alogliptin was based on 12-month data from the open-label extension study (SYR-322_OLE-012). For the resubmission, long-term safety will be based on 3 controlled studies (303, 402,

and OPI-004), which will provide controlled exposure for 12 months and up to 18 months for some subjects.

- With regard to laboratory evaluations, serum creatinine and estimated glomerular filtration rate (eGFR) estimated by the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) equations will be summarized in an additional table to evaluate renal function. In addition, shift tables will be used to summarize the number of subjects with normal renal function and mild, moderate, and severe renal impairment at baseline and their corresponding renal function at each post-baseline visit and at endpoint for both the Cockcroft-Gault and MDRD equations. Also, 2 changes will be made to the markedly abnormal criteria for laboratory values. The markedly abnormal criterion for serum creatinine will change from >1.5 x Baseline to >1.5 x Baseline AND >upper limit of normal (ULN) and a criterion will be added to evaluate alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3 x ULN in conjunction with total bilirubin >2.0 mg/dL.
    - *Internal comment: You define markedly abnormal serum creatinine as >1.5x baseline and >ULN. However, in the previous NDA submission, it was defined as >1.5x baseline. Please analyze renal data using the definition used in the original NDA (i.e. >1.5x baseline). If you wish to also analyze renal data with the revised definition, you may.*

In addition, both the alogliptin and A/P NDA resubmissions will evaluate the following AEs of special interest:

- Infections and infestations (SOC)
- Hepatotoxicity will be evaluated based on DILI Guidance and will include changes from Baseline to Endpoint, incidences of markedly abnormal results, and shift analyses for total bilirubin, AST, ALT, and gamma glutamyl transferase (GGT).
- Renal safety will be evaluated based on changes from baseline to endpoint, incidences of markedly abnormal results, and shift analyses for serum creatinine and eGFR using the Cockcroft-Gault and MDRD equations and the incidence of renal dialysis and kidney transplant.

In the A/P NDA resubmission, the safety update will include data from 4 phase 3 controlled trials (OPI-001, -002, -004, and study 301) that will be pooled into an integrated safety database ("phase 3 controlled studies"). Study groups will be the following: alogliptin, pioglitazone, and A+P. In some tables, data will also be summarized by alogliptin dose.

Internal comment: The sponsor should clarify why it is not including study 009 (alogliptin as add-on combination therapy to pioglitazone) in the integrated safety analysis for the A/P FDC NDA.

The planned analyses are similar to that conducted for the original filing with exceptions as follows: (Please also see comments above, as most also apply to the A/P NDA resubmission.)

- Cumulative exposure will be summarized for the phase 3 controlled studies overall and by study.
- Prior and concomitant CV medications will be summarized as subsets of the overall displays of prior and concomitant medications. CV medical histories and concurrent CV conditions will be summarized as subsets of the overall displays of medical histories and concurrent conditions.
- The adverse event "clusters" presented in the original filing will be replaced with the following groupings of special interest adverse events:
    - PCDR (defined as in the original filing).
    - Angioedema SMQ.
    - Acute pancreatitis SMQ.
    - Malignancies SMQ (narrow scope terms only).
    - Cardiac failure SMQ.
    - Edema (defined as in the original filing).
    - Weight gain (defined as in the original filing).
    - Bone fracture (defined as in the original filing).
- Serious special interest AEs and special interest AEs leading to discontinuation will be summarized in addition to the summaries of treatment-emergent adverse events by groupings that were included in the original filing.
- With regard to laboratory evaluations, serum creatinine and eGFR estimated by the Cockcroft-Gault and MDRD equations will be summarized in an additional table to evaluate renal function. In addition, shift tables will be used to summarize the number of subjects with normal renal function and mild, moderate, and severe renal impairment at baseline and their corresponding renal function at each post-baseline visit and at endpoint for both the Cockcroft-Gault and MDRD equations. Also, 2 changes will be made to the markedly abnormal criteria for laboratory values. The markedly abnormal criterion for serum creatinine will changed from >1.5 x Baseline to >1.5 x Baseline AND >ULN and a criterion will be added to evaluate AST >3x ULN in conjunction with total bilirubin >2 mg/dl.

Narratives: The alogliptin NDA resubmission will include patient narratives for events that occurred during studies 101, 103, 301, 303, and 402 and the alogliptin/pioglitazone FDC NDA resubmission will include patient narratives for events that occurred during study OPI-004. Narratives for deaths and other serious adverse events that occurred in the ongoing open-label extension study (012) since the alogliptin 120-day update will be included in module 5 of the alogliptin resubmission. The following narratives will be provided and presented in a similar format as in the original NDA submissions:

- Required Narratives (will be included in the clinical study reports):
    - Deaths.
    - Other serious adverse events.
    - Adverse events that led to study drug discontinuation.
- Others Narratives Previously Requested by FDA (will be included in module 5):
    - ALT/AST laboratory values >3x ULN.
    - Creatine phosphokinase (CPK) laboratory values >5x ULN (CPK was measured only in Study SYR-322_402).
    - Adverse events of pancreatitis.

With regard to other special interest adverse events (i.e. infections, skin reactions, angioedema, malignancy, and renal safety), the sponsor plans to only provide narratives for those subjects who have serious adverse events as limited information will be available for non-serious events. These will be included as part of the SAE narratives in the individual study.

Internal comment: Please provide links to the narratives in the study reports from summary tables and line listings.

For each of the new controlled studies supporting the NDA resubmissions (i.e. 101, 103, 301, 303, 402, and OPI-004), patient narratives will be provided for the events that are agreed upon in Question 11. As an ongoing study, eCRFs from Study 402 (CV outcomes) will not be included in the NDA resubmission; however, for each of the completed studies (101, 103, 301, 303, and OPI-004), the patient narratives will be accompanied by the respective patient eCRF.

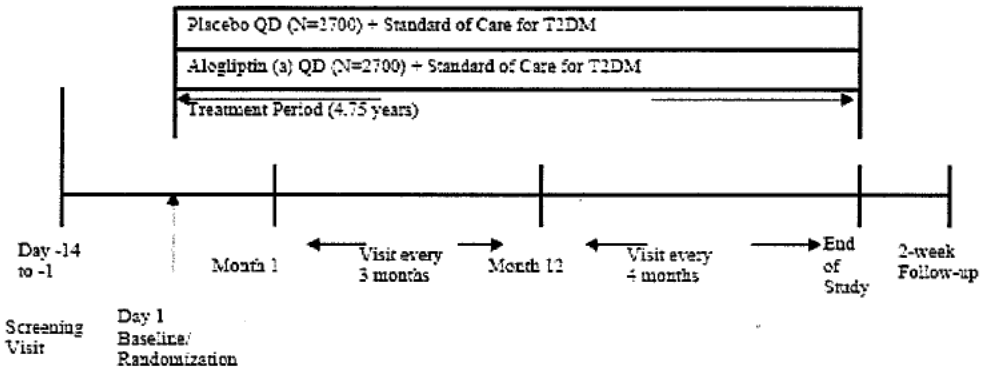
Long-term Safety: The long-term safety of alogliptin will be supported by an integrated analysis of subjects with at least 1-year (defined as 335 days) of exposure to alogliptin from 3 controlled, clinical studies. This analysis will include data from Studies 303, OPI-004, and 402 and will evaluate all adverse events and serious adverse events that occurred in this population as well as adverse events and serious adverse events that occurred in this population with an onset time greater than or equal to 1 year. At the time of the resubmission, controlled data for at least 500 subjects exposed to alogliptin for a minimum of 1 year will be included in this analysis.

Note: The complete response letter for the alogliptin NDA required the sponsor provide controlled data for at least 500 subjects with at least 1 year total exposure to alogliptin.

Internal comment: In your long-term safety analysis, you define 1 year exposure to alogliptin as 335 days. Please also include the number of patients exposed to ≥365 days (a standard year).

Cardiovascular Safety: Study 402 was designed to evaluate MACE. Deaths and adverse events that are potentially MACE in this study will be adjudicated by an independent Cardiovascular Endpoints Committee (CEC) to determine which events to include as MACE in analyses.

Study 402. 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 on the basis of changes in renal function.

Results for the primary endpoint at the time of the interim analysis for assessing non-inferiority will be summarized in the alogliptin resubmission. The primary endpoint is the primary MACE composite of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke. The secondary endpoint is the secondary MACE composite of CV death, nonfatal MI, nonfatal stroke, and urgent revascularization due to unstable angina. The statistical tests for the primary and secondary MACE composite will be conducted in a fixed, pre-specified ordering for the following 4 null hypotheses:

- H01: The hazard ratio of the primary MACE composite is ≥ 1.8 following treatment with alogliptin compared with placebo.
- H02: The hazard ratio of the primary MACE composite is ≥ 1.3 following treatment with alogliptin compared with placebo.
- H03: The hazard ratio of the secondary MACE composite is ≥ 1.0 following treatment with alogliptin compared with placebo.
- H04: The hazard ratio of the primary MACE composite is ≥ 1.0 following treatment with alogliptin compared with placebo.

Each of the 4 null hypotheses will be tested at the 1-sided 2.5% false-rejection rate. Each hypothesis is tested only if all previously tested hypotheses have been rejected. As a result, the principle of closed testing implies that the overall 1-sided false-rejection rate of the study is maintained at 2.5%.

The primary and secondary endpoint will be analyzed using Cox proportional hazards (CPH) models of the respective composites with treatment as the single factor, stratified by screening renal function (normal renal function/mild renal impairment vs. moderate/severe renal impairment including ESRD) and country.

Null hypotheses H01 and H02 will be tested using group sequential methods and separate O'Brien-Fleming spending functions. Testing for each hypothesis will be conducted using a sequence of upper bounds of 1-sided repeated confidence intervals (CIs) for the true hazard ratio (alogliptin to placebo) derived from the CPH models with critical values chosen to maintain overall simultaneous coverage probabilities of 97.5%.

Null hypotheses H03 and H04 will be tested using conventional (not repeated) 1-sided 97.5% CIs for the true hazard ratio (alogliptin to placebo) derived from CPH models for the primary and secondary endpoints fit at the time H02 is rejected. Statistical superiority of alogliptin to placebo for the respective endpoint will be claimed if a null hypothesis is rejected.

One listing of all investigator-reported CV events identified by a search of CV preferred terms will be provided. The listing will denote the following:

- Investigator-reported CV events that were adjudicated by the CEC to be MACE.
- Investigator-reported CV events that were judged not to be MACE by the CEC.

Note: This approach differs from the July 22 guidance which recommends 3 listings as follows:
1. All investigator-reported CV events that were also adjudicated by the CEC to be events
2. All investigator-reported CV events that were not thought to be events by the CEC
3. All CEC-adjudicated CV events that were not considered to be events by the investigator
As discussed at the January 14, 2010 teleconference, an investigator-endpoint report form will not be used during this study because investigators will not be responsible for assessing whether an event meets a specific endpoint; this will be the role of the CEC only.

Internal comment: At the meeting, we will ask the sponsor to clarify which events are sent to the CEC committee. For relevant events (e.g. events reported by the investigator as MI or stroke) that are not coded as MI or stroke by the CEC, the sponsor should submit an explanation for those AEs.

Note: At the April 27, 2009 meeting, the Sponsor stated that 10-20% of the patients (~300) will be on background pioglitazone therapy at the time of randomization and that approximately 80% of the patients would be on background metformin therapy at the time of randomization.

In the IAS, deaths and AEs that were potentially MACE in the completed studies within the phase 2 and 3 controlled studies group in the IAS will be retrospectively adjudicated by the same CEC and using the same definitions used for Study 402. Events in all 12 studies in the phase 2 and controlled studies group that are deemed to meet the criteria specified for the primary MACE composite in the Study 402 protocol will be analyzed in the IAS.

The number and percentage of subjects with at least 1 MACE will be reported by treatment grouping, including the "All Alogliptin" and "All Comparators" groupings. The first MACE for each subject will also be further summarized by type (CV death, nonfatal MI, and nonfatal stroke). The hazard ratio comparing the All Alogliptin grouping to the All Comparators grouping will be obtained from a CPH model of the time from randomization to the first occurrence of MACE, stratified by study. Subjects without an

event will be censored at the date of their last visit. A 1-sided 97.5% CI for the hazard ratio (alogliptin to placebo) will be reported. A listing of all MACE will be provided.

Internal comments:

- *Please confirm that you will discuss early termination of study 402 with the agency prior to terminating it.*
- *When submitting data to the agency from the sequential MACE analyses, do you intend on submitting full safety data (i.e. adverse events and laboratory data) in addition to the required renal safety analysis?*
- *At the meeting we will ask the sponsor to clarify how it will protect the integrity of ongoing study 402 when unblinding data for sequential analyses.*

Renal Dosing and Safety: In the complete response letter for the A/P NDA, the agency raised concern regarding the available dose strengths of the A/P FDC tablet for patients with renal impairment. For patients with moderate renal insufficiency, one-half of the therapeutic dose of alogliptin should be administered. Doses of alogliptin/pioglitazone FDC 12.5 mg/15 mg, 12.5 mg/30 mg and 12.5 mg/45 mg will be available for these patients.

(b) (4)

Based on a recent marketing evaluation of Januvia (an approved DPP-4 inhibitor), only a small percentage (~2%) of patients are currently prescribed the severe renal impairment dose. Assuming similar prescription patterns will occur with alogliptin, it is expected that less than 1% of patients prescribed alogliptin and pioglitazone combination therapy will have severe renal impairment. The sponsor believes that patients receiving the A/P FDC who progress to severe renal impairment can appropriately be treated with the coadministration of alogliptin 6.25 mg and pioglitazone. Therefore, the sponsor does not plan to manufacture A/P FDC dose strengths containing 6.25 mg of alogliptin.

The sponsor plans to analyze the safety data from subjects with renal impairment according to the recommendations provided on July 15, 2009. All renal function, efficacy, and safety data will be presented using the MDRD equation and the Cockroft-Gault formula.

At the time of the resubmission, renal safety will be evaluated in Study 402 and in the alogliptin IAS and will be based on the incidence of adverse events by baseline and endpoint renal impairment status and changes from baseline to endpoint, incidences of markedly abnormal results, and shift analyses for serum creatinine and eGFR.

Per the Agency's recommendations, the following criteria will be used for markedly abnormal serum creatinine and eGFR. Note that an additional criterion was added for serum creatinine.

- Serum creatinine:

  - >0.3 mg/dL increase above baseline.
  - ≥2x increase above baseline.
  - >2.0 mg/dL
- eGFR:
  - >25% reduction from baseline.
  - >50% reduction from baseline.

The final analysis for Study 402 will include the analyses described above in addition to the incidence of renal dialysis and kidney transplant and the change from baseline in renal biomarkers, kidney injury molecule-1 (Kim-1) and neutrophil gelatinase-associated lipocalin (NGAL).

Foreign Studies: In addition, safety data from several non-IND studies completed in Japan will be included in the alogliptin NDA resubmission (total subjects 1258). Specifically, 5 controlled phase 2/3 studies, 4 phase 2/3 open-label extension studies, and 3 open-label phase 2 PK studies evaluating alogliptin, and 2 phase 1 studies evaluating A/P have been completed see appendix 1). The 5 controlled studies included 4 12-week studies (CCT-001, 004, 005, and 006) and 1 24-week study (CCT-003). The sponsor will include data on an individual study basis and significant findings with regard to AEs, SAEs, and AEs leading to study drug discontinuation in the alogliptin NDA resubmission.

Phase 1 and Nonclinical Studies: In addition, the following phase 1 studies were completed and will be included in the alogliptin NDA resubmission:

- SYR-322_101: Compared PK of alogliptin 12.5 gm twice daily with 25 mg daily in 28 healthy adults
- SYR-322_103: Evaluated the absolute bioavailability of alogliptin after 12.5 mg intravenous dose and 25 mg oral dose in 21 healthy adults

The sponsor has also completed an alogliptin and metformin range-finding study in rats and has plans to conduct a definitive embryo-fetal study as well.

Data Format: For both resubmissions, the sponsor will provide SAS Version 5 transport files for all clinical data for studies not previously submitted (i.e. 101, 103, 301, 303, OPI-004, and 402 and foreign studies) and the IAS. Data set format and structure will be identical to those previously submitted. 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.

Pediatric Studies: The sponsor plans to conduct a single pediatric clinical program that will address the needs of regulators in the United States and Europe. A request for a waiver of studies in children <10 years was included in alogliptin NDA 22-271, as well

as a request for deferral of other pediatric studies until the safety and efficacy of alogliptin had been more fully characterized in adults. However, on March 11, 2008, the agency requested a pediatric development plan for alogliptin. (b) (4)

(b) (4)

Prior to initiating dose administration to subjects in the pediatric phase 3 efficacy and safety study, the sponsor intends to conduct the following 2 nonclinical studies:

- A 4-week oral toxicity study in male and female Sprague-Dawley rats to evaluate potential toxicity of alogliptin in juvenile rats.
- An 8-week oral toxicity study in male Sprague-Dawley rats to evaluate potential alogliptin-related effects on the male reproductive organs.

Previous alogliptin toxicity studies were conducted in rats that were 8 weeks of age at dose initiation. In the juvenile toxicity studies, the rats will be 4 weeks of age at initiation of dosing; an age that will more closely correspond to the age of the pediatric patients.

(b) (4)

(b) (4)

The Sponsor's Questions and the Division's Reponses (in bold):

1. Does the Agency agree with the proposed structure and contents of both NDA resubmissions?

Response: Yes, but with exceptions noted in the comments below.

2. Does the Agency agree with Takeda's plan to summarize all integrated 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: Please clarify. Does the question only pertain to the location of the integrated safety data or are you proposing to present these data differently? Clarify why you are not including Study 009 (alogliptin as add-on combination therapy to pioglitazone) in the integrated safety analysis for the alogliptin/pioglitazone fixed-dose combination NDA.

3. For the Safety Updates, Takeda plans to summarize relevant safety data (adverse events, SAEs, and adverse events leading to discontinuation) from the individual Japanese studies within Module 2.7.4 and provide the final clinical study reports for these non-IND studies in Module 5. Does the Agency find this approach acceptable?

Response: Yes, this is acceptable. Please cite the table numbers in the original study reports and provide hyperlinks where possible.

4. Does the Agency agree that the proposed integrated analyses of the phase 2 and 3 controlled studies as described in the SAPs, and the table shells are adequately designed to address the Agency's requests in Complete Response letters for the both alogliptin alogliptin/pioglitazone safety updates?

Response: Yes, but with the following caveats:

- **Please also summarize duration of exposure to study medication according to baseline renal function (mild, moderate, and, severe renal impairment as calculated by both the Cockcroft-Gault and MDRD formulae).**
- **You define markedly abnormal serum creatinine as >1.5x baseline and >ULN. However, in the previous NDA submission, it was defined as >1.5x baseline. Please analyze renal data using the definition used in the original NDA (i.e. >1.5x baseline) because such an increase in serum creatinine even within the reference range may reflect an important decline in renal function. If you wish to also analyze renal data with the revised definition, you may do so.**
- **Please clarify if adverse events will be summarized in the pooled study population and by individual study (including recently completed studies).**

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

Response: Yes, these are acceptable.

6. Does the Agency agree that the proposed primary and secondary MACE analyses as described in the SAP and the table shells for Study 402 are adequately designed to support the CV safety of alogliptin?

Note from internal meeting: We had a question about how likely it is that Study 402 would be stopped at one of the early interim looks because the 1.3 goal post was met. This refers to the first 4 interim looks after 80, 100, 125 and 150 events when the study is powered to evaluate the 1.8 goal post. Dr. Janice Derr of Statistics believes that this is

very unlikely to happen if we believe that the two study arms actually have the same hazard rate for MACE events. In addition, she notes that the final 3 interim looks to evaluate the 1.3 goal post take place after 550, 600 and 650 events. This design, with the 7 proposed interim looks, has approximately 91% power to evaluate the hazard ratio against the goal post of 1.3.

A concern that underlies this question is the number of patients who will be exposed to alogliptin in Study 402 in the event that it is stopped early. Dr. Derr believes it is the intent in this study to treat all randomized patients for at least one year. She interprets this from the study protocol, section 9.2 (Schedule of observations and procedures). Clinical visits are scheduled at months 1, 3, 6, 9, and month 12 and every 4 months until the end of the study. However, it may be useful to clarify this with Takeda.

Internal comment: At the meeting, we will ask the sponsor to clarify which events are sent to the CEC committee. For relevant events (e.g. events reported by the investigator as MI or stroke) not coded as MI or stroke by the CEC, the sponsor should submit an explanation for those AEs.

Responses: Please clarify the minimum duration of treatment exposure for all patients enrolled in Study 402. If you intend to prematurely terminate Study 402 (e.g., if you meet the 1.3 goalpost based on an interim analysis), you should discuss these plans with FDA before implementation to ensure that FDA agrees that there is sufficient overall exposure to study medication.

7. Should the Agency find the statistical methodology and fixed, pre-specified order acceptable, if the final analysis demonstrates statistical superiority on the secondary MACE composite endpoint, would these results be supportive of a labeling claim?

Response: It would be premature at this point to answer question 7, as labeling will be a review issue.

8. A table of contents of the proposed tables, listings, and figures to be included in the interim analysis for Study 402 is also provided in Appendix C. Does the Agency agree with the proposed data presentations planned for the alogliptin and alogliptin/pioglitazone FDC resubmissions?

Note from internal meeting: There is a concern about the description of the internal blinded team and the internal unblinded team and their duties in the event that the 1.8 goal post is met, which initiates the submission of the NDA, following which Study 402 is continued until the 1.3 goal post is met or the study is terminated (See Appendix C, p. 35/52, the second paragraph of section 9.15.1 "DMC, unblinded team, and confidentiality of interim data and analysis"). Dr. Todd Sahlroot of Statistics will discuss this issue with Bob O'Neill.

Internal comment: At the meeting we will ask the sponsor to clarify how they will protect the integrity of ongoing study 402 when unblinding data for sequential analyses.

Response: When submitting data to the agency from the sequential MACE analyses, do you intend on submitting full safety data (i.e. adverse events and laboratory data) from the interim analysis of study 402 in addition to the required renal safety analysis?

9. Does the Agency agree that the proposed integrated analysis as described in the SAP and the table shells are adequately designed to support the CV safety of alogliptin?

Response: Please clarify whether the integrated analysis of cardiovascular safety from the controlled Phase 2 and Phase 3 studies, as described in Appendix E, excludes the results from Study 402, the dedicated cardiovascular study. However, we note that it is also acceptable to conduct two analyses, one with and one without Study 402.

10. Does the Agency agree that the proposed analyses and table shells are appropriately designed to assess the long-term safety of alogliptin?

Response: For all analyses of duration of exposure (e.g., Table 8.4.2.6), please also present one-year data using a cutoff of 365 days.

11. Does the Agency agree with Takeda's definitions for the special interest adverse events?

Response: No, we do not agree. Please also do the following:

- **Cutaneous toxicity, including ulceration, necrosis, mixed cell inflammation, hemorrhage, edema and granulation tissue, has been observed with other DDP4 inhibitors. Your definition of PCDR events includes high-level group terms in the immune system disorders SOC and skin and subcutaneous disorders SOC from MedDRA. However, the only ulcer term included is "venous ulcer pain." Although alogliptin does not appear to be associated with cutaneous toxicity in humans, you should broaden the PCDR analyses to include preferred terms related to skin ulceration, skin necrosis, skin mixed cell inflammation, skin hemorrhage, edema and skin granulation tissue.**
- **In addition to describing events of acute pancreatitis as adverse events of interest, also provide data on serum amylase and lipase (including reference range) and imaging results obtained in patients with suspected or confirmed pancreatitis.**
- **For infections, include an analysis of organism type (e.g., bacterial, fungal, viral, other).**

12. Does the Agency agree with types of narratives that Takeda proposes to include in the NDA resubmissions?

Response: Yes, we agree. Please provide links to the narratives in the study reports from summary tables and line listings.

13. Does the Agency find this submission plan acceptable and agree that submitting patient profiles in the NDA resubmissions is not necessary?

Response: Yes, we agree with your plan to submit subject narratives for the events agreed to in question 12 but not the eCRFs from ongoing study 402.

14. Does the Agency agree with Takeda's proposal to not manufacture alogliptin/pioglitazone FDC dose strengths that contain alogliptin 6.25 mg and agree that the product labeling can appropriately address dosing patients with severe renal impairment through co-administration of alogliptin and pioglitazone tablets?

Response: Yes, we agree.

15. Does the Agency agree that the proposed analyses and table shells for the IAS and interim analysis are appropriately designed to evaluate the safety of alogliptin in subjects with renal impairment?

Response: The analyses and proposed data presentation are acceptable.

16. With regard to the analysis of adverse events by baseline and endpoint renal status for the IAS and final analysis for Study 402, Takeda defines endpoint renal status as the subject's renal status at the time of last renal assessment. Therefore, for this analysis adverse events will be summarized according to renal impairment (normal, mild, moderate, and severe or ESRD) at Baseline and according to renal impairment at the last renal assessment. Does the Agency agree with this definition of endpoint for this analysis?

Response: The proposed analyses are acceptable.

17. In the FDA Advice/Information Request letter dated 15 July 2009 regarding Study 402, the Agency stated that if a substantial percentage of patients experience a change in severity status during the course of the study, a secondary analysis should be conducted by renal severity subgroup according to the actual severity status of patients at the time period in which the study endpoint is measured. Takeda would like clarification on what percentage of patients experiencing a change in severity status during the course of the study would require Takeda to conduct the analysis based on renal severity status at endpoint for the final analysis.

Notes from internal meeting: We talked about a "substantial percentage" being 25-30%, with the understanding that approximately 400 to 500 subjects with moderate renal impairment and 100 severe renal impairment will be enrolled in study 405 and exposed to alogliptin for at least one year (see p. 23/36, section 2.2.2.3). From a statistical perspective, this would give a reasonable number of patients who progressed from moderate to severe renal impairment from which to summarize the percentage of adverse events of interest. However, this suggestion is certainly open to discussion.

Response: If ≥25% of patients experience a change in severity status during the course of the study, you should conduct the analysis based on renal severity status at endpoint for the final analysis.

18. Does the Agency agree with Takeda's proposal (b) (4) ?

Response: No, we do not agree. The proposal (b) (4) will be a review issue.

19. If Takeda wishes to submit data to extend the expiry of alogliptin tablets or to support a new manufacturing site, would it be acceptable to submit these to the NDA for the Agency's review and approval prior to the NDA resubmission for alogliptin, considering these data are not being submitted to address items in the Complete Response letter?

Response: No, we do not agree with your proposal to submit amendments outside of a review cycle (i.e., without an applicable review clock.) As you state, the information in the proposed amendments does not address a known deficiency in the application. Therefore, we recommend that you submit the information in a post-approval supplement. Alternatively, it may be included in the submission designated as "Complete Response". We remind you to provide adequate information on the new manufacturing site (e.g., site address and contact, GMP inspection readiness, comparative multi-point dissolution profiles of the product manufactured at the new Kilruddery site and at the original Osaka site, and stability data from 3 product batches manufactured at the new site).

20. Similar to the review timelines described in the Guidance document, Good Review Management Principles and Practices for PDUFA Products, Takeda would like to confirm that the Agency will plan to initiate labeling discussions at least 4 weeks prior to the scheduled action dates for each product.

Response: Should results from your application support approval, we plan to initiate labeling discussions at least 4 weeks prior to the scheduled action dates for each product.

Question 21: If the alogliptin and alogliptin/pioglitazone NDA resubmissions are submitted simultaneously, Takeda would like to confirm that a concurrent action will be taken by the Agency on both of these applications.

Response: If both NDAs are resubmitted at the same time, they will be on the same review clock and will have the same user fee goal date. A concurrent action is likely, but the possibility exists that the actions taken will not be concurrent.

Question 22: Takeda would like to obtain feedback regarding the need for an Advisory Committee meeting in light of the 6-month review cycle for Complete Response Submissions and the Agency's prior full review of alogliptin. Can the Agency comment at this time if an Advisory Committee meeting will be necessary?

Response: This decision will be made after the resubmission of these NDAs.

23. If Takeda notifies the Agency 4 months prior to submitting the NDA resubmissions, would the Agency be willing to initiate the process for re-review of 'Nesina' and (b) (4) at that time? If the Agency agrees with this proposal, would the Agency be able to conduct the re-review and confirm the acceptability of the proprietary names within a reasonable timeframe (e.g. 4 weeks)?

Note: The proposed proprietary names, 'Nesina' for alogliptin and (b) (4) for alogliptin/pioglitazone FDC, were found acceptable by the Agency during the first-cycle review of the alogliptin and A/P NDAs, although they must be re-reviewed following the NDA resubmissions of both applications.

Response: The Division of Medication Error Prevention and Analysis (DMEPA) reviews trade names. You should submit a request for trade name review when the complete response is submitted. DMEPA's review timeline is 90 days from the date the request is received.

Question 24: If Takeda decides to pursue different trade names for alogliptin and/or the A/P FDC product for launch, could Takeda submit such names for the Office of Surveillance and Epidemiology (OSE) to review and approve? For trade names that are subject of an NDA resubmission, what are the internal timelines associated with its review and approval?

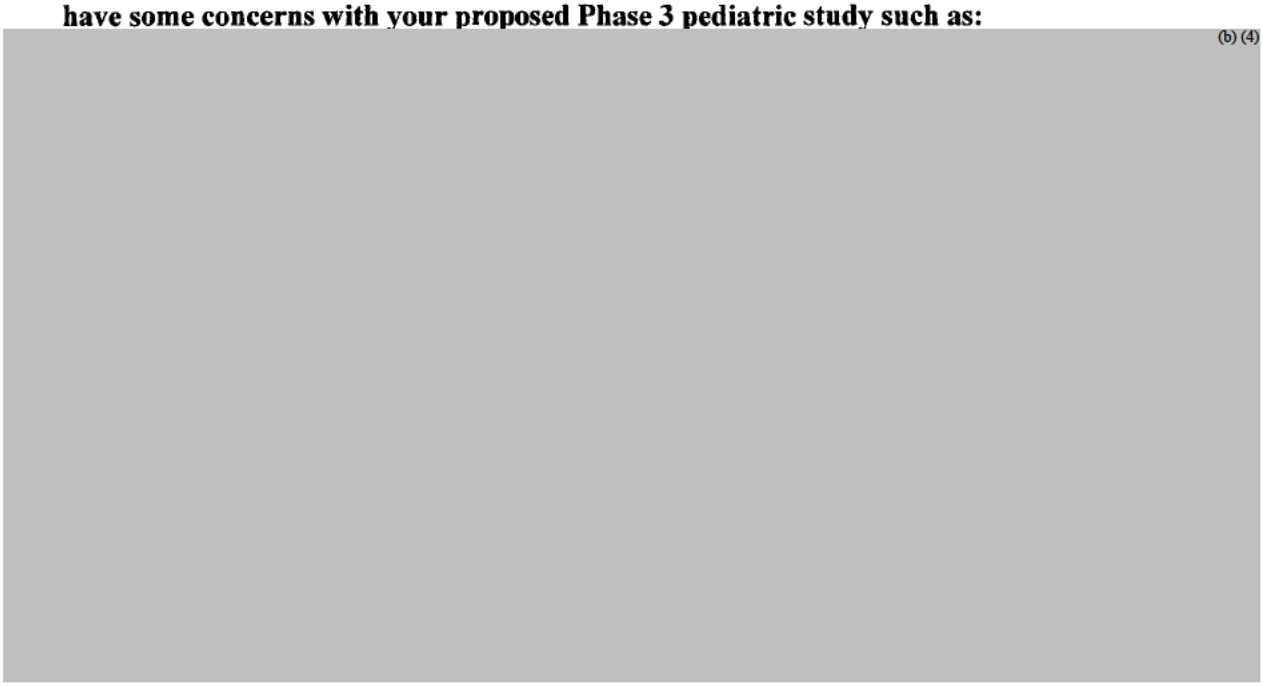
Response: In the NDA resubmission, you may submit two different trade names for DMEPA to review. DMEPA's review timeline is 90 days from the date they receive the request. This review is generally finalized 90 days prior to the action date. If you wish to pursue alternate names, you will need to withdraw the names that were found to be conditionally acceptable and submit a request for review of the alternate names. This review will follow the same timelines as above.
Please also 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).

25. Does Agency agree that the pediatric clinical studies as described above will satisfy the requirements of PREA for alogliptin?

Response: We cannot comment on whether or not your proposed pediatric study will satisfy the requirements of PREA until the NDA is resubmitted and your

proposal is discussed with the Pediatric Review Committee (PeRC). However, we have some concerns with your proposed Phase 3 pediatric study such as:

(b) (4)



26. Takeda would also like to obtain feedback from the Agency regarding the utility of the proposed pediatric plan to qualify for exclusivity under the Best Pharmaceuticals for Children Act (BPCA). A revised Proposed Pediatric Study Request under Section 505A and BPCA will be submitted under separate cover following approval.

Response: We cannot into an agreement regarding a written request until after NDA approval.

Other FDA Comments:

1. **When presenting changes from baseline in laboratory parameters (e.g., Table 15.3.4.5.2) include change from baseline to the last available on-treatment measurement (intent-to-treat with last-observation-carried-forward)**
2. **It appears that the integrated analyses will use MedDRA version 12.0. If earlier versions of MedDRA were used for the individual study reports, include a table showing those preferred terms that were coded to new preferred terms as a result of the MedDRA version change.**

Appendix 1. Summary of foreign clinical studies (Reproduced from the sponsor)

Study No.	Study Design, Population, Treatment Duration
SYR-322-4833/CPH-001	**Design:** Phase 1, open-label, randomized 2-period crossover study to determine the bioequivalency of alogliptin and AD-4833 tablets when administered as individual tablets and as combination product and to determine the effect of food on the pharmacokinetics of combination product. **Population:** Japanese healthy male subjects; aged 20 to 35 years, inclusive. **Treatment Duration:** Single-dose.
SYR-322-4833/CPH-002	**Design:** Phase 1, Open-label, randomized 2-period crossover study to determine the bioequivalency of alogliptin and AD-4833 tablets when administered as individual tablets and as combination product and to determine the effect of food on the pharmacokinetics of combination product. **Population:** Japanese healthy male subjects; aged 20 to 35 years, inclusive. **Treatment Duration:** 2 days.
SYR-322/CPH-003	**Design:** Phase 2, open-label study to assess the effect of age on pharmacokinetics, safety and pharmacodynamics of a single-dose of alogliptin in healthy elderly and non-elderly adult male subjects. **Population:** Japanese healthy male subjects; aged 65 to 85 years for elderly subject or aged 20 to 35 years for non-elderly subject, inclusive. **Treatment Duration:** Single-dose.
SYR-322/CPH-004	**Design:** Phase 2, open-label study to assess the effect of voglibose on the pharmacokinetics of alogliptin. **Population:** Japanese healthy male subjects; aged 20 to 35 years, inclusive. **Treatment Duration:** 2 days.
SYR-322/CPH-007	**Design:** Phase 2, open-label, randomized, crossover study to determine the food effect on the pharmacokinetics, pharmacodynamics, safety and tolerability of single dose of the commercial alogliptin tablets (12.5 and 25 mg). **Population:** Japanese healthy male subjects; aged 20 to 35 years, inclusive. **Treatment Duration:** 2 days.
SYR-322/CCT-001	**Design:** Phase 2, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of alogliptin. **Population:** Men or women, 20 years of age or older, with T2DM and inadequate glycemic control on diet and exercise alone. **Treatment Duration:** 12 weeks.
SYR-322/OCT-001	**Design:** Long-term, open-label extension study to investigate the long-term safety of alogliptin. **Population:** The subjects who have completed the phase 2 dose-ranging study (SYR-322/CCT-001). **Treatment Duration:** 40 weeks (52 weeks from the start of treatment in the phase 2 dose-ranging study).
SYR-322/CCT-003	**Design:** Phase 2/3, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of SYR-322 when used in combination with α-glucosidase inhibitor. **Population:** The subjects who have completed the phase 2 dose-ranging study (SYR-322/CCT-001). **Treatment Duration:** 24 weeks.
SYR-322/OCT-003	**Design:** Long-term, open-label extension study to investigate the long-term safety of alogliptin when used in combination with α-glucosidase inhibitor in subjects with T2DM. **Population:** The subjects who have completed the phase 2 dose-ranging study (SYR-322/CCT-003). **Treatment Duration:** 40 weeks (52 weeks from the start of treatment in the core phase 2/3 α-glucosidase inhibitor add on study).

Study No.	Study Design, Population, Treatment Duration
SYR-322/CCT-004	**Design:** Phase 2/3, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of alogliptin when used in combination with thiazolidinedione **Population:** Men or women, 20 years of age or older, with T2DM and inadequate glycemic control on pioglitazone as well as diet and exercise **Treatment Duration:** 12 weeks
SYR-322/OCT-004	**Design:** Long-term, open-label extension study to investigate the long-term safety of alogliptin when used in combination with thiazolidinedione. **Population:** The subjects who have completed the phase 2/3 thiazolidinedione add on study (SYR-322/CCT-004). **Treatment Duration:** 40 weeks (52 weeks from the start of treatment in the core phase 2/3 thiazolidinedione add on study).
SYR-322/CCT-005	**Design:** Phase 2/3, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of alogliptin when used in combination with sulfonylurea. **Population:** Men or Women, 20 years of age or older, with T2DM and inadequate glycemic control on sulfonylurea as well as diet and exercise. **Treatment Duration:** 12 weeks.
SYR-322/OCT-005	**Design:** Long-term, open-label extension study to investigate the long-term safety of alogliptin when used in combination with sulfonylurea and/or metformin. **Population:** The subjects who have completed the phase 2/3 sulfonylurea add on study (SYR-322/CCT-005) or biguanide add on study(SYR-322/CCT-006). **Treatment Duration:** 40 weeks (52 weeks from the start of treatment in the core phase 2/3 sulfonylurea add on study or biguanide add on study).
SYR-322/CCT-006	**Design:** Phase 2/3, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of alogliptin when used in combination with metformin. **Population:** Men or Women, 20-64 years of age, with T2DM and inadequate glycemic control on biguanide. **Treatment Duration:** 12 weeks.

Appendix 2. Proposed structure of the alogliptin NDA resubmission (Reproduced from the sponsor)

Module	Section	New or Updated Information
1		• Updated draft product label. • All applicable updated regional information.
2	2.4	• Updated nonclinical overview.
	2.5	• Updated clinical overview.
	2.6.6	• Additional nonclinical written summaries including range-finding and embryo-fetal development studies.
	2.6.7	• Additional nonclinical tabular summaries including range-finding and embryo-fetal development studies.
	2.7.1	• Pharmacokinetic data from Studies 101 and 103.
	2.7.3	• Efficacy data from Studies 301, 303, OPI-001, OPI-002, and OPI-004.
	2.7.4 (a)	***Part 1: Summary of Safety by Individual Study*** • MACE analyses and an overall safety evaluation from Study 402. • Safety data from Studies 101, 103, 301, 303, OPI-001, OPI-002, and OPI-004 and foreign studies. • Updated SAE summary table for Study 012 (since the alogliptin 120-day safety update). ***Part 2: Integrated Safety Analyses of Controlled Clinical Studies*** • Pooled MACE analysis of all controlled phase 2 and 3 studies. • Safety update evaluating a pooled analysis of all phase 2 and 3 controlled studies (adding studies 402, 301, 303, OPI-001, OPI-002, and OPI-004). • Long-term safety evaluation from 1-year controlled studies 303, 402, and OPI-004.
	2.7.5	• List of new references cited in 2.7.
	2.7.6	• Synopses for Studies 101, 103, 301, 303, OPI-001, OPI-002, and OPI-004.
4		• Nonclinical study reports including the range-finding and embryo-fetal development studies.
5	5.2	• Updated table of clinical studies.
	5.3	• Clinical study reports for Studies 101, 103, 301, 303, and OPI-004 (OPI-001 and OPI-002 were previously submitted in the alogliptin NDA) and foreign studies. • Narratives for Study 402, any requested narratives not included in the clinical study reports for Studies 101, 103, 301, 303, and OPI-004, and SAE narratives for Study 012. • Tables, listings, and graphs for Study 402 and the integrated analyses. NOTE: The integrated analyses will be summarized in Module 2.7.4 and not repeated as a separate report in this module.
	5.4	• Copies of new references.

(a) Module 2.7.4 from NDA 22-426 for alogliptin/pioglitazone FDC will also be submitted to NDA 22-271 for alogliptin.

Appendix 3. Proposed structure of the A/P NDA resubmission (Reproduced from the sponsor)

Module	Section	New or Revised Information
1		– Updated draft product label. – All applicable updated regional information.
2	2.4	– Updated nonclinical overview.
	2.5	– Updated clinical overview.
	2.7.3	– Efficacy data from Studies OPI-004 and 301.
	2.7.4 (a)	***Part 1: Summary of Safety by Individual Study*** – Safety data from Studies OPI-004 and 301and foreign studies. ***Part 2: Integrated Safety Analyses of Controlled Clinical Studies*** – Safety update evaluating a pooled analysis of phase 3 controlled studies (adding Studies OPI-004 and 301).
	2.7.5	– List of new references cited in 2.7.
	2.7.6	– Synopses for Studies OPI-004 and 301.
5	5.2	– Updated table of clinical studies.
	5.3.	– Clinical study reports for Studies OPI-004 and 301 and foreign studies. – Any additional requested narratives not included in the clinical study reports for Studies OPI-004 and 301.
	5.3.5.3	– Tables, listings, and graphs for the integrated analyses. NOTE: The integrated analyses will be summarized in Module 2.7.4 and not repeated as a separate report in this module.
	5.4	– Copies of new references.

(a) Module 2.7.4 from NDA 22-271 for alogliptin will also be submitted to NDA 22-426 for alogliptin/pioglitazone

Appendix 4. Study protocol 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 to 17 years with type 2 diabetes (Reproduced from the sponsor)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22426	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	ALOGLIPTIN/PIOGLITAZONE TABLET
NDA-22271	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS

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
02/24/2010

HYLTON V JOFFE
02/24/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-271 & 22-426 **Applicant: Takeda** **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

Reference ID: 2997887

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 arythmogenic potential of the product (*e.g.*, 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).

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 (*e.g.*, 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.

Reference ID: 2997887

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

Reference ID: 2997887

NDAs:

- 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)

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.

Alolgiptin/pioglizone 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)

	Number (%) of Subjects					
	Original NDA			NDA Resubmission		
Preferred Term	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)

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) *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) *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:

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

Summary Review for Regulatory Action

Date	September 1, 2009
From	Mary H. Parks, M.D.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	22-426
Applicant Name	Takeda
Date of Submission	September 22, 2008
PDUFA Goal Date	July 22, 2008
Proprietary Name / **Established (USAN) Name**	(b) (4) (alogliptin-pioglitazone fixed dose combination tablets)
Dosage Forms / Strength	Alogliptin-pioglitazone (in mgs) 12.5/15, 12.5/30, 12.5/45, 25/15, 25/30, 25/45
Proposed Indication(s)	Fixed-dose combination as an adjunct to diet and exercise to improve glycemic control when treatment with both alogliptin and pioglitazone is appropriate
Action/Recommended Action for NME:	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	NA
OSE/DMEPA	Jinhee Jahng, Pharm.D. Kellie Taylor, Pharm.D.
OSE/DPV	NA
OSE/DRISK	No reviews completed at this time (deferred)

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

This NDA is for the fixed-dose combination (FDC) of alogliptin and pioglitazone whose proposed tradename is (b) (4) 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 insulinotropic 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.

Pioglitazone, a PPAR-gamma agonist, was approved in 1999 and is a member of the thiazolidinedione (TZD) class. Other FDCs containing two anti-diabetic drugs have been approved with the indication, "as an adjunct to diet and exercise to improve glycemic control when treatment with both agents is appropriate". Implicit in this indication is that the decision to initiate therapy with these products as initial therapy or only after inadequate control with the single agents is left to the discretion of the prescriber.

For this NDA, the unapproved single agent, alogliptin was reviewed under a separate NDA 22-271 and received a complete response action on June 26, 2009. As a result, (b) (4) will also receive a CR letter pending the deficiencies outlined in the action letter for NDA 22-271 are satisfactorily addressed. The NDA for the FDC containing alogliptin and pioglitazone contained three Phase 3 studies. The CV safety data for these 3 studies were reviewed under NDA 22-271 and will not be discussed again in this memo. This memo will only discuss issues specific to the FDC, including safety concerns not identified in NDA 22-271.

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. Alogliptin was not presented before an advisory committee panel because it was deemed deficient for approval.

The deficiency precluding approval of alogliptin 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. As discussed extensively in the reviews for NDA 22-271, alogliptin was not able to meet these requirements and was issued a complete response letter on June 26, 2009, with the need to conduct a dedicated CV safety trial to address this primary deficiency. As a result, the NDA for this fixed-dose combination containing alogliptin and pioglitazone will also receive a complete response action.

In addition to this primary deficiency noted for NDA 22-271, other safety concerns were identified which will need to be better characterized in ongoing and future trials. These other safety concerns will be extended to NDA 22-426 for this FDC.

3. CMC/Device

This drug product is composed of alogliptin benzoate and pioglitazone hydrochloride, formulated as (b) (4) film-coated, immediate-release tablet. Alogliptin

is proposed for marketing as 6.25, 12.5 and 25 mg tablets and pioglitazone is approved at dosage strengths of 15, 30, and 45 mg tablets. The FDC will be available as: 12.5/15, 12.5/30, 12.5/45, 25/15, 25/30, 25/45 mg/mg (alogliptin/pioglitazone) and will be available as physician samples (7- (b) (4) count HDPE bottles and 7-count blister packs) and commercial package configurations of 30-, 90, and 500-count HDPE bottles. CMC has agreed to grant 24 months shelf-life.

The Office of Compliance has issued a Withhold recommendation after its inspection of the drug substance manufacturer for pioglitazone (b) (4) The primary issue was related to cross contamination and the Office of Compliance is still holding discussions with the firm. Two other manufacturing sites were identified in the CMC review; however, ONDQA can not recommend approval if any of the manufacturing sites proposed under this NDA has a Withhold recommendation issued by OC. This deficiency will not be identified in the Complete Response letter as it is addressed separately in a Warning letter issued by OC.

4. Nonclinical Pharmacology/Toxicology

The nonclinical data for the individual components for this FDC have been reviewed under the respective NDAs for alogliptin and pioglitazone. Pharmtox recommended approval of alogliptin based on adequate safety margins. In the NDA for this FDC, nonclinical studies did not demonstrate an exacerbation of risks observed with either individual component, except for an effect on fetal weight and non-teratogenic visceral variations which were not deemed clinically relevant. These conclusions were based primarily on studies performed in rats, including a 13-week subchronic toxicity study and a reproductive toxicology study. As noted by Dr. Carlson, the known toxicities associated with pioglitazone use, in particular on the cardiac and hematopoetic organs, were not potentiated by the co-administration of alogliptin.

Alogliptin and its metabolites were not increased by the co-administration of pioglitazone. Alogliptin co-treatment increased the Cmax and AUC of M-II metabolite of pioglitazone by approximately 2- to 3-fold but this is a minor metabolite of pioglitazone and this finding was not deemed to be clinically relevant.

The overall recommendation from pharmacology/toxicology is approval with no additional nonclinical studies requested post-approval for this FDC drug product.

5. Clinical Pharmacology/Biopharmaceutics

There were 5 clinical pharmacology studies conducted in support of this NDA. I am only summarizing the findings from two of these studies that are considered pivotal to the approvability of this application. Other aspects of the clinical pharmacology program are not summarized in my memo as this has already been extensively reviewed and discussed under NDA 22-271. Similarly, the reader is referred to the NDA for pioglitazone (NDA 21-073) for details of this drug's clinical pharmacology development program and study results.

Study 322OPI-101 is a BE study comparing the highest (alogliptin 25 mg + pioglitazone 45 mg) and lowest (alogliptin 12.5 mg + pioglitazone 15 mg) proposed dosage strengths of the to-be-marketed FDC tablets with the co-administered individual tablets. A biowaiver was granted for the intermediate dosage strengths by ONDQA.

The following tables are derived from Dr. Ritesh Jain's review. These results demonstrate that both the highest and lowest dosage strengths of the FDC are bioequivalent to the individual alogliptin and pioglitazone tablets.

Table 1: Pharmacokinetic Parameters and Bioequivalence Statistics of Alogliptin 12.5 mg and Pioglitazone 15 mg When Administered as Individual Tablets and as FDC product (SYR-322-4833 BL).

PK parameters	Geometric Least Squares Mean		Ratio T/R*100 (90% CI)
	SYR-322-4833 BL (12.5 mg +15 mg) (Test)	Alogliptin 12.5 mg + Pioglitazone 15 mg (Reference)	
Alogliptin (Plasma)			
C_{max} (ng/mL)	48.23	50.28	95.94 (91.83-100.23)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	826.84	824.23	100.32 (99.00-101.65)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	904.72	904.17	100.06 (98.6-101.4)
Pioglitazone (Serum)			
C_{max} (ng/mL)	612.22	626.25	97.76 (91.82-104.08)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	5707.70	5774.19	98.85 (95.42-102.404)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	6399.01	6429.75	99.52 (96.58-102.55)

Table 2: Pharmacokinetic Parameters and Bioequivalence Statistics of Alogliptin 25 mg and Pioglitazone 45 mg When Administered as Individual Tablets and as FDC product (SYR-322-4833 BL).

PK parameters	Geometric Least Squares Mean		Ratio T/R*100 (90% CI)
	SYR-322-4833 BL (25 mg +45 mg) (Test)	Alogliptin 25 mg + Pioglitazone 45 mg (Reference)	
Alogliptin (Plasma)			
C_{max} (ng/mL)	104.10	106.15	98.07 (93.33-103.06)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	1582.33	1601.99	98.77 (97.58-99.98)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	1694.76	1719.46	98.56 (97.40-99.74)
Pioglitazone (Serum)			
C_{max} (ng/mL)	1276.53	1303.92	97.90 (89.34-107.28)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	14978.78	14369.87	104.24 (98.62-110.18)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	16789.67	15961.30	105.19 (98.19-112.69)

The second study is Study 322OPI-006, a food-effect study evaluating the effect of a high-fat meal on the single-dose PK of the to-be-marketed highest dosage strength. The results of this

study indicate no effect of food on AUC or Cmax of alogliptin or pioglitazone with comparing drug levels under fed and fasted states. (See Table 3 in Dr. Jain's review).

Overall, the Office of Clinical Pharmacology has found the data they've reviewed acceptable. The DSI audit of the pivotal BE study was found to be adequate and there are no approvability issues from the clinical pharmacology perspective.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The glucose-lowering effect of alogliptin has been extensively discussed under NDA 22-271. 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. This memo will only summarize the findings from 3 clinical trials submitted to NDA 21-271 in support of the FDC. All 3 studies were 26 weeks in duration and were double-blind, randomized trials. Selected details of these 3 studies are summarized in the following table.

Table 7.1. Pivotal Phase 3 Studies

Study Name	Treatment groups (n)	Background therapy	Screening HbA1c	Average Baseline HbA1c/ Duration of DM
PI-001	Placebo (129) Pio 15 mg (130) Pio 30 mg (129) Pio 45 mg (120) Alo 12.5 mg (128) Alo12.5/Pio15 (130) Alo12.5/Pio30 (130) Alo12.5/Pio45 (130) Alo 25 (129) Alo25/Pio15 (130) Alo25/Pio30 (130) Alo25/Pio45 (130)	Metformin	7.5%-10%	8.5/6.2 yrs
PI-002	Alo 25 mg (164) Pio 30 mg (163) Alo12.5/Pio30 (164) Alo25/Pio30 (164)	Diet and exercise	7.5%-11%	8.8/3.2 yrs
009	Placebo (97) Alo 12.5 mg (197) Alo 25 mg (199)	Pioglitazone (15, 30, or 45 mg) alone or in combination	7.0%-10%	8.0/7.6 yrs

with metformin or
SU

Dr. Janice Derr's statistical review thoroughly describes the trial design, patient baseline characteristics and dispositions. She also provides a detailed discussion on the different statistical approaches to determining efficacy in Study PI-001. I will not elaborate on this and will refer the reader to Section 3.1.5 of her review. However, the appropriate statistical approach to summarizing efficacy findings will need to be revisited during labeling negotiations in the future should this NDA be approved. I would point out that regardless of approach undertaken, the efficacy results are consistent such that I would conclude the FDC provides superior efficacy compared to either alogliptin or pioglitazone monotherapy. On average, one can expect an additional HbA1c reduction of 0.4-0.6% of the FDC over pioglitazone monotherapy, reflective of the contribution from alogliptin to the FDC. These results are also consistent with the efficacy findings from NDA 22-271. One can expect an additional HbA1c reduction of 0.4-0.9% of the FDC over alogliptin monotherapy, reflective of the contribution from pioglitazone to the FDC. Further supportive of the primary efficacy results are the data from the secondary efficacy endpoints for fasting plasma glucose and proportion of patients achieving HbA1c goals of < 7% and < 6.5%. Dr. Pratt has summarized these in her medical review of this NDA. Below is a Table summarizing the expected efficacy of the FDC compared to pioglitazone (± other OADs) observed in the 3 Phase 3 trials. Please see Tables 5-7 from Dr. Derr's review for complete presentation of the primary efficacy findings.

Table 7.2. Summary of Primary Efficacy Results of the FDC vs Pioglitazone (Adapted from Table 5-7 in Dr. Derr's review)

	Baseline Mean HbA1c ± SD		**Adj Mean Chg from Baseline at Wk 26 ± SE**		**Diff in Adj Mean Chg, Combo-Control LS Mean (95% CI)**
	Combo	**Control**	**Combo**	**Control**	
Study PI-001*					
Alo25 + Pio45/30/15 vs Pio45/30/15	8.5 ± 0.7	8.5 ± 0.7	-1.42 ± 0.05	-0.89 ± 0.05	-0.53 (-0.66,-0.41)
Alo12.5 + Pio45/30/15 vs Pio45/30/15	8.5 ± 0.7	8.5 ± 0.7	-1.43 ± 0.05	-0.89 ± 0.05	-0.54 (-0.67,-0.41)
Study PI-002					
Alo25+Pio30 vs P30 Alo25+Pio30 vs A25	8.8 ± 1.0 8.8 ± 1.0	8.8 ± 1.0 8.8 ± 1.0	-1.71 ± 0.08 -1.71 ± 0.08	-1.15±0.08 -0.96±0.08	-0.56 (-0.78,-0.33) -0.75 (-0.98,-0.53)
Alo12.5+Pio30 vs P30	8.9 ± 1.0	8.8 ± 1.0	-1.56±0.08	-1.15±0.08	-0.40 (-0.63,-0.18)
Study 009**					
Alo25 vs pbo	8.0±8.0	8.0±8.0	-0.80±0.06	-0.19±0.08	-0.61 (-0.80,-0.41)
Alo12.5 vs pbo	8.1±8.1	8.0±8.0	-0.66±0.06	-0.19±0.08	-0.47 (-0.67,-0.28)

*Efficacy results based on Applicant's method which evaluated the linear combination of the alogliptin 25 plus pio combination treatment groups to the linear combinations of pioglitazone monotherapy at α=0.05. If this comparison is significant then the same method applied to the linear combination of the alogliptin 12.5 plus pio combination treatment groups. **All patients on background pioglitazone with or without metformin or a SU.

Overall, the statistical review has not identified any deficiencies in the efficacy data precluding approval pending all safety issues are adequately addressed.

8. Safety

The safety of alogliptin has been extensively reviewed under NDA 22-271. In particular, a detailed discussion of CV safety, including data from Study PI-001 and 002 were also included in that NDA review and will not be summarized again here. However, to the extent that the NDA for alogliptin was not approved because of insufficient data to rule-out an excess CV risk in the setting of numeric imbalances in CV events not favoring alogliptin, this NDA will also receive a CR letter with CV safety concerns listed as a primary deficiency.

This memo will focus on any unique safety concerns not already identified in NDA 22-271. Since the CR letter for alogliptin has already identified additional safety concerns for hypersensitivity reactions including angioedema, hepatotoxicity, pancreatitis, skin reactions, and renal toxicity as safety signals to monitor in ongoing and future clinical trials, this development program for the FDC will also need to incorporate prospective assessments for these same safety concerns.

Dr. Pratt's safety review in this NDA focused on the 3 Phase 3 studies and the 120-day safety update which includes an uncontrolled open-label extension study OLE-012. There were 1,267 patients exposed to the FDC or the combination of alogliptin + pioglitazone in controlled treatment periods; however, this duration was limited to 6 months or less. Her review did not identify any safety signal that has not been observed with pioglitazone or alogliptin individually. The following points should be noted:

- The cardiac and fluid-related side effects associated with pioglitazone were not potentiated by the combined use with alogliptin. In the controlled portion of PI-001 and 002, the incidence of ischemic heart disease was 3.1% with pioglitazone compared to 1.8% and 1.4% in the combination and alogliptin monotherapy groups, respectively. Peripheral edema was noted in 3.5% of pioglitazone-treated patients compared to 2.7% and 1.4% in the combination and alogliptin monotherapy groups, respectively.

- Anemia, a known side-effect of TZDs, was slightly higher in the combination group (2.3%) than pioglitazone (1.5%) and alogliption (0.2%).

- A greater mean percent reduction in lymphocytes was observed in the combination drug group and alogliptin monotherapy than pioglitazone monotherapy. This is of interest as some other DPP4-inhibitors have also been associated with decreased lymphocyte in the nonclinical and clinical setting. There was a mean % reduction of 1.1-1.7% observed with the two alogliptin treatment groups compared to 0.5% in the pioglitazone group.

- Unfavorable changes in renal safety (BUN, creatinine, and albumin/cr ratio) parameters were more apparent in the combination drug group than the individual therapies. For example, 1.2% and 1.6% of the alogliptin and combination groups, respectively, had a post-baseline high abnormal serum creatinine versus 0.7% in the pioglitazone group. Shifts in creatinine clearance (using both the Cockcroft-Gault

and MDRD formula) from normal to mild or moderate occurred more often with the combination group than the individual therapies. The FDC will not include a 6.25 mg dose for alogliptin, which is the recommended dose for patients with severe renal impairment based on the renal pK study conducted under NDA 22-271. Dr. Pratt does provide a case narrative of a patient with baseline severe renal impairment who was randomized to alogliptin 25 mg in study OPI-002. Based on these observations, the applicant will need to manufacture a FDC that also contains the 6.25 mg dose because there is a high likelihood that patients with T2DM who have severe renal impairment will be prescribed the FDC. Furthermore, as this is a chronic medication, a patient with mild to moderate renal impairment may progress to severe renal disease while on the FDC necessitating a reduction in the amount of alogliptin to 6.25 mg.

- One other DPP4 inhibitor has not been approved because of a liver safety signal that was initially identified when it was administered with a TZD. In this NDA, there was not an increased rate of transaminases with the combination therapy and review of case narratives for transaminases > 3xULN and >10xULN did not identify a hepatic safety signal.

As the applicant is required to conduct a large CV safety study, many of these additional safety concerns noted in the alogliptin NDA will need to be assessed in this required study.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

This application was not discussed before the Pediatrics Research Committee (PeRC) as it and NDA 22-271 are not being approved for marketing. (b) (4)

[redacted]

11. Other Relevant Regulatory Issues

- DSI Audits – please see Section 3.1 of Dr. Pratt's review. No outstanding issues.
- Financial Disclosures – please see Section 3.3 of Dr. Pratt's review. No outstanding issues.

12. Labeling

Deferred as this application will receive a complete response action.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Complete Response

- Risk Benefit Assessment

The applicant has provided sufficient evidence that the fixed-dose combination of alogliptin 12.5 mg or 25 mg with pioglitazone 15, 30, or 45 mg provides superior efficacy based on HbA1c reduction compared to the individual components. However, the NDA for alogliptin was not approved due to numeric imbalances in CV adverse events, not favoring alogliptin, and an overall low CV event rate in all pooled studies (including the combination therapies) which failed to rule-out an unacceptable excess risk for cardiovascular events. Consequently, this NDA will not be approved pending the completion of a dedicated CV safety study to address the deficiencies summarized in the CR letter for NDA 22-271.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Not applicable

- Recommendation for other Postmarketing Requirements and Commitments

Not applicable

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22426	ORIG 1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	ALOGLIPTIN/PIOGLITAZONE TABLET

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/s/

MARY H PARKS
09/02/2009

CURTIS J ROSEBRAUGH
09/02/2009

Summary Basis for Regulatory Action

Date	September 2, 2009
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	NDA 22-426
Applicant Name	Takeda Pharmaceuticals
Proprietary / Established (USAN) Names	(b) (4) Alogliptin-pioglitazone fixed combination
Dosage Forms / Strength	Tablets (alogliptin-pioglitazone) 12.5/15 mg, 12.5/30 mg, 12.5/45 mg, 25/15 mg, 25/30 mg, 25/45 mg
Proposed Indication(s)	Fixed-dose combination as an adjunct to diet and exercise to improve glycemic control when treatment with both alogliptin and pioglitazone is appropriate
Action:	*Complete Response*

Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding alogliptin-pioglitazone fixed-dose combination (FDC). I refer the reader to the thorough review of Dr. Mary Parks, with which I am in full agreement. I also refer the reader to my detailed review for NDA 22-271 which was for alogliptin used as a single agent to improve glycemic control. The review and conclusions for NDA 22-271 apply to this application (NDA 22-246) as well. As such, this review will be brief and supplements the conclusions of Dr. Parks.

NDA 22-271 received a complete response (CR), mainly because the sponsor had not provided evidence that alogliptin does not result in an unacceptable increase in cardiovascular risk. Therefore, until the sponsor provides adequate cardiovascular safety data for alogliptin used as a single ingredient (and addresses the other deficiencies outlined in the action letter), we will not be able to approve FDCs.

Regarding the efficacy of this FDC, as Dr. Parks points out, the glucose lowering effect (measured by HbA1c reduction) of alogliptin as a single agent, as demonstrated in the trials contained within NDA 22-271, is in the range of 0.4 to 0.6 % for the 12.5 and 25 mg doses. This application included efficacy data from three clinical trials which demonstrated that the FDC provides superior efficacy compared to either alogliptin (0.4-0.9% additional HbA1c reduction) or pioglitazone (0.4-0.6% additional HbA1c reduction) monotherapy. This indicates that the FDC has greater efficacy than either individual component.

Dr. Parks noted that there were not any new safety signals for the FDC that had not already been observed with either of the individual ingredients.

I am in agreement with Dr. Parks (please see her complete review) and recommend that this application receive a complete response.

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/s/

CURTIS J ROSEBRAUGH
09/02/2009

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-426
Submission Code	N
Letter Date	9-19-08
Stamp Date	9-22-08
PDUFA Goal Date	7-22-09
Reviewer Name	Valerie S. W. Pratt, M.D.
Review Completion Date	7-1-09
Established Name	Alogliptin/Pioglitazone (SYR-322-4833)
(Proposed) Trade Name	(b) (4)
Therapeutic Class	DPP-4 inhibitor
Applicant	Takeda
Priority Designation	S
Formulation	Tablet
Dosing Regimen	12.5+15, 12.5+30, 12.5+45, 25+15, 25+30, 25+45 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 for alogliptin (based on the December 2008 diabetes cardiovascular guidance) and there is a numerical imbalance against alogliptin in cardiovascular serious adverse events as explained in my NDA 22-271 review. As the risk/benefit ratio did not favor approval of alogliptin, this fixed dose combination (FDC) of alogliptin + pioglitazone (A+P; NDA 22-426) which bridges to the original alogliptin NDA (NDA 22-271) is also not currently approvable.

The sponsor will need to do the following to address the identified deficiencies and support approvability:

- Rule out unacceptable cardiovascular risk with alogliptin 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 submitted a new drug application (NDA) for the new molecular entity (NME), dipeptidyl peptidase-4 (DPP4) inhibitor alogliptin (SYR-322) in a fixed dose combination with the thiazolidinedione (TZD) pioglitazone (a peroxisome proliferator-activated receptor γ [PPARγ] agonist) (b) (4)

Alogliptin is a DDP4 inhibitor, which increases incretin hormones including GLP-1 and glucose dependent insulinotropic polypeptide (GIP). DDP4 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.

Pioglitazone is a PPARγ agonist. PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of insulin responsive genes involved in the control of glucose and

lipid metabolism. It decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Pioglitazone reduces hyperglycemia, hyperinsulinemia, and hypertriglyceridemia. It is not an insulin secretagogue. Pioglitazone has been approved for use within the United States since July 15, 1999.

The sponsor is proposing the use of 12.5+15, 12.5+30, 12.5+45, 25+15, 25+30, or 25+45 mg alogliptin/pioglitazone daily as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D). However, it was communicated to the sponsor on May 7, 2008, that the new indication for a T2D FDC product such as SYR-322-4833 is "A+P is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both alogliptin and pioglitazone is appropriate." A+P may be dosed with or without food.

As an increase in alogliptin exposure was observed in subjects with moderate (Creatinine clearance [CrCl] = 30-50 ml/min) and severe (CrCl<30 ml/min but not on hemodialysis) renal impairment and end stage renal disease (ESRD; on hemodialysis with no or negligible urine output), the sponsor recommends the following:

- Dose reduction in patients with moderate renal impairment
- A+P is not recommended for patients with severe renal impairment or ESRD, because no formulation of SYR-322-4833 has been developed that provides the dose of alogliptin required for these patients.

Systemic exposure to alogliptin was similar between subjects with moderate (Child-Pugh score 7-9) hepatic impairment and healthy subjects. (Alogliptin was not studied in mild or severe hepatic impairment.) Therefore, no dose adjustment is recommended for SYR-322-4833 for patients with mild to moderate hepatic impairment. SYR-322-4833 is not recommended for patients with severe hepatic impairment, because alogliptin was not evaluated in these subjects.

Bioequivalence studies were conducted for only the highest (25/45 mg) and lowest (12.5/15 mg) fixed dose strengths. The sponsor requests a biowaiver for 4 doses (12.5/30, 12.5/45, 25/15, and 25/30 mg) that are not evaluated in the in vivo study. Five biopharmaceutics studies were also conducted.

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 ≥ 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 (not alogliptin tested up to 31x exposures beyond the maximum recommended clinical dose), which is thought to result from cross-reactivity with DPP-8 and DPP-9. Vildagliptin, which is currently marketed in a few countries outside of the United States, may cause hepatoxicity. Vildagliptin's sponsor has been asked to conduct a dedicated hepatic safety study. Alogliptin will not be approved because the sponsor did not rule 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.

Two TZDs, pioglitazone and rosiglitazone, have been approved in the United States since 1999. Both of the pioglitazone and rosiglitazone labels contain black boxes warning for the following:

- TZDs cause or exacerbate congestive heart failure (CHF) in some patients.
- TZDs are not recommended in patients with symptomatic heart failure and initiation is contraindicated in subjects with established NYHA Class III or IV heart failure.

Rosiglitazone contains the additional black box warning that a meta-analysis of 42 clinical studies showed rosiglitazone to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction (MI). Pioglitazone does not appear to increase the risk for atherosclerotic cardiovascular events based on the PROactive trial.

Potential adverse events associated with TZDs also include fluid retention, edema, weight gain, anemia, macular edema, and bone fractures in females. Pioglitazone is also associated with ovulation in premenopausal anovulatory women and postmarketing reports of hepatitis and hepatic enzyme elevations ≥ 3x the upper limit of normal (ULN). Reports of hepatic failure with and without fatal outcome have been received, although causality has not been established.

The sponsor conducted three 26-week phase 3 studies to evaluate the safety and efficacy of alogliptin which are reviewed here. Pivotal studies 01-05-TL-322OPI-001 and 01-06-TL-322OPI-002 (OPI-001 and OPI-002) were 26-week, randomized, double blind, placebo controlled studies in diabetics with and without metformin, respectively. Supportive study SYR-322-TZD-009 (TZD-009) was a 26-week trial that tested alogliptin versus placebo as add-on to pioglitazone. More TZD-009 study subjects received alogliptin than placebo due to the 1:2:2 (placebo: alogliptin 12.5 mg: alogliptin 25 mg) randomization. Studies OPI-002 and OPI-001 used a 1:1:1:1 randomization scheme. Relevant information from the 120-day safety update, which includes uncontrolled, long term data from the TZD-009 subpopulation in study OLE-012, is also included as appropriate.

Across the A+P phase 3 program, the mean age of subjects ranged from 52.6-55.4 years. The majority of subjects were < 65 years and Caucasian (70.5-80.3%). The mean BMI ranged from 31.1-32.8. The mean duration of diabetes in the initial combination study (3.2 years) was lower than the add-on to metformin (6.2 years) and the add-on to pioglitazone (7.6 years) studies.

The primary efficacy variable for the studies was the change in HbA1c study endpoint (after 26 weeks of treatment) compared to baseline. The mean baseline HbA1c ranged from 8.0-8.9% in

the 3 phase 3 trials. In study OPI-002, the A25+P30 group achieved a statistically significant decrease in HbA1c at week 26 compared with A25 and P30 alone (-0.40 and -0.56, respectively). The A12.5+P30 group also showed a statistically significant decrease in HbA1c at week 26 compared to P30 alone (-0.75). In study OPI-001, both the A12.5+P and A25+P groups achieved statistically significant decreases in HbA1c at week 26 compared with the pioglitazone alone grouping (-0.54 and -0.53, respectively). In study TZD-009, both the 12.5 and 25 mg doses achieved statistically significant LS mean differences in HbA1c reductions from baseline to week 26 compared to placebo (-0.47 and -0.61, respectively).

The major secondary efficacy parameters were the percentage of alogliptin-treated subjects achieving HbA1c < 6.5% and < 7%, and mean changes in FPG and body weight. The statistically significant results with regards to HbA1c and FPG levels were as follows:

- Study OPI-002:
  - A significantly higher percentage of subjects in both the A12.5+P30 and A25+P30 groups achieved HbA1c levels ≤7.0% and ≤6.5% compared with the P30 and A25 alone groups.
  - The A25+P30 group achieved a statistically significant decrease in FPG at week 26 compared with either the A25 alone group or the P30 alone group (-24.5 and -12.9 mg/dl, respectively).
  - The A12.5+P30 group also showed a statistically significant decrease in FPG at week 26 compared with the P30 alone group (-11.2 mg/dl).
- Study OPI-001:
  - A significantly higher percentage of subjects in both the A12.5+P grouping and the A25+P grouping achieved HbA1c levels ≤7.0% and ≤6.5% compared with the pioglitazone grouping alone.
  - With regard to FPG, there was a statistically significant overall treatment effect for both combination groupings (A12.5+P and A25+P) compared with the pioglitazone along grouping at every time point from week 1 to 26, based on LS means. At week 26, the LS mean changes were -18.6, -28.8, -45.2, and -44.2 for the A25, P30, A12.5+P, and A25+P groupings, respectively.
- Study TZD-009:
  - A statistically significant number of alogliptin subjects achieved HbA1c ≤7.0% and ≤6.5% compared to placebo.
  - The LS mean decreases in FPG observed in alogliptin-treated subjects were statistically significant compared with the placebo group (-14.1 and -13.9 mg/dl for the alogliptin 25 and 12.5 mg groups, respectively).

When the change from baseline in body weight at week 26 was compared in studies OPI-002, OPI-001, and TZD-009, only study OPI-002 A25+P30 subjects showed a significant change when compared to the A25 alone or P30 alone groups. These subjects experienced an LS mean increase of 0.95 and 3.43 kg, respectively. Although the other groups did not exhibit a statistically significance change in body weight from baseline, body weight generally increased. The LS mean change in weight when alogliptin was used with pioglitazone in studies OPI-002, OPI-001, and TZD-009 was 1.98 kg.

Treated subjects achieved generally consistent mean reductions in HbA1c levels from baseline to week 26 in all subpopulations (gender, age, race, ethnicity, and baseline BMI), although some subgroups have small sample sizes that limit conclusions.

The safety data consist of all randomized subjects who received ≥ 1 dose of study drug. This review focused on two pivotal phase 3 clinical studies (OPI-002 and OPI-001), one supportive phase 3 study (TZD-009), and the 120-day Safety Update which includes the uncontrolled study OLE-012 subgroup TZD-009. 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 study TZD-009. Studies OPI-002 and OPI-001, which investigated alogliptin co-administration with pioglitazone, had a 1:1 randomization. Studies excluded subjects with serum creatinine ≥ 2.0 mg/dl (studies involving metformin had stricter criteria).

The core alogliptin trials were randomized, blinded, and controlled. 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. Alogliptin will not be approved because the sponsor did not rule out an unacceptable increase in cardiovascular risk (based on the December 2008 diabetes cardiovascular guidance) and a numerical imbalance against alogliptin in cardiovascular serious adverse events. The sponsor has been asked to conduct a long-term CV outcomes trial. **Please refer to my alogliptin NDA 22-271 review, section 7 Review of Safety for more information pertaining to the cardiovascular safety of alogliptin.**

Supportive study TZD-009 was not pooled with data from FDC studies OPI-002 and OPI-001, because OPI-002 and OPI-001 subjects had no previous exposure to pioglitazone whereas TZD-009 subjects did. Thus, 12 treatment arms (4 OPI-002 arms and 12 OPI-001 arms) were evaluated in the integrated database. Only 2 of the combination arms were common to both studies (alogliptin 12.5 and 25 mg with pioglitazone 30 mg). Of the dose groupings evaluated, the majority of subjects received alogliptin alone or in combination with pioglitazone (1528/2207; 69.2%) and a small number of subjects received only placebo (129/2207; 5.8%). Therefore, the pooled data is presented at the compound level excluding the placebo-only group (except disposition and exposure which do include the placebo-only group). The 3 treatment groupings are as follows:

- Alogliptin grouping: all subjects who received alogliptin with pioglitazone placebo
- Pioglitazone grouping: all subjects who receive pioglitazone with alogliptin placebo
- Combination grouping: all subjects who received alogliptin with pioglitazone

NDA 22-426. Dose groups		
Placebo +	**Alogliptin 12.5 mg +**	**Alogliptin 25 mg +**
Placebo (OPI-001)	Placebo (OPI-001)	Placebo (both studies)
Pioglitazone 15 mg (OPI-001)	Pioglitazone 15 mg (OPI-001)	Pioglitazone 15 mg (OPI-001)
Pioglitazone 30 mg (both studies)	Pioglitazone 30 mg (both studies)	Pioglitazone 30 mg (both studies)
Pioglitazone 45 mg (OPI-001)	Pioglitazone 45 mg (OPI-001)	Pioglitazone 45 mg (OPI-001)

Exposure data is shown below. The demographic and baseline characteristics of subjects in the controlled phase 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 controlled phase 3 study groups of A+P, the mean patient age was 53.1 years. The majority of subjects were White (74.9%). The percentage of Asian and Black subjects ranged between 4-7%. Approximately half of subjects were male. The majority were obese with a mean duration of diabetes of 5.4 years and mean HbA1c of 8.6%.

NDA 22-426. Controlled and uncontrolled A+P exposure. NOTE: Uncontrolled data has a September 15, 2008 cutoff)

Study	**Exposure**		
	≥ 6 mo	**≥ 12 mo**	**≥ 18 mo**
Controlled TZD-009	315		
Controlled OPI-001	688		
Controlled OPI-002	264		
Controlled total	**1267**		
Uncontrolled OLE-012 data (subgroup TZD-009)	378	192	158
Uncontrolled OLE-012 data (subgroups TZD-009, OPI-001, & OPI-002)*	1330		

*Subjects form TZD-009 who chose to rollover into the OLE-012 continued their TZD background therapy during the extension study. In contrast, subjects from FDC studies OPI-001 and OPI-002 were randomized in a blinded fashion to alogliptin alone, pioglitazone alone, or a combination of both in these studies. As a result, subjects from FDC studies OPI-001 and OPI-002 who enrolled in OLE-012 were not permitted to receive pioglitazone initially upon entry into study OLE-012. Therefore, these subjects were not included in the 120-day Safety Update as they did not all receive continuous pioglitazone therapy.

No deaths were reported in study OPI-002. A total of 4 deaths occurred in studies OPI-001, TZD-009, and OLE-012; 2 of these were reported in the 120 day safety update (September 15, 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 was only 1 death among alogliptin-treated patients.

A total of 28 (2.5%) A+P 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 the 2 pivotal controlled phase 3 studies of A+P. In these 2 pivotal FDC studies, TESAEs were most common in the infection and infestation disorders SOC (0.5%) followed by cardiac, gastrointestinal, and nervous system disorders (0.4% each). In supportive study TZD-009 and the uncontrolled OLE-012 study TZD-009 subgroup, TESAEs were most common in the cardiac disorders and infection and infestation disorders SOCs.

In the pooled 2 pivotal controlled phase 3 studies (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 included diarrhea, nausea, edema peripheral, weight increased, liver tests

abnormal, and dizziness. In supportive study TZD-009, discontinuation due to AEs was similar between treatment groups (placebo 3.1%, A12.5 4.1%, and A25 3.0%); no dose-related trend was seen.

The sponsor analyzed the following as AEs of interest for alogliptin treatment in pooled OPI-001 and OPI-002 trials:

- Cardiovascular (CV) AEs of interest cluster: The incidence was highest in the pioglitazone group (11.1%), followed by the combination (9.1%) and alogliptin (5.7%) groups.
- Ischemic heart disease: The incidence was highest in the pioglitazone group (pioglitazone 3.1%, combination 1.8%, alogliptin 1.4%). Ten subjects experienced SAEs in the ischemic heart disease cluster (pioglitazone 4, A+P 4, and alogliptin 2). Three subjects were discontinued as a result of the AE (combination 2, pioglitazone 1).
- Cardiac arrhythmias cluster: The incidence of AEs was greatest in the pioglitazone group (pioglitazone 4.2%, A+P 3.6%, alogliptin 1.7%). The incidence of the most common AEs, palpitations and tachycardia, was higher however in the A+P group, although the percent incidence was low (0.5%).
- Angioedema cluster: The incidence was highest in the pioglitazone group (4.2% vs. A+P 3.3% and alogliptin 2.4%). Edema peripheral, a known AE of pioglitazone, accounted for the majority of the agioedema cluster events.
- Potential cutaneous drug reaction cluster (The customized MedDRA query of PCDR events did not include most ulcers; only venous ulcer pain was included.): In the 2 pivotal studies of A+P under NDA 22-426, the overall incidence of PCDR AEs was higher in the combination grouping (7.6%) than the pioglitazone and alogliptin groupings (6.5% and 6.2%, respectively). The most frequently reported AEs in this cluster were again pruritis and rash. There were no PCDR SAEs, although AEs led to discontinuation in 6 subjects (5 A+P, 1 pioglitazone).

As requested, on May 20, 2009, the sponsor provided an analysis of pancreatitis cases occurring with alogliptin and comparators in the controlled phase 2/3 clinical trials. The analysis was performed by using the SMQ of "acute pancreatitis" in MedDRA version 10.0. Overall, the pancreatitis event rate, based on all preferred terms included in this SMQ, was low and similar to placebo (~5%).

The sponsor analyzed the following as AEs of interest for pioglitazone treatment treatment in pooled OPI-001 and OPI-002 trials:

- Cardiac failure cluster: The incidence in the pioglitazone group was greater than that of the A+P and alogliptin groups (4.0% vs. 3.4% and 1.4%, respectively).
- Edema cluster: AEs in the edema cluster occurred more commonly in the pioglitazone group when compared to the A+P and alogliptin groups (3.8% vs. 3.3% and 1.7%, respectively). The most common AE was edema peripheral which also occurred more commonly in the pioglitazone group (3.5% vs. 2.7% and 1.4%, respectively).

- Weight gain cluster: The incidence was similar in the pioglitazone and A+P groups (2.5% and 2.4%, respectively, vs. 0.5% alogliptin). There were no SAEs in the weight gain cluster, although 2 subjects (both A+P) discontinued due to weight increased.
- Bone fracture cluster: The rate of bone fractures in the 2 pivotal trials was similar in the pioglitazone and A+P groups (2.0% and 1.8%, respectively, vs. 1.2% alogliptin).
- Neoplasms benign, malignant, and unspecified SOC: The incidence was highest in the A+P group, although it was similar to the pioglitazone group (A+P 0.9%, pioglitazone 0.7%, and alogliptin 0.2%). Most events which occurred more frequently in the A+P group were isolated events, although skin papilloma and seborrheic keratosis occurred at 0.3% and 0.2% respectively. Overall, the incidence of AEs in this SOC was low.

In pivotal studies OPI-002 and OPI-001, 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 nasopharnygitis (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%). 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).

In supportive study TZD-009, cardiac disorders occurred more often in the alogliptin 12.5 and 25 mg groups when compared to placebo (3.0% and 6.5% vs. 1.0%). The most common events in the cardiac disorder SOC were atrial fibrillation, cardiac failure, MI, coronary artery disease, and ventricular extrasystoles. Nervous system events occurred more often in the alogliptin groups in TZD-009 (15.2% and 16.6% vs. 10.3%). The most common nervous system events were headache and dizziness. Respiratory, thoracic, and mediastinal events occurred more often in the alogliptin groups (8.1% and 9.5% vs. 5.2%); cough and epistaxis were the most common AEs. Adverse events in the blood & lymphatic, ear & labyrinth, and immune system SOCs were also more common the alogliptin groups; anemia and vertigo were the most common AEs in these SOCs.

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. In the pivotal studies, infection and infestation events occurred more often in the A+P group than the alogliptin and pioglitazone groups (27.5% vs 25.2% and 25.1%). Upper respiratory infection, pharyngitis, bronchitis, and sinusitis all occurred more often in the A+P and/or alogliptin group than the pioglitazone group. However, in supportive study TZD-009, infections and infestations were more common the placebo group when compared to alogliptin 12.5 and 25 mg (37.1% vs. 34.8% and 33.7%).

Standard safety laboratory data were obtained in all studies at baseline, during the treatment period, and at study end. This reviewer focused the review of laboratory and vital sign data in the pivotal phase 3 studies, OPI-002 and OPI-001, which evaluated the safety and efficacy of the to-be-marketed dose combinations of alogliptin and pioglitazone.

Men were required to have a hemoglobin level ≥ 12 g/dl and women ≥ 10 g/dl to enroll in the controlled phase 3 studies. Pioglitazone has been associated with dose-related decreases in hemoglobin and hematocrit, which are likely related to increased plasma volume. As expected, small decreases in the pioglitazone and A+P groups' hematocrit and hemoglobin were seen compared to alogliptin alone (hematocrit: -1.61% and -1.61% vs. -0.87%; hemoglobin: -0.30 and -0.41 g/dl vs. -0.08 g/dl). Lymphocytes and platelets decreased slightly (lymphocytes: A+P -1.1%, Pio 0.5%, Alo -1.7 %; platelets: A+P -6.2, Pio -5.7, Alo -5.0). Monocytes increased slightly (A+P 1.1%, Pio 0.8%, Alo 0.5%). Overall, the mean changes from baseline to endpoint in hematology results were minor and not clinically meaningful.

Few shifts among low, normal, and high categories from baseline to endpoint were observed for most variables across groupings. Exceptions included decreased hemoglobin and hematocrit and increased lymphocytes and monocytes, which were slightly more common in the A+P group. (Both the pioglitazone and A+P groups had a 6.4% incidence of increased lymphocytes.) As explained above, the hemoglobin and hematocrit shifts were expected in the groups taking pioglitazone. The shift towards an increased lymphocyte percentage is not consistent with the mean change from baseline to endpoint which was negative.

In the pivotal, controlled phase 3 studies, subjects were required to have ALT <2.5x ULN (OPI-002) or ≤2.5x ULN (OPI-001), and creatinine < 2.0 mg/dl (males and females in OPI-002) or < 1.5 mg/dl (males in OPI-001) or < 1.4 mg/dl (females in OPI-001). The mean change from baseline to endpoint in serum BUN and creatinine increased slightly more in the A+P group when compared to the alogliptin and pioglitazone groups (BUN: 1.4 vs. 0.7 and 0.2 mg/dl; creatinine: 0.04 vs. 0.02 and 0.02 mg/dl, respectively). However, AST and ALT improved (i.e. decreased) on average in the A+P group (-2.1 for AST and -4.1 mU/ml for ALT). The mean change from baseline to endpoint in sodium and LDH was greatest in the A+P group, although values were similar to comparators. Alkaline phosphatase decreased the most in the A+P group (-7.0 mU/ml).

The incidence of markedly abnormal chemistry results in the pivotal phase 3 studies OPI-001 and OPI-002 in the A+P group were similar or less than comparators, except for serum creatinine (A+P 1.6% vs. alogliptin 1.2% and pioglitazone 0.7%). In total, 26 subjects had creatinine levels >1.5x baseline during treatment. Only 3 of the 26 subjects, all in the A+P group, had creatinine levels that also exceeded the ULN. Uric acid also increased in the A+P and alogliptin groups (1.8% and 2.7% vs. 0.6%), although the incidence of gout AEs was similar across study groups in the pivotal phase 3 trials (0-0.2%).

When shifts in chemistry values were reviewed, more A+P subjects experienced normalization of AST, ALT, and alkaline phosphatase (A+P: 67.2, 69.3, and 62.0%; alogliptin: 45.7, 47.3,

36.9%, pioglitazone: 56.8, 65.3, 49.3%, respectively). However, more A+P subjects also experienced increases in BUN and magnesium (A+P: 9.3 and 7.2%; alogliptin: 6.4 and 6.5%; pioglitazone: 8.9 and 5.9%, respectively).

The change from baseline to endpoint in creatinine clearance was low in all treatment groups and varied on the formula used (CG: -0.84 to -2.98 ml/min; MDRD: -1.53 to -3.91 ml/min). Slightly more subjects in the A+P group experienced a shift from normal to mild or moderate renal impairment when compared to the alogliptin and pioglitazone groups using both CG and MDRD formulas.

Subjects with a urine albumin/creatinine ratio of > 1000 mcg/mg (>113 mg/mol) were excluded from the pivotal, controlled phase 3 studies. The mean change in albumin/creatinine ratios from baseline to endpoint increased in the A+P and pioglitazone groups when compared to alogliptin (24.3 and 12.0 vs. -2.6 µg/mg), although median change was more similar (-6 and -6 vs. -4) However, sample sizes for this measurement were small and thus complicate data interpretation.

Hypoglycemic events were classified as severe (blood glucose <60 mg/dl requiring assistance), mild/moderate with or without symptoms (blood glucose <50 mg/dl), and symptomatic mild/moderate (blood glucose < 60 mg/dl with symptoms). The pioglitazone group had the greatest incidence of severe hypoglycemia (pioglitazone 2.0%, A+P 0.1%, and alogliptin 0%). The greatest incidence of blood glucose <50 mg/dl with or without symptoms occurred in the A+P group (0.8% vs. pioglitazone 0.4% and alogliptin 0.2%).

The changes from baseline to endpoint in blood pressure and heart rate were similar between treatment groups. The percentage of subjects with abnormal vital sign measurements postbaseline were similar between the treatment groups, although slightly more A+P and pioglitazone subjects experienced increased systolic and diastolic blood pressure when compared to the alogliptin group (systolic: 3.4 and 4.2 vs. 2.2%; diastolic: 4.5 and 5.5 vs. 3.6%).

A standard 12-lead ECG was obtained at screening, baseline, week 12, and the end of treatment visit in the pivotal, controlled phase 3 studies. Additional ECGs were performed at the discretion of the investigator. The mean change in ECG intervals was <5 msec for all groups and near zero in the A+P group. 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 pivotal controlled phase 3 studies.

The effect of renal impairment; hepatic impairment; and age, gender, and race were investigated in special safety studies under alogliptin IND 69,707. (Please refer to the clinical pharmacology and clinical review of alogliptin NDA 22-271.)

Pioglitazone is associated with dose-related increases in weight and decreases in hemoglobin and hematocrit. No dose-related trend was seen in pivotal studies OPI-002 and OPI-001 with respect to death or study withdrawal (i.e. voluntary or AE discontinuation). A small dose-related trend was seen in the incidence of SAEs and AEs in study OPI-002 but not OPI-001 (A25 0.6%, P30

3.7%, A12.5+P30 0.6%, A25+P30 4.9%), although this was not driven by any particular preferred terms (PTs). As discussed above, in both studies, slightly more A25+P subjects had serum creatinine levels 1.5x baseline.

No significant difference was seen between the alogliptin, pioglitazone, and A+P groups in time to onset of AEs.

The pivotal A+P phase 3 studies were analyzed with respect to gender, age, race, and BMI.

- Adverse events more commonly occurred in females (63.3-65.4% vs. 54.4-61.9%). In the A+P group, the incidences of edema peripheral, urinary tract infection, and headache were ≥2% greater in females than males.
- The majority of subjects were < 65 years old (84.1-88.4%), which complicated age and treatment group comparison due to samples sizes as low as 49 in the ≥65 year alogliptin group. AEs occurred, on average, slightly more often in the < 65 year old group (60.7-62.6% vs. 44.9-63.1%). The difference in the incidence of AEs of interest between the 2 age groups was <2%. Headache was the most common AE of interest in the <65 year group (5.7%), whereas back pain was most common in the ≥65 year group (6.3%). However, one AE (not of interest), anemia, occurred noticeably more often in the ≥65 years A+P group.
- The majority of subjects in the pivotal studies were Caucasian (>70%). Asian subjects represented 7.3-10.2% of the treatment group population; Blacks represented 4.2-5.8% of the studied population. AEs occurred more often in the Asian and Black groups. The percentage incidences of AEs of interest varied between groups, probably in part due to the variation in sample size. Asians were at slightly higher risk for AEs in the blood and lymphatic system disorder SOC.
- AEs occurred in a similar percentage of nonobese and obese subjects (58.3-64.4%). The difference in the AE event rate between the A+P nonobese and obese subjects was ≤2% for AEs of interest, except for nasopharyngitis (2.7% vs. 5.1%) and back pain (2.9% vs. 5.8%).

The sponsor tallied AEs by summary baseline renal impairment category. The incidence of AEs was similar between treatment groups within renal impairment categories, except for moderate renal impairment. More AEs occurred in A+P treated subjects with baseline moderate renal impairment (CG and MDRD formulas: 85.7% and 76.9%, respectively)., although the small sample size limits conclusions. (Please refer to section 7.5.4 Drug-Disease Interactions for more information.)

The sponsor did not analyze the pivotal phase 3 A+P studies by hepatic impairment, although study SYR-322-023 assessed the single dose PK of alogliptin 25 mg in subjects with and without hepatic impairment. Moderate hepatic impairment did not significantly affect alogliptin exposure. Please refer to the clinical pharmacology and clinical reviews of alogliptin NDA 22-271.

Compared with normal controls, subjects with Child-Pugh Grade B/C hepatic impairment have approximately a 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values. Pioglitazone should not be initiated if a patient has clinical evidence of active liver disease or serum transaminase levels (ALT) >2.5x ULN.

No A+P drug-drug interaction studies were conducted for this NDA. Please refer to the clinical pharmacology and clinical reviews of alogliptin NDA 22-21 and the pioglitazone prescribing information.

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 (≥ 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.

In a 2-year carcinogenicity study of pioglitazone in male and female rats, benign and/or malignant urinary bladder transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). A 2-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11x the maximum recommended human oral dose based on mg/m^2); no drug-induced tumors were observed in any organ.

No new cases of bladder tumor were identified during a prospective evaluation of urinary cytology in >1,800 patients who received pioglitazone for up to 1 year. In two 3-year studies comparing pioglitazone to placebo or glyburide, there were 16/3656 (0.44%) report of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was < 1 year at the time of bladder cancer diagnosis, there were 5 (0.16%) cases on pioglitazone and 2 (0.05%) on placebo.

Fetal growth and developmental effects occur at maternally toxic doses with alogliptin. In rats, the concentration of alogliptin in milk is 2x maternal plasma concentration, thus fetal exposure with breastfeeding is expected in humans.

Pioglitazone is pregnancy category C; it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is secreted in the milk of lactating rats; it is not know if pioglitazone is secreted in human milk.

The following pregnancies were also reported in the pivotal phase 3 A+P program in subjects who received alogliptin:

- 412/3119: 32 year old female with a history spontaneous abortion and 2 Cesarean-sections experienced a spontaneous abortion on day 80.
- 830/3002: 46 year old female with a history of 4 pregnancies (1 live birth, 3 spontaneous abortions) experienced an abortion spontaneous on day 197 of study OPI-001.

On September 24, 2008, the Pediatric Review Committee (PeRC) decided that alogliptin studies would be deferred in ages 10-16 years and waived in ages 0-9 years. On May 26, 2009, the sponsor proposed a pediatric development plan for A+P. (b) (4)

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) in a fixed dose combination with the thiazolidinedione (TZD) pioglitazone (a peroxisome proliferator-activated receptor γ [PPARγ] agonist) (b) (4) The sponsor is proposing the use of 12.5+15, 12.5+30, 12.5+45, 25+15, 25+30, or 25+45 mg alogliptin/pioglitazone daily as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D). However, it was communicated to the sponsor on May 7, 2008, that the new indication for a T2D FDC product such as SYR-322-4833 is "A+P is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both alogliptin and pioglitazone is appropriate." A+P may be dosed with or without food.

As an increase in alogliptin exposure was observed in subjects with moderate (Creatinine clearance [CrCl] = 30-50 ml/min) and severe (CrCl<30 ml/min but not on hemodialysis) renal impairment and end stage renal disease (ESRD; on hemodialysis with no or negligible urine output), the sponsor recommends the following:

- Dose reduction in patients with moderate renal impairment
- A+P is not recommended for patients with severe renal impairment or ESRD, because no formulation of SYR-322-4833 has been developed that provides the dose of alogliptin required for these patients.

Systemic exposure to alogliptin was similar between subjects with moderate (Child-Pugh score 7-9) hepatic impairment and healthy subjects. (Alogliptin was not studied in mild or severe hepatic impairment.) Therefore, no dose adjustment is recommended for SYR-322-4833 for patients with mild to moderate hepatic impairment. SYR-322-4833 is not recommended for patients with severe hepatic impairment, because alogliptin was not evaluated in these subjects.

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)
    - Rosigitazone (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 Unites States. Pioglitazone has been approved for use within the United States since July 15, 1999.

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 ≥ 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 (not alogliptin), which is thought to result from cross-reactivity with DPP-8 and DPP-9. Vildagliptin, which is currently marketed in a few countries outside of the United States, may cause hepatoxicity. Vildagliptin's sponsor has been asked to conduct a dedicated hepatic safety study. Alogliptin will not be approved because the sponsor did not rule 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.

Two TZDs, pioglitazone and rosiglitazone, have been approved in the United States since 1999. Both of the pioglitazone and rosiglitazone labels contain black boxes warning the following:

- TZDs cause or exacerbate congestive heart failure (CHF) in some patients.
- TZDs are not recommended in patients with symptomatic heart failure and are contraindicated in subjects with established NYHA Class III or IV heart failure.

Rosiglitazone contains the additional black box warning that a meta-analysis of 42 clinical studies showed rosiglitazone to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction (MI). Pioglitazone does not appear to increase the risk for atherosclerotic cardiovascular events based on the PROactive trial.

Potential adverse events associated with TZDs also include fluid retention, edema, weight gain, anemia, macular edema, and bone fractures in females. Pioglitazone is also associated with ovulation in premenopausal anovulatory women and postmarketing reports of hepatitis and hepatic enzyme elevations ≥ 3x the upper limit of normal (ULN). Reports of hepatic failure with and without fatal outcome have been received, although causality has not been established.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

NOTE: This A+P FDC NDA cross-references studies completed under alogliptin IND 69,707. These studies were recently reviewed under alogliptin NDA 22-271. Please refer to my review of NDA 22-271. Of key importance is the fact that NDA 22-271 requires a complete response 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 as explained in my NDA 22-271 review. As the risk/benefit ratio did not favor approval of alogliptin, this FDC of A+P (NDA 22-426) which bridges to the original alogliptin NDA 22-271 is also not currently approvable.

A pre-IND meeting was held for the A+P FDC on February 8, 2006. At this meeting, concurrence was reached on 1) the design of the pivotal coadministration study and 2) the regulatory strategy to support the SYR-322-4833 FDC product. A 4-way bioequivalence (BE) study was recommended with the highest and lowest strengths (25/45 and 12.5/15 mg, respectively) in combination and with 2 individual drugs. The 30 mg pioglitazone BE study could be waived based on comparable dissolution profiles. The sponsor's plan to conduct a phase 3, 26-week coadministration study (01-05-TL-322OPI-001 [OPI-001]) and single dose, pharmacokinetic (PK) study to assess the effect of food on SY-322-4833 25/45 mg was acceptable.

On January 23, 2008, the sponsor requested a type B pre-new drug application (pre-NDA) meeting. The meeting request was denied, although responses to the February 15, 2008 meeting document were provided to the sponsor on May 7, 2008. Further response clarification was conveyed on June 2, 2008. These responses included the following:

- A strong recommendation that the sponsor submit a complete stability package in the original NDA, including at least 12 months of long term data.
- Agreement that combination toxicology and embryofetal toxicology studies support the nonclinical component for filing.
- Agreement that the proposed PK and drug-interaction programs for single agents will likely support the registration of the FDC product.
- Clarification of the new indication for T2D FDC products.
- Agreement with the proposed approaches for the presentation of the integrated safety data and for discussing study 009 separately from the FDC studies.
- The Pediatric Review Committee (PeRC) will provide input on whether or not studies in the pediatric population may be deferred.

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.

Pioglitazone was approved for use in the United States on July 15, 1999. Another TZD, rosiglitazone, was approved for use in the United States on May 25, 1999.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The 3 controlled, phase 3 studies (01-06-TL-322OPI-002, 01-05-TL-322OPI-001, and SYR-322-TZD-009) pertinent to the claimed indication that are reviewed here were each conducted in multiple countries (average 19 countries, range 13-23 countries).

Three study sites were inspected. The investigators and reason for site selection are listed below:

- Dr. Danielo Lopez (OPI-001 site 716): This site was a high US enroller (23 randomized) and had a complaint pending.
- Dr. Ronald Sockolov (OPI-001 site 774): This site was a high US enroller (10 randomized) and had never been inspected.
- Dr. Rafael Canadas (OPI-002 site 12): This site was inspected in December 2007 when official action was indicated. Voluntary action is currently indicated due to an employee complaint, although the allegations could not be documented in the field.

Outcomes of the Division of Scientific Investigations' inspections were as follows:

- Dr. Danielo Lopez: No action indicated.
- Dr. Ronald Sockolov:
    - The clinical investigator failed to report AEs "increased pedal edema, cellulitis, and upper respiratory infection," because he didn't think they were "significant." There were no unreported cardiac AEs.
    - DSI Recommendation: Voluntary action indicated
- Dr. Rafael Canadas:
    - Did not ensure that the investigation was conducted according to the investigational plan
    - Diabetes education was not provided as specified in the protocol.
    - A Spanish-speaking diabetes educator was not provided for some subjects.
    - DSI Recommendation: Voluntary action indicated

Overall, DSI concluded that data from all sites are acceptable in support of the proposed indication.

FDA's Bioresearch Monitoring Program, which evaluates the research conduct and ensures the rights, safety, and welfare of human subjects are protected, investigated Dr. Rebecca Mayol-Sharp's site, which participated in studies OPI-001 and OLE-012. Voluntary action was indicated due to subject physical examination and vital sign records as well as drug disposition records.

3.2 Compliance with Good Clinical Practices

According to the sponsor, the 3 clinical studies pertinent to the claimed indication that are reviewed here (01-06-TL-322OPI-002, 01-05-TL-322OPI-001, and SYR-322-TZD-009) 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 3 controlled, phase 3 clinical studies pertinent to the claimed indication were as follows:

- 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 subjects

  Deviations 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.
- 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.

In addition, 3 A+P subjects in study OPI-002 should have been labeled as having a major protocol deviation for receiving a treatment different from the randomized treatment. 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, (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, (b) (6) received $295,000 (since December 2002) and $202,700 (since October 2003), respectively. Both investigators participated in study (b) (4)
The number of subjects contributed by each investigator was small. Therefore, the data submitted (b) (6) are not expected to impact the overall conclusions of the trials.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry Manufacturing and Controls (CMC) recommendation is pending an overall recommendation from the Office of Compliance (completion of establishment inspections) and the sponsor's response to the CMC IR letter. The sponsor agreed to complete 36-month long-term, intermediate and 6-month accelerated stability studies for 3 commercial lots of the drug product. In addition, the sponsor agrees to add one commercial lot to the stability program each year following approval. Please refer to Theodore Carver's review.

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 (≥ 200x 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, immunoglobin-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 DDP4 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 (the maximum 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.

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 (≥ 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.

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.

In a 2-year carcinogenicity study of pioglitazone in male and female rats, benign and/or malignant urinary bladder transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). A 2-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11x the maximum recommended human oral dose based on mg/m^2); no drug-induced tumors were observed in any organ.

No new cases of bladder tumor were identified during a prospective evaluation of urinary cytology in >1,800 patients who received pioglitazone for up to 1 year. In two 3-year studies comparing pioglitazone to placebo or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was < 1 year at the time of bladder cancer diagnosis, there were 5 (0.16%) cases on pioglitazone and 2 (0.05%) on placebo.

Pioglitazone is pregnancy category C; it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17x and 40x the maximum recommended human oral dose based on mg/m^2). Delayed parturition and embryotoxicity (e.g. increased postimplantation losses, delayed development, and reduced fetal weights were observed in rats at oral doses ≥40 mg/kg/day (approximately 10x the maximum recommended human oral dose based on mg/m^2). In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40x the maximum recommended human oral dose based on mg/m^2). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses ≥10 mg/kg during late gestation and lactation (approximately 2x the maximum recommended human oral dose based on mg/m^2).

Pioglitazone is secreted in the milk of lactating rats; it is not known if pioglitazone is secreted in human milk.

Regarding the A+P FDC, on April 13, 2006, the agency advised the sponsor to conduct 1) a 90-day combination toxicity study in the most sensitive species (i.e. nonrodent) and 2) a rat embryofetal development study. The request for the nonrodent study was due to concerns about DPP-4 inhibitor-related skin lesions. The sponsor conducted 4- and 13-week monkey studies to investigate cutaneous toxicity; the results were negative (see above). Thus, the sponsor decided to conduct the 90-day combination toxicity study in rats. Pharmacology/toxicology accepts this study design because of the negative skin findings in monkeys and the dog is not recommended for PPAR combination studies. The 90-day FDC rat study showed no apparent toxicokinetic (TK) drug interactions, although toxicity expected from pioglitazone was seen (i.e. increased heart weight and adipocyte changes).

Please refer to Dr. David Carlson's review and the pioglitazone label for full details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Alogliptin is a DDP4 inhibitor, which increases incretin hormones including GLP-1 and glucose dependent insulinotropic polypeptide (GIP). DDP4 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, DDP9, or related DASH enzymes (PREP, FAP/seprase, tryptase). Alogliptin's DPP4 selectivity is similar to sitagliptin and superior to vildagliptin.

Pioglitazone is a PPARγ agonist. PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of insulin responsive genes involved in the control of glucose and lipid metabolism. It decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Pioglitazone reduces hyperglycemia, hyperinsulinemia, and hypertriglyceridemia. It is not an insulin secretagogue.

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 of NDA 22-271, 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)

	Alogliptin vs Placebo		
Add-on Therapy	Alogliptin 12.5 mg	Alogliptin 25 mg	Difference Between Alogliptin 12.5 mg and 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.

Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, improves hepatic sensitivity to insulin, and improves dysfunctional glucose homeostasis. In T2D patients, this results in lower plasma glucose concentrations, lower plasma insulin levels, and lower hemoglobin A1c (HgbA1c) values.

Patients with lipid abnormalities were included in clinical trials with pioglitazone. These patients had mean decreases in triglycerides, mean increases in high-density lipoproteins (HDL) cholesterol, and no consistent mean changes in low-density lipoproteins (LDL) and total cholesterol.

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 Cmax (Tmax), clearance (CL/F), volume of distribution (Vdz/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.

Serum concentrations of total pioglitazone remain elevated 24 hours after once daily dosing. Following oral administration in the fasting state, pioglitazone concentrations peak within 2 hours. Food slightly delays the time to peak serum concentrations but does not alter the extent of absorption. Steady-state serum concentrations of both pioglitazone and total pioglitazone (i.e. pioglitazone plus active metabolites) are achieved within 7 days.

Following oral administration, 15-30% of the pioglitazone dose is recovered in the urine. Renal elimination is negligible; the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into bile either unchanged or as metabolites and eliminated in the feces. The mean serum half-life of pioglitazone and total pioglitazone ranges from 3-7 hours and 16-24 hours, respectively. Pioglitazone has an calculated apparent clearance, CL/F, of 5-7 L/h. Please refer to pioglitazone label for full details.

Regarding the FDC, bioequivalence studies were conducted for only the highest (25/45 mg) and lowest (12.5/15 mg) fixed dose strengths. The sponsor requests a biowaiver for 4 doses (12.5/30, 12.5/45, 25/15, and 25/30 mg) that are not evaluated in the in vivo study. The 5 sponsor-conducted biopharmaceutics studies are as follows:

- 322OPI-101 "A pivotal bioequivalence study with the highest and lowest strength of proposed commercial (FDC) tablet and individual tablets of alogliptin and pioglitazone": The FDC met the standards for bioequivalence to the alogliptin 12.5 & 25 mg and pioglitazone 15 & 45 mg individual tablets.
- 01-06-TL-322OPI-006 "A single dose food effect study on the proposed commercial formulation": There was no effect of food on total or peak exposures in subjects who received SYR-322-4833 25+45 mg. The median Tmax of pioglitazone increased by approximately 2 hours when SYR-322-4833 BL 25 mg + 45 mg were administered under fed conditions compared to fasted conditions.
- 01-06-TL-322-OPI-007 "A pilot relative bioavailability study with the highest and lowest strength of proposed commercial (FDC) tablet and individual tablets of alogliptin and pioglitazone": The relative bioavailability of alogliptin and pioglitazone were similar when dosed as SYR-322-4833 BL (FDC) as compared to when dosed individually at both dosage strengths, **but failed for peak concentration**.
- 01-06-TL-322OPI-005 and 322OPI-101: These 2 additional bioequivalence studies used FDC tablets (SYR-322-4833 (b) (4) and SYR-322-4833 (b) (4), respectively) but not the

proposed commercial FDC tablets. These 2 FDC formulations (12.5+15 mg and 25+45 mg) **failed** to meet the standards for bioequivalence to the alogliptin 12.5 & 25 mg and pioglitazone 15 & 45 mg individual tablets.

The lowest dose proposed for alogliptin in the FDC is 12.5 mg. The sponsor recommends that the FDC not be used in subjects with severe renal impairment or ESRD.

Please refer to Dr. Ritesh Jain's review for full details.

5 Sources of Clinical Data

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				
01-06-TL-322OPI-006 1-United States	Randomized, open label, 2 sequence, 2 period crossover Food effect (PK)	24 healthy subjects	1d (7d washout for crossover)	FDC 25/45 mg fasted (12/11) FDC 25/45 mg (12/12) fed
5.3.1.2 Comparative bioavailability and bioequivalence studies				
01-06-TL-322OPI-007 1-United States	Randomized, open label, 4 sequence, 4 period crossover Relative bioavailability (PK)	16 healthy subjects	1d (7d washout for crossover)	FDC 12.5/15 mg (4/4) Alo 12.5 + Pio 15 mg (4/4) FDC 25/45 mg (4/4) Alo 25 + Pio 45 mg (4/4)
322OPI-101 1-United States	Randomized, open label, 4 sequence, 4 period crossover Bioequivalence (PK)	72 healthy subjects	1d (7d washout for crossover)	FDC 12.5/15 mg (18/16) Alo 12.5 + Pio 15 mg (18/18) FDC 25/45 mg (18/16) Alo 25 + Pio 45 mg (18/16)
5.3.5.1 Study reports of controlled clinical studies pertinent to the claimed indication				
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 ≥ 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)
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) Total (493/384)
5.3.5.4 Other clinical studies				
01-06-TL-322OPI-005(c) 1-United States	Randomized, open label, 4 sequence, 4 period crossover Bioequivalence (PK)	68 healthy subjects	1d (7d washout for crossover)	FDC 12.5/15 mg (17/17) Alo 12.5 + Pio 15 mg (17/15) FDC 25/45 mg (17/15) Alo 25 + Pio 45 mg (17/15)
322OPI-102(c) 1-United States	Randomized, open label, 4 sequence, 4 period crossover Bioequivalence (PK)	83 healthy subjects	1d (7d washout for crossover)	FDC 12.5/15 mg (23/12) Alo 12.5 + Pio 15 mg (20/15) FDC 25/45 mg (19/12) Alo 25 + Pio 45 mg (21/12)

5.2 Review Strategy

This reviewer focused her review on the controlled clinical studies pertinent to the claimed indication, including 01-06-TL-322OPI-002 (OPI-002), 01-06-TL-322OPI-001 (OPI-001), and SYR-322-TZD-009 (TZD-009). Please note that many of the safety elements of these 3 studies were also reviewed under alogliptin NDA 22-271.

Clinical study reports were first reviewed, including the selected case report forms and datasets. The author then reviewed the Summary of Clinical Efficacy, Integrated Analysis of Safety, 120-day Safety Update (August 27, 2008), as well as other responses to clinical information requests. The 120-day Safety Update included study TZD-009 subgroup analysis of the third interim analysis of uncontrolled, open-label extension study SYR-322-OLE (OLE-012 cutoff date of September 15, 2008).

5.3 Discussion of Individual Studies

The sponsor conducted three 26-week phase 3 studies (OPI-001, OPI-002, and TZD-009) to evaluate the safety and efficacy of alogliptin. Pivotal studies OPI-001 and OPI-002 were 26-week, randomized, double blind, placebo controlled studies in diabetics with and without metformin, respectively. Supportive study TZD-009 was a 26-week trial that tested alogliptin versus placebo as add-on to pioglitazone. The section below provides a detailed description of the study designs.

Study TZD-009 subgroup analysis of the third interim analysis of uncontrolled, open-label extension study was provided in the 120-day Safety Update. Please refer to my review of alogliptin NDA 22-271 for a detailed description of the OLE-012 study design.

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-TZD-009:

Study phase and dates conducted: Phase 3 study completed February 24, 2006-August 2, 2007.

Objectives:
Primary: To determine the efficacy of alogliptin administered with pioglitazone as compared to pioglitazone alone on HbA1c change from baseline
Secondary:

- To evaluate other measures of glycemic control after treatment with alogliptin with pioglitazone as compared to pioglitazone 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 pioglitazone as compared to a pioglitazone alone, determined by changes in fasting proinsulin, insulin, and C-peptide
- To evaluate changes in body weight following treatment with alogliptin with pioglitazone as compared to a pioglitazone alone

- To evaluate the safety of alogliptin in combination with pioglitazone as compared to pioglitazone 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 pioglitazone as compared with pioglitazone 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 pioglitazone (with or without metformin or SFU) versus pioglitazone alone (with or without metformin or 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 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. 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 pioglitazone (with or without metformin or SFU) (n=100), 12.5 mg alogliptin with pioglitazone (with or without metformin or SFU) (n=200), or alogliptin 25 mg with pioglitazone (with or without metformin or SFU) (n=200). Subjects were stratified by HbA1c at week -1 (< or ≥ 8%), geographic region, and baseline treatment regimen.

SYR-322-TZD-009. Study design (Reproduced from the sponsor)

Screening and Washout 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-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-TZD-009. Study schedule (Reproduced from the sponsor)

	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 (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**
Informed consent	X														
Inclusion/exclusion assessment	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(c)									X	X					
Laboratory tests															
Hematology, serum chemistry(d,e,f)	X				X	X	X	X	X	X	X	X	X	X	
Urinalysis(g)	X					X					X			X	
Proinsulin						X			X	X	X	X	X	X	
Insulin						X			X	X	X	X	X	X	
C-peptide	X					X			X	X	X	X	X	X	

	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 (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
HbA1c(h)	X				X	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 pioglitazone(j)		X	X	X	X	X	X	X	X	X	X	X	X		
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	

AE=adverse event, BMI=body mass index, CRP=C-reactive protein, ECG=electrocardiogram, ET=early termination, HbA1c=glycosylated hemoglobin, TSH=thyroid stimulating hormone.
(a) The Screening Visit was scheduled within the 14 days 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 ET) 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 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 obtained as part of serum chemistry, fasting blood samples for plasma glucose were also 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/mL) 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 ET) 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) Pioglitazone was dispensed at the start of the Run-in/Stabilization Period, and as needed at subsequent visits.

SYR-322-TZD-009. Clinical laboratory tests (Reproduced from the sponsor)

Hematology	Serum Chemistry	Urinalysis
White blood cell count with autodifferential	Albumin	Qualitative:
Platelet count	Alkaline phosphatase	Appearance
Hemoglobin	Alanine aminotransferase	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	
Other	Potassium	Quantitative:
C-reactive protein	Sodium	Albumin/creatinine ratio
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)	
	** always drawn in a separate tube for this study*	

Diagnostic Screening:	
Serum	**Urine**
Thyroid-stimulating hormone	hCG (for pregnancy) (women of childbearing potential)
Human chorionic gonadotropin (hCG) (for pregnancy) (women of childbearing potential)	

Main inclusion criteria:

- Age 18-80 years diagnosed with T2D (ADA criteria)
- 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. **NOTE: Minimum metformin dose prior to randomization was not specified in the protocol, although the mean baseline dose was 1,688 mg.**
- Signed informed consent form
- No treatment with antidiabetic agents other than a TZD alone or in combination with either metformin or a SFU within the 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)
- Body mass index (BMI) $\geq$ 23 kg/m^2 and $\leq$ 45 kg/m^2
- Fasting c-peptide $\geq$ 0.8 ng/ml
- HbA1c between 7.0-10.0% at screening
- Regular use of other, nonexcluded mediations was allowed if a stable dose had been established for at least the 4 weeks prior to screening. The use of prescription or over the counter medications pro re nata (PRN; as needed) was allowed at the discretion of the investigator
- Diastolic blood pressure (BP) $\leq$ 110 mmHg and systolic BP $\leq$ 180 mmHg
- Neither pregnant or lactating
- Using adequate contraception if a women is of childbearing potential (i.e. not surgically sterile and/or not postmenopausal) for the duration of participation in 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 $\geq$ 12 g/dl for males and $\geq$ 10 g/dl for women
- Hepatic transaminase levels $\leq$ 2.5x the upper limit of normal (ULN)

- Serum creatinine ≤2.0 mg/dl
- TSH ≤ 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 ≥ 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:

- 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
- History of albumin/creatinine ratio > 1000 mcg/mg at screening. If elevated, the subject was to be rescreened within 1 week
- History of laser treatment for proliferative retinopathy within 6 months prior to screening
- History of New York Heart Association Class III or IV heart failure regardless of therapy
- History of coronary angioplasty, coronary stent placement, coronary bypass surgery, or myocardial infarction within 6 months prior to screening
- 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 in association with ACE inhibitors or angiotensin-II receptor blockers (ARBs)
- History of alcohol or substance abuse within the last 2 years
- Receipt of any investigational drug within the preceding 30 days or a history of receipt of any investigational antidiabetic drug within the 3 months prior to screening
- History of treated diabetic gastroparesis
- History of hemoglobinopathy that could affect HbA1c
- Prior treatment in an investigational study of alogliptin

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 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). Subjects received dietary, exercise, and hypoglycemia education. Subjects were to take their study drug prior to the first meal of the day with 8 ounces of water. If randomized subjects met any of the following rescue criteria, they were removed from the study and completed an early termination visit. If subjects 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 ≥ 8.5% and ≤ 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.

Following randomization, if a subject was on a SFU and had problems with hypoglycemia, the SFU dose could be down titrated until any recurrent hypoglycemic 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 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) 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 ≥ 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 ≤ 6.5, 7.0, and 7.5%
  - Incidence of week 26 HbA1c decrease from baseline ≥ 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).

2) 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 TZD-009, 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 TZD-009, 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 TZD-009:

- 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: These criteria were similar to study TZD-009

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 TZD-009, 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 ≥ 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 ≥ 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 ≥ 8.5% and ≤ 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 TZD-009:

- 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

3) 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 TZD-009, 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 TZD-009, 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-Treatment	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 TZD-009:

- T2D subjects who were treated with metformin ≥ 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 ≥ 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 ≥ 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 TZD-009.

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 TZD-009, 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 ≥ 8.5% and ≤ 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

6 Review of Efficacy

Efficacy Summary

The sponsor proposes that A+P (SYR-322-4833) be indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with T2D. However, it was communicated to the sponsor on May 7, 2008, that the new indication for a T2D FDC product such as SYR-322-4833 is "A+P is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both alogliptin and pioglitazone is appropriate."

The sponsor conducted three 26-week phase 3 studies to evaluate the safety and efficacy of alogliptin which are reviewed here. Pivotal studies 01-05-TL-322OPI-001 and 01-06-TL-322OPI-002 (OPI-001 and OPI-002) were 26-week, randomized, double blind, placebo controlled studies in diabetics with and without metformin, respectively. Supportive study SYR-322-TZD-009 (TZD-009) was a 26-week trial that tested alogliptin versus placebo as add-on to pioglitazone. More TZD-009 study subjects received alogliptin than placebo due to the 1:2:2 (placebo: alogliptin 12.5 mg: alogliptin 25 mg) randomization. Studies OPI-002 and OPI-001 used a 1:1:1:1 randomization scheme.

Across the A+P phase 3 program, the mean age of subjects was ranged from 52.6-55.4 years. The majority of subjects were < 65 years and Caucasian (70.5-80.3%). The mean BMI ranged from 31.1-32.8. The mean duration of diabetes in the initial combination study (3.2 years) was lower than the add-on to metformin (6.2 years) and the add-on to pioglitazone (7.6 years) studies.

The primary efficacy variable for the studies was the change in HbA1c study endpoint (after 26 weeks of treatment) compared to baseline. The mean baseline HbA1c ranged from 8.0-8.9% in the 3 phase 3 trials. In study OPI-002, the A25+P30 group achieved a statistically significant decrease in HbA1c at week 26 compared with A25 and P30 alone (-0.40 and -0.56, respectively). The A12.5+P30 group also showed a statistically significant decrease in HbA1c at week 26 compared to P30 alone (-0.75). In study OPI-001, both the A12.5+P and A25+P groups achieved statistically significant decreases in HbA1c at week 26 compared with the pioglitazone alone grouping (-0.54 and -0.53, respectively). In study TZD-009, both the 12.5 and 25 mg doses achieved statistically significant LS mean differences in HbA1c reductions from baseline to week 26 compared to placebo (-0.47 and -0.61, respectively).

The major secondary efficacy parameters were the percentage of alogliptin-treated subjects achieving HbA1c < 6.5% and < 7% and mean changes in FPG and body weight. The statistically significant results with regards to HbA1c and FPG levels were as follows:

- Study OPI-002:
  - A significantly higher percentage of subjects in both the A12.5+P30 and A25+P30 groups achieved HbA1c levels ≤7.0% and ≤6.5% compared with the P30 and A25 alone groups.
  - The A25+P30 group achieved a statistically significant decrease in FPG at week 26 compared with either the A25 alone group or the P30 alone group (-24.5 and -12.9 mg/dl, respectively).
  - The A12.5+P30 group also showed a statistically significant decrease in FPG at week 26 compared with the P30 alone group (-11.2 mg/dl).
- Study OPI-001:
  - A significantly higher percentage of subjects in both the A12.5+P grouping and the A25+P grouping achieved HbA1c levels ≤7.0% and ≤6.5% compared with the pioglitazone grouping alone.
  - There was a statistically significant overall treatment effect for both combination groupings (A12.5+P and A25+P) compared with the pioglitazone along grouping at every time point from week 1 to 26, based on LS mean changes in FPG. At week 26, the LS mean changes in FPG were -18.6, -28.8,, -45.2, and -44.2 mg/dL for the A25, P30, A12.5+P, and A25+P groupings, respectively.
- Study TZD-009:
  - A statistically significant number of alogliptin subjects achieved HbA1c ≤7.0% and ≤6.5% compared to placebo.
  - The LS mean decreases in FPG observed in alogliptin-treated subjects were statistically significant compared with the placebo group (-14.1 and -13.9 mg/dl for the alogliptin 25 and 12.5 mg groups, respectively).

When the change from baseline in body weight at week 26 was compared in studies OPI-002, OPI-001, and TZD-009, only study OPI-002 A25+P30 subjects showed a significant change when compared to the A25 alone or P30 alone groups. These subjects experienced an LS mean increase of 0.95 and 3.43 kg, respectively. Although the other groups did not exhibit a

statistically significance change in body weight from baseline, body weight generally increased. The LS mean change in weight when alogliptin was used with pioglitazone in studies OPI-002, OPI-001, and TZD-009 was 1.98 kg.

Treated subjects achieved generally consistent mean reductions in HbA1c levels from baseline to week 26 in all subpopulations (gender, age, race, ethnicity, and baseline BMI), although some subgroups have small sample sizes that limit conclusions.

6.1 Indication

The sponsor proposes that A+P (SYR-322-4833) be indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with T2D. **However, it was communicated to the sponsor on May 7, 2008, that the new indication for a T2D FDC product such as SYR-322-4833 is "A+P is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both alogliptin and pioglitazone is appropriate."**

6.1.1 Methods

Alogliptin + pioglitazone have been studied in 8 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 2 pivotal, controlled phase 3 clinical studies pertinent to the claimed indication that were submitted to NDA 22-426 (01-06-TL-322OPI-002 [OPI-002] and 01-05-TL-322OPI-001 [OPI-001]) and supportive controlled phase 3 study SYR-322-TZD-009 (TZD-009). Supportive study TZD-009 was reviewed in its entirety in my alogliptin NDA 22-271 review; key safety elements of OPI-002 and OPI-001 were also reviewed in that document. Please refer to my alogliptin NDA 22-271 review for a description of the statistical methods employed in study TZD-009.

In studies OPI-002 and OPI-001, 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. The primary model included study treatment and geographic region as class effects, and baseline HbA1c (and, in study OPI-001 baseline metformin dose) as continuous covariates. For the primary analysis, the overall average HbA1c response of the A25+Pio group was compared with the overall average HbA1c response of 1) A25 alone and P30 alone in study OPI-002 or 2) Pio alone group in study OPI-001 at the 2-sided 0.05 significance level using a contrast derived from the primary model. Only if this comparison was statistically significant was the overall average HbA1c response of the A12.5+Pio group compared with the overall average HbA1c response of the 1) P30 alone group in OPI-002 or 2) the Pio alone group in OPI-001 in a step-down manner using a separate contrast derived from the same model. In study OPI-002, the generalizability of the treatment effect was evaluated for the primary analysis within a supportive ANCOVA model that added treatment-by-region interaction and treatment-by-baseline HbA1c interaction to the primary model.

NDA 22-426. Nomenclature for groupings in study OPI-001	
Group name	**Groups included**
Pioglitazone alone group (n=387)	P15 (n=129)
	P30 (n=129)
	P45 (n=129)
A12.5+P group (n=390)	A12.5+P15 (n=130)
	A12.5+P30 (n=130)
	A12.5+P45 (n=130)
A25+P group (n=390)	A25+P15 (n=130)
	A25+P30 (n=130)
	A25+P45 (n=130)

In study OPI-001, no significance level adjustment was made for the multiple comparisons using this step-down strategy. As a supportive analysis, each of the individual combination A+P treatment groups was compared with the component treatment groups receiving alogliptin alone and pioglitazone alone at the 2-sided 0.05 significance level using the same model with no multiplicity adjustment. Finally, as an additional supportive analysis, each of the individual combination A+P treatment groups was compared with the placebo treatment group at the 2-sided 0.05 significance level using the same model with no multiplicity adjustment.

In both OPI-002 and OPI-001, all secondary continuous variables were analyzed at each visit using the FAS and the primary analysis model as specified for the analysis of HbA1c, but with the corresponding baseline value modeled as covariate.

Please refer to Dr. Janice Derr's statistical reviews for full details.

More TZD-009 study subjects received alogliptin than placebo due to the 1:2:2 (placebo: alogliptin 12.5 mg: alogliptin 25 mg) randomization. Studies OPI-002 and OPI-001 used a 1:1:1:1 randomization scheme. Please also refer to section 5.1 Tables of Clinical Studies for more information.

6.1.2 Demographics

Across the A+P phase 3 program, the mean age of subjects was ranged from 52.6-55.4 years. The majority of subjects were < 65 years and Caucasian (70.5-80.3%). The mean BMI ranged from 31.1-32.8. The mean duration of diabetes in the initial combination study (3.2 years) was lower than the add-on to metformin (6.2 years) and the add-on to pioglitazone (7.6 years) studies.

1) 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/m^2) 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**

	Placebo (n=97)	Alogliptin		Overall (n=493)
		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 (≥ 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 SOCs.

All subjects in each treatment group took concomitant medications. The most common (≥ 10% subjects) included acetylsalicyclic 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.

2) 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/m^2.

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 (≥ 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 SOCs.

Most subjects (78-89% subjects) in each treatment group took concomitant medications. The most common nondiabetes concomitant medications were as follows: renin-angiotensin agents (34%), lipid-modifying agents (28%), analgesics (19%), beta-blocking agents (15%), diuretics (14%), cardiac therapy (12%), and calcium channel blockers (11%). In general, the percentage of subjects receiving a particular concomitant medications as similar among treatment groups.

3) OPI-001: (Please refer to the table in section 6.1.3.) The majority of subjects were female (55%) and Caucasian (approximately 70%). The mean age was 54 years, BMI 31 kg/m^2, 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 SOCs.

Most subjects (99-100%) in each treatment group took concomitant medications. The most common nondiabetes concomitant medications were as follows: renin-angiotensin agents (48%), lipid-modifying agents (33%), anti-bacterials for systemic use (21%), analgesics (19%), diuretics (17%), beta-blocking agents (16%), drugs for acid-related disorders (11%), and cardiac therapy (11%). In general, the percentage of subjects receiving a particular concomitant medications as similar among treatment groups.

6.1.3 Patient Disposition

1) TZD-009: 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.

2) 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. These infrequent protocol deviations are not expected to affect study conclusions.

3) 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%). More pioglitazone subjects were discontinued due to a major protocol violation (alogliptin 1.6%; pioglitazone 3.1-6.2%). 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. These infrequent protocol deviations are not expected to affect study conclusions.

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 Duration (y)	6	6	6	6	8	6	6	6	7	7	7	6	6
Metformin(mg)	1937	1902	1851	1893	1854	1919	1910	1822	1920	1880	1867	1885	1887

6.1.4 Analysis of Primary Endpoint

The primary efficacy variable for the studies was the change in HbA1c study endpoint (after 26 weeks of treatment) compared to baseline. HbA_{1c} is an appropriate endpoint for the following reasons:

- HbA1c 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 HbA1c 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).
- HbA1c has excellent reliability, predicts several diabetes-specific complications, and provides the current basis for treatment decisions (American Diabetes Association 2006).
- Lowering HbA1c 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 HbA1c 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 HbA1c ranged from 8.0-8.9% in the 3 phase 3 trials. In study OPI-002, the A25+P30 group achieved a statistically significant decrease in HbA1c at week 26 compared with A25 and P30 alone (-0.40 and -0.56, respectively). The A12.5+P30 group also showed a statistically significant decrease in HbA1c at week 26 compared to P30 alone (-0.75). In study OPI-001, both the A12.5+P and A25+P groups achieved statistically significant decreases in HbA1c at week 26 compared with the pioglitazone alone grouping (-0.54 and -0.53, respectively). In study TZD-009, both the 12.5 and 25 mg doses achieved statistically significant LS mean differences in HbA1c reductions from baseline to week 26 compared to placebo (-0.47 and -0.61, respectively).

NDA 22-426. Summary of change from baseline in HbA1c (LOCF). Full analysis set is displayed in regular text; per protocol set is displayed in italics.

Study	N	Base-line HbA1c (%) mean (SD)	Change in HbA1c (%) LS mean (SE)	LS mean differ-ence (SE)	95% CI for the LS mean difference	p-value	LS mean differen ce (SE)	95% CI for the LS mean difference	p-value
OPI-002				**Versus P30**			**Versus A25**		
A25	164	8.80 (0.99)	-0.96 (0.08)						
P30	163	8.76 (1.01)	-1.15 (0.08)						

A25+P30	163	8.80 (0.96)	-1.71 (0.08)	-0.56 *-0.48*	-0.78, -0.33 *-0.70, -0.26*	<0.001 *<0.001*	-0.75 *-0.77*	-0.98, -0.53 *-0.99, -0.55*	<0.001 *<0.001*
A12.5+P30	164	8.85 (1.04)	-1.56 (0.08)	-0.40 *-0.47*	-0.63, -0.18 *-0.69, -0.25*	<0.001 *<0.001*			
OPI-001				Versus placebo					
A12.5	122	8.56 (0.71)	-0.82 (0.072)						
A25	123	8.59 (0.66)	-1.03 (0.072)						
P15	127	8.45 (0.67)	-0.75 (0.079)						
P30	123	8.46 (0.68)	-0.92 (0.081)						
P45	126	8.54 (0.71)	-1.00 (0.080)						
Placebo+P	387	8.49 (0.69)	-0.89 (0.05)						
A12.5+P	390	8.50 (0.68)	-1.43 (0.05)	-0.54 *-0.52*	-0.67, -0.41 *-0.65, -0.39*	<0.001 *<0.001*			
A25+P	390	8.54 (0.69)	-1.42 (0.05)	-0.53 *-0.51*	-0.66, -0.41 *-0.64, -0.38*	<0.001 *<0.001*			
TZD-009				Versus placebo					
Alo 25	195	8.01 (0.84)	-0.80 (0.06)	-0.61 *-0.54*	-0.80, -0.41 *-0.74, -0.33*	< 0.001 *<0.001*			
Alo 12.5	196	8.08 (0.91)	-0.66 (0.06)	-0.47 *-0.41*	-0.67, -0.28 *-0.61, -0.20*	< 0.001 *<0.001*			
Placebo	95	7.97 (0.82)	-0.19 (0.08)						

In study OPI-002, by week 4 (the first timepoint of measurement), all groups achieved a decrease in HbA1c that continued throughout week 26. When changes from baseline were observed over time, statistically significantly greater reductions in HbA1c were observed in the A25+P30 group at every time point compared with the P30 group alone group, and at every time point except week 4 compared with the A25 alone group. The A12.5+P30 group resulted in statistically significantly greater reductions in HbA1c compared with the P30 alone group at every time point, although these reductions were not as large as those seen with A25+P30.

In study OPI-001, both the A12.5+Pio and A25+Pio groupings achieved statistically significant decreases in HbA1c at every time point from week 4 to week 26 compared with the pioglitazone alone grouping.

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% and mean changes in FPG and body weight.

In study OPI-002, a significantly higher percentage of subjects in both the A12.5+P30 and A25+P30 groups achieved HbA1c levels ≤7.0% and ≤6.5% compared with the P30 alone group.

A significantly higher percentage of subjects in the A25+P30 group achieved HbA1c levels of ≤7.0% and ≤6.5% compared with subjects in the A25 alone group. A higher percentage of subjects in the A25+P30 group achieved HbA1c levels ≤7.0% compared with the A12.5+P30 group, although this was not tested statistically; a similar percentage of subjects in these groups achieved HbA1c ≤6.5%.

In study OPI-001, a higher percentage of subjects in both the A12.5+P grouping and the A25+P grouping achieved HbA1c levels ≤7.0% and ≤6.5% compared with alogliptin 12.5 and 25 mg as well as the pioglitazone alone grouping. (The later group was statistically significant). The A12.5+P grouping had a similar percent of subjects achieving these HbA1c levels when compared with the A25+P groupings.

In study TZD-009, a statistically significant number of alogliptin subjects achieved HbA1c ≤7.0% and ≤6.5% compared to placebo.

NDA 22-426. Number (%) of subjects who achieved HbA1c levels ≤ 6.5% and ≤ 7.0% at week 26 in the phase 3 studies

Study	**N**	**HbA1c ≤ 6.5%**		**HbA1c ≤ 7.0%**		**HbA1c ≤ 6.5%**	**HbA1c ≤ 7.0%**
		# subjects (%)	**p-value**	**# subjects (%)**	**p-value**	**p-value**	**p-value**
OPI-002		**Versus P30**				**Versus A25**	
A25	164	19 (11.6%)		40 (24.4%)			
P30	163	27 (16.6%)		55 (33.7%)			
A25+P30	163	45 (27.4%)	0.016	103 (62.8%)	<0.001	0.005	<0.001
A12.5+P30	164	43 (26.4%)	0.021	87 (53.4%)	<0.001		
OPI-001		Versus placebo					
A12.5	128	11 (8.6%)		29 (22.7%)			
A25	129	16 (12.4%)		35 (27.1%)			
P15	129	8 (6.2%)		33 (25.6%)			
P30	129	15 (11.6%)		38 (29.5%)			
P45	129	25 (19.4%)		47 (36.4%)			
Placebo	387	48 (12.4%)		118 (30.5%)			
A12.5+P	390	109 (27.9%)	<0.001	213 (54.6%)	<0.001		
A25+P	390	114 (29.2%)	<0.001	218 (55.9%)	<0.001		
TZD-009		Versus placebo					
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%)	-		

In study OPI-002, the mean FPG values at baseline were similar among groups (184.5-198.7 mg/dl). The A25+P30 group achieved a statistically significant decrease in FPG at week 26 compared with either the A25 alone group or the P30 alone group (-24.5 and -12.9 mg/dl, respectively). The A12.5+P30 group also showed a statistically significant decrease in FPG at week 26 compared with the P30 alone group (-11.2 mg/dl).

The primary analysis of study OPI-001 showed that the mean FPG values at baseline were similar for the pioglitazone alone, A12.5+P, and A25+P groupings (177.5-179.3 mg/dl). There

was a statistically significant overall treatment effect for both combination groupings (A12.5+P and A25+P) compared with the pioglitazone along grouping at every time point from week 1 to 26, based on LS means. The A12.5+P and A25+P groups' changes in FPG from baseline also exceeded that of alogliptin and pioglitazone alone. At week 26, the LS mean changes were -18.6, -28.8, -45.2, and -44.2 for the A25, P30, A12.5+P, and A25+P groupings, respectively.

In study TZD-009, the LS mean decreases observed in alogliptin-treated subjects were statistically significant compared with the placebo group (-14.1 and -13.9 mg/dl for the alogliptin 25 and 12.5 mg groups, respectively).

NDA 22-426. Summary of change from baseline in FPG (FAS set)

Study	**N**	**Baseline FPG mean (SD)**	**Change in FPG LS mean (SE)**	**LS mean difference (SE)**	**95% CI for the LS mean difference**	**p-value**	**LS mean difference (SE)**	**95% CI for the LS mean difference**	**p-value**
OPI-002				**Versus P30**			**Versus A25**		
A25	164	188 (51)	-25.8 (3.3)						
P30	163	189 (54)	-37.3 (3.3)						
A25+P30	163	185 (50)	-50.2 (3.3)	-12.9	-22.0, -3.8	0.006	-24.5	-33.5, -15.4	<0.001
A12.5+P30	164	199 (60)	-48.5 (3.3)	-11.2	-20.3, -2.0	0.017			
OPI-001									
A12.5	122	183 (50)	-13.2 (3.6)						
A25	126	184 (49)	-18.6 (3.5)						
P15	127	177 (47)	-23.6 (3.5)						
P30	125	175 (43)	-28.8 (3.6)						
P45	129	181 (54)	-32.4 (3.5)						
Placebo+P	387	178 (48)	-28.3 (2.0)						
A12.5+P	390	179 (48)	-45.2 (2.0)	-16.9	-22.5, -11.3	<0.001			
A25+P	390	179 (46)	-44.2 (2.0)	-15.9	-21.5, -10.2	<0.001			
TZD-009									
Alo 25	199	170 (46)	-19.1 (2.7)	-14.1	-23.3, -5.0	0.003			
Alo 12.5	197	173 (47)	-19.7 (2.7)	-13.9	-23.1, -4.8	0.003			
Placebo	97	172 (52)	-5.7 (3.8)						

When the change from baseline in body weight at week 26 was compared in studies OPI-002, OPI-001, and TZD-009, only study OPI-002 A25+P30 subjects showed a significant change when compared to the A25 alone or P30 alone groups. These subjects experienced an LS mean increase of 3.43 and 0.95 kg, respectively. Although the other groups did not exhibit a statistically significance change in body weight from baseline, body weight generally increased. The LS mean change in weight when alogliptin was used with pioglitazone in studies OPI-002, OPI-001, and TZD-009 was 1.98 kg..

NDA 22-426. 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 differ-ence (SE)**	**95% CI for the LS mean difference**	**p-value**	**LS mean differ ence (SE)**	**95% CI for the LS mean difference**	**p-value**
OPI-002				**Versus P30**			**Versus A25**		
A25	164	86 (19)	-0.3 (0.3)						
P30	163	85 (16)	2.2 (0.3)						
A25+P30	163	83 (19)	3.1 (0.3)	0.95	0.12, 1.78	0.025	3.43	2.61, 4.24	<0.001
A12.5+P30	164	83 (20)	2.5 (0.3)	0.32	-0.51, 1.15	0.448			
OPI-001									
A12.5	122	85 (19)	-0.0 (0.3)						
A25	123	83 (18)	-0.7 (0.3)						
P15	122	84 (19)	0.9 (0.3)						
P30	122	85 (20)	1.9 (0.3)						
P45	124	82 (17)	1.7 (0.3)						
Placebo+P	387	84 (18)	1.5 (0.2)						
A12.5+P	390	84 (19)	1.8 (0.2)	0.32	-0.14, 0.79	0.173			
A25+P	390	84 (18)	1.9 (0.2)	0.38	-0.08, 0.85	0.109			
TZD-009									
Alo 25	199	95(20)	1.1 (0.2)	0.05	-0.74, 0.84	0.900			
Alo 12.5	197	93 (21)	1.5 (0.2)	0.42	-0.37, 1.22	0.294			
Placebo	97	96 (22)	1.0 (0.3)	-		-			

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/m^2, ≥ 30 kg/m^2). Most subjects were Caucasian in the 5 key studies. Treated subjects 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.

NDA 22-426. Mean change from baseline to week 26 in HbA1c (%) by subgroup (LOCF). NE = Not estimable										
	OPI-002				**OPI-001**			**TZD-009**		
	A25	**P30**	**A12.5+P30**	**A25+P30**	**P**	**A12.5+P**	**A25+P**	**Placebo**	**12.5**	**25**
Age (y)										
< 65	-0.94	-1.16	-1.57	-1.77	-0.88	-1.42	-1.44	-0.22	-0.66	-0.80
≥ 65	-1.08	-1.03	-1.57	-1.32	-0.85	-1.40	-1.37	0.11	-0.71	-0.78
Gender										
Male	-1.03	-1.08	-1.29	-1.46	-0.76	-1.33	-1.39	-0.09	-0.64	-0.78
Female	-0.89	-1.21	-1.85	-1.89	-0.97	-1.49	-1.46	-0.28	-0.71	-0.83
Race										
Am native	-0.90	NE	NE	NE	NE	-2.27	-2.10	-2.30	-0.40	-0.40
Asian	-0.92	-1.24	-1.95	-1.93	-0.69	-1.86	-1.68	-0.52	-0.98	-0.83
Black	-1.36	-0.90	-1.75	-1.27	-0.88	-1.48	-1.15	-0.07	-1.00	-1.11
Pacific isl	NE	NE	NE	NE	NE	NE	NE	-	-0.80	-
White	-0.94	-1.14	-1.54	-1.70	-0.84	-1.29	-1.34	-0.10	-0.8	0.77
Other	-0.82	-1.23	-1.07	-1.97	-1.09	-1.86	-1.70	-0.28	-0.69	-0.82
Ethnicity										
Hisp	-1.03	-1.27	-1.58	-1.86	-0.97	-1.60	-1.49	-0.13	-0.65	-0.88
Non-Hisp	-0.91	-1.06	-1.57	-1.62	-0.78	-1.26	-1.38	-0.18	-0.68	-0.78

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

The pioglitazone doses selected for evaluation in the alogliptin+pioglitazone development program were based on the approved doses of pioglitazone (15, 30, and 45 mg) and doses evaluated in the phase 3 alogliptin development program (12.5 and 25 mg). However, pivotal study OPI-002 evaluated only 1 pioglitazone dose (30 mg). Please refer to the ACTOS package insert and my clinical review of alogliptin NDA 22-271 for more information.

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

The three phase 3 A+P clinical studies (OPE-002, OPI-001, and TZD-009) each had 26 week treatment periods. Thus, this reviewer can only comment on the persistence of efficacy to week 26. Please refer to the above comments.

Although the sponsor is conducting an open label extension study (SYR-322-OLE-012), this study is uncontrolled and does not require the coadministration of A+P.

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, although 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.

In study OPI-002, there was a statistically significant increase in HOMA-BCF in the A25+P30 group compared with the A25 group. Subjects in the A25+P30 group also achieved a larger increase in HOMA-BCF at week 26 compared with the P30 group, although this difference was not statistically significant.

In study OPI-001, there was a statistically significant increase in the HOMA-BCF in both the A12.5+P and A25+P groupings compared with the pioglitazone alone grouping.

In the TZD-009, improvement with 12.5 mg was numerically greater than 25 mg.

NDA 22-426. Change from baseline in HOMA-BCF at week 26 for phase 3 studies (LOCF)							
Study	**N**	**Baseline HOMA-BCF mean (SD)**	**Change in HOMA-BCF LS mean (SE)**	**LS mean difference**	**p-value**	**LS mean difference**	**p-value**

				Versus P30		Versus A25	
OPI-002							
A25	164	66.5 (69.3)	10.5 (8.5)				
P30	163	54.5 (42.9)	17.5 (8.9)				
A25+P30	164	58.1 (50.0)	39.2 (8.5)	21.7	0.079	28.7	0.018
A12.5+P30	163	58.8 (54.8)	24.9 (8.4)	7.4	0.546		
OPI-001							
Placebo	387	60.4 (142.1)	5.1 (3.0)				
A12.5	390	52.6 (45.6)	18.2 (3.1)	13.1	0.002		
A25	390	53.5 (89.4)	22.2 (3.0)	317.1	<0.001		
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)				

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 two pivotal phase 3 clinical studies (OPI-002 and OPI-001), one supportive phase 3 study (TZD-009), and the 120-day Safety Update which includes the uncontrolled study OLE-012 subgroup TZD-009. 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 study TZD-009. Studies OPI-002 and OPI-001, which investigated alogliptin as add on therapy to pioglitazone, had a 1:1 randomization. Studies excluded subjects with serum creatinine ≥ 2.0 mg/dl (studies involving metformin had stricter criteria).

The core alogliptin trials were randomized, blinded, and controlled. 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. Alogliptin will not be approved because the sponsor did not rule 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. The sponsor has been asked to conduct a long-term CV outcomes trial. **Please refer to my alogliptin NDA 22-271 review, section 7 Review of Safety for more information pertaining to the cardiovascular safety of alogliptin.**

Supportive study TZD-009 was not pooled with data from FDC studies OPI-002 and OPI-001, because OPI-002 and OPI-001 subjects had no previous exposure to pioglitazone whereas TZD-009 subjects did. Thus, 12 treatment arms (4 OPI-002 arms and 12 OPI-001 arms) were evaluated in the integrated database. Only 2 of the combination arms were common to both studies (alogliptin 12.5 and 25 mg with pioglitazone 30 mg). Of the dose groupings evaluated, the majority of subjects received alogliptin alone or in combination with pioglitazone (1528/2207; 69.2%) and a small number of subjects received only placebo (129/2207; 5.8%).

Therefore, the pooled data is presented at the compound level excluding the placebo-only group (except disposition and exposure which do include the placebo-only group). The 3 treatment groupings are as follows:

- Alogliptin grouping: all subjects who received alogliptin with pioglitazone placebo
- Pioglitazone grouping: all subjects who receive pioglitazone with alogliptin placebo
- Combination grouping: all subjects who received alogliptin with pioglitazone

NDA 22-426. Dose groups		
Placebo +	**Alogliptin 12.5 mg +**	**Alogliptin 25 mg +**
Placebo (OPI-001)	Placebo (OPI-001)	Placebo (both studies)
Pioglitazone 15 mg (OPI-001)	Pioglitazone 15 mg (OPI-001)	Pioglitazone 15 mg (OPI-001)
Pioglitazone 30 mg (both studies)	Pioglitazone 30 mg (both studies)	Pioglitazone 30 mg (both studies)
Pioglitazone 45 mg (OPI-001)	Pioglitazone 45 mg (OPI-001)	Pioglitazone 45 mg (OPI-001)

Exposure data are shown below. The demographic and baseline characteristics of subjects in the controlled phase 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 controlled phase 3 study groups of A+P, the mean patient age was 53.1 years. The majority of subjects were White (74.9%). The percentage of Asian and Black subjects ranged between 4-7%. Approximately half of subjects were male. The majority were obese with a mean duration of diabetes of 5.4 years and mean HbA1c of 8.6%.

NDA 22-426. Controlled and uncontrolled A+P exposure. NOTE: Uncontrolled data has a September 15, 2008 cutoff)

Study	**Exposure**		
	≥ 6 mo	**≥ 12 mo**	**≥ 18 mo**
Controlled TZD-009	315		
Controlled OPI-001	688		
Controlled OPI-002	264		
Controlled total	**1267**		
Uncontrolled OLE-012 data (subgroup TZD-009)	378	192	158
Uncontrolled OLE-012 data (subgroups TZD-009, OPI-001, & OPI-002)*	1330		

*Subjects form TZD-009 who chose to rollover into the OLE-012 continued their TZD background therapy during the extension study. In contrast, subjects from FDC studies OPI-001 and OPI-002 were randomized in a blinded fashion to alogliptin alone, pioglitazone alone, or a combination of both in these studies. As a result, subjects from FDC studies OPI-001 and OPI-002 who enrolled in OLE-012 were not permitted to receive pioglitazone initially upon entry into study OLE-012. Therefore, these subjects were not included in the 120-day Safety Update as they did not receive continuous pioglitazone therapy.

No deaths were reported in study OPI-002. A total of 4 deaths occurred in studies OPI-001, TZD-009, and OLE-012; 2 of these were reported in the 120 day safety update (September 15, 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 was only 1 death among alogliptin-treated patients.

A total of 28 (2.5%) A+P 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 the 2 pivotal controlled phase 3 studies of A+P. In these 2 pivotal FDC studies, TESAEs were most common in the infection and infestation disorders SOC (0.5%) followed by cardiac, gastrointestinal, and nervous system disorders (0.4% each). In supportive study TZD-009 and the uncontrolled OLE-012 study TZD-009 subgroup, TESAEs were most common in the cardiac disorders and infection and infestation disorders SOCs.

In the 2 pivotal controlled phase 3 studies (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 included diarrhea, nausea, edema peripheral, weight increased, liver tests abnormal, and dizziness. In supportive study TZD-009, discontinuation due to AEs was similar between treatment groups (placebo 3.1%, A12.5 4.1%, and A25 3.0%); no dose-related trend was seen.

The sponsor analyzed the following as AEs of interest for alogliptin treatment:

- Cardiovascular (CV) AEs of interest cluster: The incidence was highest in the pioglitazone group (11.1%), followed by the combination (9.1%) and alogliptin (5.7%) groups.
- Ischemic heart disease: The incidence was highest in the pioglitazone group (pioglitazone 3.1%, combination 1.8%, alogliptin 1.4%). Ten subjects experienced SAEs in the ischemic heart disease cluster (pioglitazone 4, A+P 4, and alogliptin 2). Three subjects were discontinued as a result of the AE (combination 2, pioglitazone 1).
- Cardiac arrhythmias cluster: The incidence of AEs was greatest in the pioglitazone group (pioglitazone 4.2%, A+P 3.6%, alogliptin 1.7%). The incidence of the most common AEs, palpitations and tachycardia, was higher however in the A+P group, although the percent incidence was low (0.5%).
- Angioedema cluster: The incidence of was highest in the pioglitazone group (4.2% vs. A+P 3.3% and alogliptin 2.4%). Edema peripheral, a known AE of pioglitazone, accounted for the majority of the agioedema cluster events.
- Potential cutaneous drug reaction cluster (The customized MedDRA query of PCDR events did not include most ulcers; only venous ulcer pain was included.): In the 2 pivotal studies of A+P under NDA 22-426, the overall incidence of PCDR AEs was higher in the combination grouping (7.6%) than the pioglitazone and alogliptin groupings (6.5% and 6.2%, respectively). The most frequently reported AEs in this cluster were again pruritis and rash. There were no PCDR SAEs, although AEs led to discontinuation in 6 subjects (5 A+P, 1 pioglitazone).

As requested, on May 20, 2009, the sponsor provided an analysis of pancreatitis cases occurring with alogliptin and comparators in the controlled phase 2/3 clinical trials. The analysis was performed by using the SMQ of "acute pancreatitis" in MedDRA version 10.0. Overall, the pancreatitis event rate was low and similar to placebo (~5%).

The sponsor analyzed the following as AEs of interest for pioglitazone treatment:

- Cardiac failure cluster: The incidence in the pioglitazone group was greater than that of the A+P and alogliptin groups (4.0% vs. 3.4% and 1.4%, respectively).
- Edema cluster: AEs in the edema cluster occurred more commonly in the pioglitazone group when compared to the A+P and alogliptin groups (3.8% vs. 3.3% and 1.7%, respectively). The most common AE was edema peripheral which also occurred more commonly in the pioglitazone group (3.5% vs. 2.7% and 1.4%, respectively).
- Weight gain cluster: The incidence was similar in the pioglitazone and A+P groups (2.5% and 2.4%, respectively, vs. 0.5% alogliptin). There were no SAEs in the weight gain cluster, although 2 subjects (both A+P) discontinued due to weight increased.
- Bone fracture cluster: The rate of bone fractures in the 2 pivotal trials was similar in the pioglitazone and A+P groups (2.0% and 1.8%, respectively, vs. 1.2% alogliptin).
- Neoplasms benign, malignant, and unspecified SOC: The incidence was highest in the A+P group, although it was similar to the pioglitazone group (A+P 0.9%, pioglitazone 0.7%, and alogliptin 0.2%). Most events which occurred more frequently in the A+P group were isolated events, although skin papilloma and seborrheic keratosis occurred at 0.3% and 0.2% respectively. Overall, the incidence of AEs in this SOC was low.

In pivotal studies OPI-002 and OPI-001, 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 nasopharnygitis (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%). 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).

In supportive study TZD-009, cardiac disorders occurred more often in the alogliptin 12.5 and 25 mg groups when compared to placebo (3.0% and 6.5% vs. 1.0%). The most common events in the cardiac disorder SOC were atrial fibrillation, cardiac failure, MI, coronary artery disease, and ventricular extrasystoles. Nervous system events occurred more often in the alogliptin groups in TZD-009 (15.2% and 16.6% vs. 10.3%). The most common nervous system events were headache and dizziness. Respiratory, thoracic, and mediastinal events occurred more often in the alogliptin groups (8.1% and 9.5% vs. 5.2%); cough and epistaxis were the most common AEs. Adverse events in the blood & lymphatic, ear & labyrinth, and immune system SOCs were also more common the alogliptin groups; anemia and vertigo were the most common AEs in these SOCs.

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. In the pivotal

studies, infection and infestation events occurred more often in the A+P group than alogliptin and pioglitazone groups (27.5% vs. 25.2% and 25.1%). Upper respiratory infection, pharyngitis, bronchitis, and sinusitis all occurred more often in the A+P and/or alogliptin group than the pioglitazone group. However, in supportive study TZD-009, infections and infestations were more common the placebo group when compared to alogliptin 12.5 and 25 mg (37.1% vs. 34.8% and 33.7%).

Standard safety laboratory data were obtained in all studies at baseline, during the treatment period, and at study end. This reviewer focused the review of laboratory data on the pivotal phase 3 studies, OPI-002 and OPI-001, which evaluated the safety and efficacy of the to-be-marketed dose combinations of alogliptin and pioglitazone.

Men were required to have a hemoglobin level ≥ 12 g/dl and women ≥ 10 g/dl to enroll in the controlled phase 3 studies. Pioglitazone has been associated with dose-related decreases in hemoglobin and hematocrit, which are likely related to increased plasma volume. As expected, small decreases in the pioglitazone and A+P groups' hematocrit and hemoglobin were seen (hematocrit: -1.61% and -1.61% vs. -0.87%; hemoglobin: -0.30 and -0.41 g/dl vs. -0.08 g/dl). Lymphocytes and platelets decreased slightly (lymphocytes: A+P -1.1%, Pio 0.5%, Alo -1.7 %; platelets: A+P -6.2, Pio -5.7, Alo -5.0). Monocytes increased slightly (A+P 1.1%, Pio 0.8%, Alo 0.5%). Overall, the mean changes from baseline to endpoint in hematology results were minor and not clinically meaningful.

Few shifts among low, normal, and high categories from baseline to endpoint were observed for most variables across groupings. Exceptions included decreased hemoglobin and hematocrit and increased lymphocytes and monocytes, which were slightly more common in the A+P group. (Both the pioglitazone and A+P groups had a 6.4% incidence of increased lymphocytes.) As explained above, the hemoglobin and hematocrit shifts were expected in the groups taking pioglitazone. The shift towards an increased lymphocyte percentage is not consistent with the mean change from baseline to endpoint which was negative.

In the pivotal, controlled phase 3 studies, subjects were required to have ALT <2.5x ULN (OPI-002) or ≤2.5x ULN (OPI-001), and creatinine < 2.0 mg/dl (males and females in OPI-002) or < 1.5 mg/dl (males in OPI-001) or < 1.4 mg/dl (females in OPI-001). The mean change from baseline to endpoint in serum BUN and creatinine increased slightly more in the A+P group when compared to the alogliptin and pioglitazone groups (BUN: 1.4 vs. 0.7 and 0.2 mg/dl; creatinine: 0.04 vs. 0.02 and 0.02 mg/dl, respectively). However, AST and ALT improved (i.e. decreased) on average in the A+P group (-2.1 and -4.1 mU/ml). The mean change from baseline to endpoint in sodium and LDH was greatest in the A+P group, although values were similar to comparators. Alkaline phosphatase decreased the most in the A+P group (-7.0 mU/ml).

The incidence of markedly abnormal chemistry results in the pivotal phase 3 studies in the A+P group were similar or less than comparators, except for serum creatinine (A+P 1.6% vs. alogliptin 1.2% and pioglitazone 0.7%). In total, 26 subjects had creatinine levels >1.5x baseline during treatment. Only 3 of the 26 subjects, all in the A+P group, had creatinine levels that also

exceeded the ULN. Uric acid also increased in the A+P and alogliptin groups (1.8% and 2.7% vs. 0.6%), although the incidenc of gout AEs was similar across study groups in the pivotal phase trials (0-0.2%).

When shifts in chemistry values were reviewed, more A+P subjects experienced normalization of AST, ALT, and alkaline phosphatase (A+P: 67.2, 69.3, and 62.0%; alogliptin: 45.7, 47.3, 36.9%, pioglitazone: 56.8, 65.3, 49.3%, respectively). However, more A+P subjects also experienced increases in BUN and magnesium (A+P: 9.3 and 7.2%; alogliptin: 6.4 and 6.5%; pioglitazone: 8.9 and 5.9%, respectively).

The change from baseline to endpoint in creatinine clearance was low in all treatment groups and varied on the formula used (CG: -0.84 to -2.98 ml/min; MDRD: -1.53 to -3.91 ml/min). Slightly more subjects in the A+P group experienced a shift from normal to mild or moderate renal impairment when compared to the alogliptin and pioglitazone groups using both CG and MDRD formulas.

Subjects with a urine albumin/creatinine ratio of > 1000 mcg/mg (>113 mg/mol) were excluded from the pivotal, controlled phase 3 studies. The mean change in albumin/creatinine ratios from baseline to endpoint increased in the A+P and pioglitazone groups when compared to alogliptin (24.3 and 12.0 vs. -2.6 µg/mg), although median change was more similar (-6 and -6 vs. -4). However, sample sizes for this measurement were small and thus complicate data interpretation.

Hypoglycemic events were classified as severe (blood glucose <60 mg/dl requiring assistance), mild/moderate with or without symptoms (blood glucose <50 mg/dl), and symptomatic mild/moderate (blood glucose < 60 mg/dl with symptoms). The pioglitazone group had the greatest incidence of severe hypoglycemia (pioglitazone 2.0%, A+P 0.1%, and alogliptin 0%). The greatest incidence of blood glucose <50 mg/dl with or without symptoms occurred in the A+P group (0.8% vs. pioglitazone 0.4% and alogliptin 0.2%).

The changes from baseline to endpoint in blood pressure and heart rate were similar between treatment groups. The percentage of subjects with abnormal vital sign measurements postbaseline were similar between the treatment groups, although slightly more A+P and pioglitazone subjects experienced increased systolic and diastolic blood pressure when compared to the alogliptin group (systolic: 3.4 and 4.2 vs. 2.2%; diastolic: 4.5 and 5.5 vs. 3.6%).

A standard 12-lead ECG was obtained at screening, baseline, week 12, and the end of treatment visit in the pivotal, controlled phase 3 studies. Additional ECGs were performed at the discretion of the investigator. The mean change in ECG intervals was <5 msec for all groups and near zero in the A+P group. 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 pivotal controlled phase 3 studies.

The effect of renal impairment; hepatic impairment; and age, gender, and race were investigated in special safety studies under alogliptin IND 69,707. (Please refer to the clinical pharmacology and clinical review of alogliptin NDA 22-271.)

Pioglitazone is associated with dose-related increases in weight and decreases in hemoglobin and hematocrit. No dose-related trend was seen in pivotal studies OPI-002 and OPI-001 with respect to death or study withdrawal (i.e. voluntary or AE discontinuation). A small dose-related trend was seen in the incidence of SAEs and AEs in study OPI-002 but not OPI-001 (A25 0.6%, P30 3.7%, A12.5+P30 0.6%, A25+P30 4.9%), although this was not driven by any particular PTs. In both studies, slightly more A25+P subjects had serum creatinine levels 1.5x baseline.

No significant difference was seen between the alogliptin, pioglitazone, and A+P groups in time to onset of AEs.

The pivotal A+P phase 3 studies were analyzed with respect to gender, age, race, and BMI.

- Adverse events more commonly occurred in females (63.3-65.4% vs. 54.4-61.9%). In the A+P group, the incidences of edema peripheral, urinary tract infection, and headache were ≥2% greater in females than males.
- The majority of subjects were < 65 years old (84.1-88.4%), which complicated age and treatment group comparison due to samples sizes as low as 49 in the ≥65 year alogliptin group. AEs occurred, on average, slightly more often in the < 65 year old group (60.7-62.6% vs. 44.9-63.1%). The difference in the incidence of AEs of interest between the 2 age groups was <2%. Headache was the most common AE of interest in the <65 year group (5.7%), whereas back pain was most common in the ≥65 year group (6.3%). However, one AE (not of interest), anemia, occurred noticeably more often in the ≥65 years A+P group.
- The majority of subjects in the pivotal studies were Caucasian (>70%). Asian subjects represented 7.3-10.2% of the treatment group population; Blacks represented 4.2-5.8% of the studied population. AEs of occurred more often in the Asian and Black groups. The percentage incidences of AEs of interest varied between groups, probably in part due to the variation in sample size. Asians were at slightly higher risk for AEs in the blood and lymphatic system disorder SOC.
- AEs occurred in a similar percentage of nonobese and obese subjects (58.3-64.4%). The difference in the AE event rate between the A+P nonobese and obese subjects was ≤2% for AEs of interest, except for nasopharyngitis (2.7% vs. 5.1%) and back pain (2.9% vs. 5.8%).

The sponsor tallied AEs by summary baseline renal impairment category. The incidence of AEs was similar between treatment groups within renal impairment categories, except for moderate renal impairment. More AEs occurred in A+P treated subjects with baseline moderate renal impairment (CG and MDRD formulas: 85.7% and 76.9%, respectively), although the small sample size limits conclusions. (Please refer to section 7.5.4 Drug-Disease Interactions for more information.)

The sponsor did not analyze the pivotal phase 3 A+P studies by hepatic impairment, although study SYR-322-023 assessed the single dose PK of alogliptin 25 mg in subjects with and without hepatic impairment. Moderate hepatic impairment did not significantly affect alogliptin exposure. Please refer to the clinical pharmacology and clinical reviews of alogliptin NDA 22-271.

Compared with normal controls, subjects with Child-Pugh Grade B/C hepatic impairment have approximately a 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but not change in the mean AUC values. Pioglitazone should not be initiated if a patient has clinical evidence of active liver disease or serum transaminase levels (ALT) >2.5x ULN.

No A+P drug-drug interaction studies were conducted for this NDA. Please refer to the clinical pharmacology and clinical reviews of alogliptin NDA 22-21 and the pioglitazone prescribing information.

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 (≥ 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.

In a 2-year carcinogenicity study of pioglitazone in male and female rats, benign and/or malignant urinary bladder transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). A 2-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11x the maximum recommended human oral dose based on mg/m^2); no drug-induced tumors were observed in any organ.

No new cases of bladder tumor were identified during a prospective evaluation of urinary cytology in >1,800 patients who received pioglitazone for up to 1 year. In two 3-year studies comparing pioglitazone to placebo or glyburide, there were 16/3656 (0.44%) report of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was < 1 year at the time of bladder cancer diagnosis, there were 5 (0.16%) cases on pioglitazone and 2 (0.05%) on placebo.

Fetal growth and developmental effects occur at maternally toxic doses with alogliptin. In rats, the concentration of alogliptin in milk is 2x maternal plasma concentration, thus fetal exposure with breastfeeding is expected in humans.

Pioglitazone is pregnancy category C; it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is secreted in the milk of lactating rats; it is not know if pioglitazone is secreted in human milk.

The following pregnancies were also reported in the pivotal phase 3 A+P program in subjects who received alogliptin:

- 412/3119: 32 year old female with a history spontaneous abortion and 2 Cesarean-sections experienced a spontaneous abortion on day 80.
- 830/3002: 46 year old female with a history of 4 pregnancies (1 live birth, 3 spontaneous abortions) experienced an abortion spontaneous on day 197 of study OPI-001.

On September 24, 2008, the Pediatric Review Committee (PeRC) decided that alogliptin studies would be deferred in ages 10-16 years and waived in ages 0-9 years. On May 26, 2009, the sponsor proposed a pediatric development plan for A+P. (b) (4)

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 two pivotal phase 3 clinical studies (OPI-002 and OPI-001), one supportive phase 3 study (TZD-009), and the 120-day Safety Update which includes study TZD-009 subgroup analysis of uncontrolled study OLE-012.

NOTE: Subjects from TZD-009 who chose to rollover into the OLE-012 continued their TZD background therapy during the extension study. In contrast, subjects from FDC studies OPI-001 and OPI-002 were randomized in a blinded fashion to alogliptin alone, pioglitazone alone, or a combination of both in these studies. As a result, subjects from FDC studies OPI-001 and OPI-002 who enrolled in OLE-012 were not permitted to receive pioglitazone initially upon entry into study OLE-012. Therefore, these subjects were not included in the 120-day Safety Update as they did not receive continuous pioglitazone therapy.

Source of data	Details
Controlled safety/efficacy trials	**3 studies:** 3 phase 3 studies of A+P (OPI-002, OPI-001, TZD-009)
Other sources of Safety data	**5 other studies:** Bioavailability and bioequivalence studies 120-day safety update Spontaneous reports/literature reports

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 study TZD-009. Studies OPI-002 and OPI-001, which investigated alogliptin as add on therapy to 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. 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. **Please refer to my alogliptin NDA 22-271 review, section 7 Review of Safety for more information pertaining to the cardiovascular safety of alogliptin.**

In the opinion of this reviewer, the following errors in coding occurred:

- 3 OPI-002 A+P subjects should have been labeled as having a major protocol deviation for receiving a treatment different from the randomized treatment. Please see section 6.1.3 Patient Disposition for more information.
- 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.
- OPI-002 313-2509: The reason for study discontinuation on day 113 (i.e. AE of BUN increased on day 1) was miscoded. Creatinine at the time of discontinuation on day 113 was 3.3 mg/dl; this was more likely the reason for discontinuation.

While the number of potential miscodes is small in comparison to the total population studied, the presence of miscoded MACE events and CV SAEs in the original alogliptin NDA adds further uncertainty to the cardiovascular data which has already been called into question. Please refer to my review of alogliptin NDA 22-271 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 2 pivotal A+P studies (OPI-002 and OPI-001) as well as supportive study TZD-009 and the 120-day Safety Update, which includes an interim analysis of the TZD-009 subpopulation in uncontrolled study OLE-012.

Supportive study TZD-009 was not pooled with data from FDC studies OPI-002 and OPI-001, because OPI-002 and OPI-001 subjects had no previous exposure to pioglitazone whereas TZD-

009 subjects did. Thus, 12 treatment arms (4 OPI-002 arms and 12 OPI-001 arms) were evaluated in the integrated database. Only 2 of the combination arms were common to both studies (alogliptin 12.5 and 25 mg with pioglitazone 30 mg). Of the dose groupings evaluated, the majority of subjects received alogliptin alone or in combination with pioglitazone (1528/2207; 69.2%) and a small number of subjects received only placebo (129/2207; 5.8%). Therefore, the pooled data is presented at the compound level excluding the placebo-only group (except disposition and exposure which do include the placebo-only group). The 3 treatment groupings are as follows:

- Alogliptin grouping: all subjects who received alogliptin with pioglitazone placebo
- Pioglitazone grouping: all subjects who receive pioglitazone with alogliptin placebo
- Combination grouping: all subjects who received alogliptin with pioglitazone

NDA 22-426. Dose groups		
Placebo +	**Alogliptin 12.5 mg +**	**Alogliptin 25 mg +**
Placebo (OPI-001)	Placebo (OPI-001)	Placebo (both studies)
Pioglitazone 15 mg (OPI-001)	Pioglitazone 15 mg (OPI-001)	Pioglitazone 15 mg (OPI-001)
Pioglitazone 30 mg (both studies)	Pioglitazone 30 mg (both studies)	Pioglitazone 30 mg (both studies)
Pioglitazone 45 mg (OPI-001)	Pioglitazone 45 mg (OPI-001)	Pioglitazone 45 mg (OPI-001)

NOTE: Due to the similarities in study design, I generally agree with the pooled study groups. 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

As requested, on May 22, 2009, the sponsor clarified the number of subjects exposed to alogliptin + pioglitazone in controlled trials TZD-009, OPI-001, and OPI-002 with and without the uncontrolled data from study OLE-012 subgroup TZD-009. The results are as follows:

NDA 22-426. Controlled and uncontrolled A+P exposure. NOTE: Uncontrolled data has a September 15, 2008 cutoff)			
Study	**Exposure**		
	≥ 6 mo	**≥ 12 mo**	**≥ 18 mo**
Controlled TZD-009	315		
Controlled OPI-001	688		
Controlled OPI-002	264		
Controlled total	**1267**		
Uncontrolled OLE-012 data (subgroup TZD-00)	378	192	158
Uncontrolled OLE-012 data (subgroups TZD-009, OPI-001, & OPI-002)*	1330		
*Subjects form TZD-009 who chose to rollover into the OLE-012 continued their TZD background therapy during the extension study. In contrast, subjects from FDC studies OPI-001 and OPI-002 were randomized in a blinded fashion to alogliptin alone, pioglitazone alone, or a combination of both in these studies. As a result, subjects from			

FDC studies OPI-001 and OPI-002 who enrolled in OLE-012 were not permitted to receive pioglitazone initially upon entry into study OLE-012. Therefore, these subjects were not included in the 120-day Safety Update as they did not receive continuous pioglitazone therapy.

COMMENT: 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 to alogliptin NDA 22-271, 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. Alogliptin (NDA 22-271) will not be approved due to unacceptable increase in cardiovascular risk (based on the December 2008 diabetes cardiovascular guidance) and a numerical imbalance against alogliptin in cardiovascular serious adverse events.

The sponsor analyzed the following as AEs of interest for alogliptin treatment:

- Cardiovascular (CV) AEs of interest cluster
- Ischemic heart disease
- Cardiac arrhythmias cluster
- Angioedema cluster
- Potential cutanous drug reaction cluster

Two TZDs, pioglitazone and rosiglitazone, have been approved in the United States since 1999. Both of the pioglitazone and rosiglitazone labels contain black boxes warning the following:

- TZDs cause or exacerbate CHF in some patients.
- TZDs are not recommended in patients with symptomatic heart failure and initiation is contraindicated in subjects with established NYHA Class III or IV heart failure.

Rosiglitazone contains the additional black box warning that a meta-analysis of 42 clinical studies showed rosiglitazone to be associated with an increased risk of myocardial ischemic events such as angina or MI.

Potential adverse events associated with TZDs also include fluid retention, edema, weight gain, anemia, macular edema, and bone fractures in females. Pioglitazone is also associated with ovulation in premenopausal anovulatory women and postmarketing reports of hepatitis and hepatic enzyme elevations $\geq$ 3x ULN. Reports of hepatic failure with and without fatal outcome have been received, although causality has not been established.

The sponsor analyzed the following as AEs of interest for pioglitazone treatment:

- Cardiac failure cluster
- Edema cluster
- Weight gain cluster
- Bone fracture cluster
- Neoplasms benign, malignant, and unspecified SOC

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:

(b) (4)

Clinical pharmacology, however, recommended 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 of NDA 22-271 and my clinical review of NDA 22-271, 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 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 controlled phase 3 study groups of A+P, the mean patient age was 53.1 years. The majority of subjects were White (74.9%). The percentage of Asian and Black subjects ranged between 4-7%. Approximately half of subjects were male. The majority were obese with a mean duration of diabetes of 5.4 years and mean HbA1c of 8.6%.

NDA 22-426. Demographics and baseline characteristics of subjects in controlled phase 3 studies OPI-002 and OPI-001

	Alo + Pio studies, n=1107
Age, mean (SD)	53.1 (9.8)
Male, n (%)	496 (44.8)
Race, n (%)	
White	829 (74.9)
Asian	81 (7.3)
Black	46 (4.2)
Other	151 (13.6)
BMI ≥ 30, n (%)	590 (53.3)
Mean DM duration (years)	5.4 (5.2)
Mean HbA1c (SD)	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.

The pioglitazone doses (15, 30, and 45 mg) were chosen as they are currently marketed; pre- and post-marketing studies support their use.

7.2.3 Special Animal and/or In Vitro Testing

The sponsor performed 2 QT studies (SYR-322-004 and SYR-322-019) which were submitted to alogliptin NDA 22-271. 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 and reviewed under NDA 22-271:

- 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 NDA 22-271 for full details.

According to the December 11, 2008 Actos label, peak concentrations are observed within 2 hours after oral administration of pioglitazone. Food slightly delays the time to peak serum concentration to 3-4 hours, but does not alter the extent of absorption. Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxyl derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser extent, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1. Pioglitazone is not a strong CYP3A4 enzyme inducer.

After oral administration, approximately 15-30% of the pioglitazone dose is recovered in the urine. Renal elimination is negligible. The drug is excreted primarily as metabolites and their conjugates. Most of the oral dose is likely excreted into bile unchanged or as metabolites and eliminated in the feces.

The mean serum half-life of pioglitazone and total pioglitazone (i.e. pioglitazone plus active metabolites) ranges from 3-7 hours and 16-24 hours respectively. Please refer to the Actos label for full details, including drug-drug interactions.

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 ≥ 5% of patients treated with sitagliptin and more commonly than placebo-treated patients

Monkeys develop necrotic skin lesions after exposure to some DPP-4 inhibitors (not alogliptin), which is thought to result from cross-reactivity with DPP-8 and DPP-9. Vildagliptin, which is currently in development, may cause hepatoxicity. Vildagliptin's sponsor has been asked to conduct a dedicated hepatic safety study. Saxagliptin, which is currently under NDA review, is associated with lymphocyte reductions. Alogliptin will not be approved this cycle because the sponsor did not rule out an unacceptable increase in cardiovascular risk (based on the December 2008 diabetes cardiovascular guidance) and a numerical imbalance against alogliptin in cardiovascular serious adverse events.

Two TZDs, pioglitazone and rosiglitazone, have been approved in the United States since 1999. Both of the pioglitazone and rosiglitazone labels contain black boxes warning the following:

- TZDs cause or exacerbate congestive heart failure (CHF) in some patients.
- TZDs are not recommended in patients with symptomatic heart failure and initiation is contraindicated in subjects with established NYHA Class III or IV heart failure.

Rosiglitazone contains the additional black box warning that a meta-analysis of 42 clinical studies showed rosiglitazone to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction (MI).

Potential adverse events associated with TZDs also include fluid retention, edema, weight gain, anemia, macular edema, and bone fractures in females. Pioglitazone is also associated with ovulation in premenopausal anovulatory women and postmarketing reports of hepatitis and hepatic enzyme elevations ≥ 3x the upper limit of normal (ULN). Reports of hepatic failure with and without fatal outcome have been received, although causality has not been established.

The sponsor appropriately evaluated for these potential risks by analyzing them as AEs of interest:

- Alogliptin
  - Cardiovascular (CV) AEs of interest cluster
  - Ischemic heart disease
  - Cardiac arrhythmias cluster
  - Angioedema cluster
  - Potential cutanous drug reaction cluster
- Pioglitazone treatment
  - Cardiac failure cluster
  - Edema cluster
  - Weight gain cluster
  - Bone fracture cluster
  - Neoplasms benign, malignant, and unspecified SOC

Study SYR-322-006 also evaluated alogliptin PK in subjects with renal impairment under NDA 22-271. Results indicated that dose reduction is needed in patients with moderate to severe renal impairment, including ESRD. 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 under NDA 22-271.

However, 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 NDA 22-271, 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 became clear that the sponsor had not fully evaluated the potential for cardiovascular risk. Thus, alogliptin NDA 22-271 will not be approved. (Please refer to NDA 22-271 section 7.3.5 Submission Specific Primary Safety Concerns for full details.) As alogliptin is included in the FDC NDA 22-426, CV safety concern still exists. The sponsor has been asked to address this is a long-term CV outcomes trial.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in study OPI-002. A total of 4 deaths occurred in studies OPI-001, TZD-009, and OLE-012; 2 of these were reported in the 120-day safety update (September 15, 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 was only 1 death among the alogliptin-treated patients. The narratives of the deaths are as follows:

OPI-001:

- 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.**

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.

OLE-012 (120-day safety update [January 16, 2009]):

- 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 the 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."**

NDA 22-271. Deaths in subjects exposed to alogliptin and pioglitazone (120-day safety cutoff of September 15, 2008)

Subject	Age/Sex	Day of death (Days after last dose)	Preferred term	Possible contributing factors
TZD-009				
463/9003	62 M	42 (42)	Sudden death	Abnormal ECG
OLE-012				

228/9002	73 M	121 (115)	Pneumonia, cardio-respiratory arrest	Recent pneumonia, hospitalization
325/9004	64 M	68	Hypertensive heart disease*	

7.3.2 Nonfatal Serious Adverse Events

A total of 28 (2.5%) A+P 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 the 2 pivotal controlled phase 3 studies of A+P. In these 2 pivotal FDC studies, TESAEs were most common in the infection and infestation disorders SOC (0.5%) followed by cardiac, gastrointestinal, and nervous system disorders (0.4% each). In supportive study TZD-009 and the uncontrolled OLE-012 study TZD-009 subgroup, TESAEs were most common in the cardiac disorders and infection and infestation disorders SOCs.

NDA 22-426. Treatment-emergent SAEs by system organ class in the 2 pivotal phase 3 controlled studies of alogliptin + pioglitazone (i.e. studies OPI-002 and OPI-001)

	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, pueperium, 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 in the 2 pivotal phase 3 controlled studies of alogliptin + pioglitazone (i.e. studies OPI-002 and OPI-001)

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 22-426. TESAES by system organ class (and preferred term if ≥2 subjects overall) in TZD-009, which administered pioglitazone with/without metformin or SFU with alogliptin or placebo

System organ class	**Placebo (n=97)**	**A12.5 (n=198)**	**A25 (n=199)**
Subjects with ≥ 1 TESAE	**4 (4.1)**	**5 (2.5)**	**13 (6.5)**
Total TESAEs	**5**	**6**	**16**
Cardiac disorders	0	2 (1.0)	5 (2.5)
Myocardial infarction	0	1 (0.5)	2 (1.0)
Angina pectoris	0	1 (0.5)	1 (0.5)
Cardiac failure congestive	0	0	2 (1.0)
Gastrointestinal disorders	0	1 (0.5)	0
General disorders & administrative site	0	1 (0.5)	0
Immune system disorders	0	0	1 (0.5)
Infections & infestations	1 (1.0)	0	5 (2.5)
Appendicitis	1 (1.0)	0	1 (0.5)
Cellulitis	0	0	2 (1.0)
Injury, poisoning, & procedural comp.	0	0	1 (0.5)
Metabolism & nutrition	1 (1.0)	0	0
Neoplasms, benign, malignant, & unspecified	2 (2.1)	0	0
Nervous system	0	0	1 (0.5)
Renal and urinary	1 (1.0)	1 (0.5)	0
Reproductive system & breast	0	0	1 (0.5)
Respiratory, thoracic, & medistinal	0	0	1 (0.5)

NDA 22-426. SAEs that occurred in ≥2 subjects in uncontrolled study OLE-012 study TZD-009 subgroup as reported in the 120-day Safety Update (cutoff September 15, 2008)

System organ class – Preferred term	**A12.5+P (n=250)**	**A25+P (n=284)**	**Overall (n=450)**
Overall (any SAE)	**11 (4.4)**	**28 (9.9)**	**39 (8.7)**
Cardiac disorders	3 (1.2)	12 (4.2)	15 (3.3)
Myocardial infarction	1 (0.4)	3 (1.1)	4 (0.9)
Acute myocardial infarction	0	2 (0.7)	4 (0.4)
Angina pectoris	1 (0.4)	1 (0.4)	2 (0.4)
Atrial fibrillation	0	2 (0.7)	2 (0.4)
Cardiac failure congestive	0	2 (0.7)	2 (0.4)
Infections and infestations	1 (0.4)	9 (3.2)	10 (2.2)
Cellulitis	0	3 (1.1)	3 (0.7)
Appendicitis	1 (0.4)	1 (0.4)	2 (0.4)
Pneumonia	0	2 (0.7)	2 (0.4)

I reviewed all cardiac, neurologic, hypoglycemic, hypersensitivity, accidental (to assess for hypoglycemia), and uncommon TESAE narratives, including pregnancies, in the controlled phase 3 trials. Narratives for major adverse cardiovascular events (MACE), including cardiovascular and neurologic events, were reviewed under alogliptin NDA 22-271 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.

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.

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 [βHCG] level 52.62 mlU/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 (βHCG 6.6 mlU/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. βHCG 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.

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, propanolol, and cetrizine. 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 anteroseptal 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.**

7.3.3 Dropouts and/or Discontinuations

In the 2 pivotal controlled phase 3 studies (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 (OI-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)

Narratives of abnormal liver tests which led to discontinuation are as follows:

- 002/055-2516 (A12.5+P30): 44 year old male with a history of T2D, back pain, and neuropaty experienced a liver function test abnormality on day 1 which led to withdrawal. Concomitant medications were ultracet, ibuprofen, and metaxalone. The values did not reach 3x ULN. Both levels return to normal at the termination visit on day 50.

Subject 002/055-2516. Liver function values (Reproduced from the sponsor)

	ALT	AST	Total Bilirubin
Reference Ranges	5-25 mU/mL	8-22 mU/mL	0.10-1.10 mg/dL
Baseline			
Study Day 1	46	22	0.48
Study Day 8	47	31	0.66
Study Day 14	34	19	0.54
Study Day 33	32	18	0.46
Last Observation			
Study Day 50	17	9	0.61

- 002/057-2503 (pioglitazone): 65 year old male with a history of T2D, alcoholism, hyperlipidemia, hypertension, and liver function test abnormal experienced abnormal liver function tests on day 85 which led to withdrawal. Concomitant medications included duloxetine, hydrochloride, propranolol hydrochloride, simvastatin, and ramipril. Study drug was discontinued as a result of the abnormal liver function tests. The subject was withdrawn on day 118. The event was ongoing.

Subject 002/057-2503. Liver function values (Reproduced from the sponsor)

	ALT	AST	Total Bilirubin	GGT	Alkaline Phosphatase	LDH
Reference Ranges	5-25 mU/mL	8-22 mU/mL	0.10-1.10 mg/dL	5-29 mU/mL	32-72 mU/mL	40-100 mU/mL
Baseline						
Study Day 1	52	44	0.53	182	66	99
Reading Prior to Elevation						
Study Day 61	49	58	0.42	218	54	89
Elevation						
Study Day 85	56	84	0.47	252	60	103
Unscheduled						
Study Day 97	60	74	0.47	283	60	115
Last Observation						
Study Day 118	47	88	1.05	447	74	107

In supportive study TZD-009, discontinuation due to AEs was similar between treatment groups (placebo 3.1%, A12.5 4.1%, and A25 3.0%); no dose-related trend was seen.

Please refer to section 6.1.3 Patient Disposition for more information.

7.3.4 Significant Adverse Events

NOTE: Please refer to the major adverse cardiovascular event (MACE) analyses of alogliptin studies, including OPI-002 and OPI-001, in my clinical review of alogliptin NDA 22-271.

<u>The sponsor analyzed the following AEs of interest for alogliptin treatment in the 2 pivotal trials:</u>

- CV AEs of interest cluster:

  - Preferred terms (PTs) in the following standardized MedDRA queries (SMQs) v10.0: cardiac arrhythmias, cardiac failure, cerebrovascular accidents (CVAs), convulsions, ischemic heart disease, and Torsade de Pointes/QT prolongation.
  - PTs that mapped to the following: "cardiac disorders" SOC as their primary SOC, "investigations" SOC as primary and included in the high-level term (HLT) of "ECG investigations", "nervous system disorders" SOC as primary and included in the HLT of "central nervous system hemorrhages and CVAs", and "general disorders and administration site conditions" SOC as primary and included in the HLT of "death and sudden death."
  - The following PTs: chest pain, chest discomfort, noncardiac chest pain, and musculoskeletal pain
- Ischemic heart disease:
  - PTs included in the MedDRA v10.0 SMA for "ischemic heart disease".
  - To ensure that nonspecific angina events were not excluded, selected PTs (chest pain, chest discomfort, noncardiac chest pain, and musculoskeletal pain) were also included
- Cardiac arrhythmias cluster: PTs included in MedDRA v10.0 SMQ for "cardiac arrhythmias"
- Angioedema cluster: PTs in the MedDRA v10.0 SMQ for "angioedema"
- Potential cutaneous drug reaction (PCDR) cluster: PTs that map to the following HLT in MedDRA v10.0 as primary or nonprimary HLT: allergic conditions not elsewhere classified (NEC); allergies to foods, food additives, drugs, and other chemicals; anaphylactic responses; angioedemas; dermal and epidermal conditions NEC, dermatitis and eczema; dermatitis ascribed to specific agent; erythemas; exfoliative conditions; papulosquamous conditions; pruritis NEC; rashes, eruptions, and exanthemas NEC; and urticarias

COMMENT: The customized MedDRA query of PCDR events did not include most ulcers; only venous ulcer pain was included.

Cardiovascular events are AEs of special interest because 1) T2D subjects are at higher risk for these events than the general population and 2) there was a numerical imbalance against alogliptin in cardiovascular SAEs in the clinical review of alogliptin NDA 22-271.

The presence of cardiovascular risk factors at baseline were similar among the 3 groupings (i.e. combination, pioglitazone, and alogliptin) in this study pool population. Approximately half of subjects had hypertension and 17.8-20.7% used tobacco. Less than 15% of subjects entered studies OPI-002 and OPI-001 with a condition in the cardiac disorders SOC. Prohibited conditions included NYHA Class III or IV heart failure; angioedema associated with angiotensin-converting enzyme inhibitors or angiotensin-II receptor inhibitors; or history within 6 months of angioplasty, coronary bypass surgery, or MI.

The incidence of CV AEs of interest was highest in the pioglitazone group (11.1%), followed by the combination (9.1%) and alogliptin (5.7%) groups. The most frequently reported AE was

edema peripheral (alogliptin 1.4%, pioglitazone 3.5%, A+P 2.7%). The highest incidence of other events in the combination grouping was 0.5% (palpitations, tachycardia, and pitting edema).

NDA 22-426. Summary of cardiovascular AEs of interest cluster (≥2 subjects overall) (Reproduced from the sponsor)

	Number of Subjects (%)		
Preferred Term (a)	**ALO N=421**	**PIO N=550**	**ALO+PIO N=1107**
Overall (any AE in cluster)	24 (5.7)	61 (11.1)	101 (9.1)
Edema peripheral	6 (1.4)	19 (3.5)	30 (2.7)
Palpitations	1 (0.2)	1 (0.2)	6 (0.5)
Tachycardia	0	1 (0.2)	6 (0.5)
Pitting edema	0	1 (0.2)	5 (0.5)
Angina pectoris	1 (0.2)	3 (0.5)	4 (0.4)
Atrioventricular block first degree	0	1 (0.2)	4 (0.4)
Bundle branch block left	0	2 (0.4)	4 (0.4)
Myocardial ischemia	1 (0.2)	3 (0.5)	4 (0.4)
Bundle branch block right	0	3 (0.5)	3 (0.3)
Musculoskeletal chest pain	0	2 (0.4)	3 (0.3)
Noncardiac chest pain	2 (0.5)	4 (0.7)	3 (0.3)
Supraventricular extrasystoles	0	0	3 (0.3)
Syncope	2 (0.5)	1 (0.2)	3 (0.3)
Atrial fibrillation	0	0	2 (0.2)
Chest pain	1 (0.2)	2 (0.4)	2 (0.2)
ECG QT prolonged	1 (0.2)	0	2 (0.2)
ECG ST segment depression	0	0	2 (0.2)
ECG repolarization abnormality	2 (0.5)	0	2 (0.2)
Left atrial hypertrophy	0	0	2 (0.2)
Myocardial infarction	1 (0.2)	1 (0.2)	2 (0.2)
Edema	0	0	2 (0.2)
Sinus bradycardia	0	3 (0.5)	2 (0.2)
Angina unstable	1 (0.2)	1 (0.2)	1 (0.1)
Bundle branch block	0	1 (0.2)	1 (0.1)
Cardiac failure congestive	0	2 (0.4)	1 (0.1)
ECG ST-T change	1 (0.2)	0	1 (0.1)
ECG abnormal	0	1 (0.2)	1 (0.1)
Extrasystoles	0	1 (0.2)	1 (0.1)
Left ventricular hypertrophy	1 (0.2)	1 (0.2)	1 (0.1)
Sinus tachycardia	1 (0.2)	0	1 (0.1)
Ventricular extrasystoles	0	4 (0.7)	1 (0.1)
Bradycardia	0	2 (0.4)	0
Coronary artery disease	1 (0.2)	1 (0.2)	0
QRS axis abnormal	1 (0.2)	1 (0.2)	0

Of the CV AEs of interest that occurred in ≥ 2 subjects, there were 11 SAEs (A+P 3, pioglitazone 5, and alogliptin 3). The 3 SAEs in the combination grouping were as follows:

- Angina unstable (001/833-3004): 44 year old male with T2D and hypertension who discontinued the study due to the SAE.
- Myocardial ischemia (001/296-3007): 48 year old male with a history of T2D, tobacco use, hypertension, dyslipidemia, and obesity who experienced myocardial ischemia on day 174 yet completed the study.

- Syncope (002/040-2513): 43 year old woman with T2D, dyslipidemia, and hypertension (on losartan/hydrochlorothiazide) who completed the study.

Overall, the fact that the incidence of CV AEs of interest, including SAEs, was less in the combination group than the pioglitazone group is reassuring.

The incidence of ischemic heart disease AEs was highest in the pioglitazone group (pioglitazone 3.1%, combination 1.8%, alogliptin 1.4%). Noncardiac AEs (musculoskeletal chest pain, noncardiac chest pain, and chest pain) contributed to approximately half of the AEs in each group. The most frequently reported AEs in the ischemic heart disease cluster were angina pectoris, myocardial ischemia, musculoskeletal chest pain, noncardiac chest pain, and chest pain, which all occurred more often in the pioglitazone group.

Ten subjects experienced SAEs in the ischemic heart disease cluster (pioglitazone 4, A+P 4, and alogliptin 2). Three subjects were discontinued as a result of the AE (combination 2, pioglitazone 1). A+P subjects who experienced an SAE are as follows:

- 002/665-2509: 57 year old male with a history of T2D, MI in 1997, dyslipidemia, hypothyroidism, obesity, and 38 years tobacco use experienced an acute MI on day 26, which was medically managed and led to study discontinuation.
- 001/833-3004: 44 year old male with a history of T2D and hypertension experienced unstable angina on day 9. He had chest pain, diaphoresis, and palpitations after taking his study drug and a 15-second syncope while driving. He was admitted to the hospital and medically managed. Cardiac enzymes did not meet criteria for a myocardial infarction, although study drug was discontinued on day 9 due to the SAE.
- 001/296-3007: See above narrative.
- 001/397-3011: 66 year old male with T2D, dyslipdemia, and hypertension experienced coronary artery stenosis on day 77. An exercise tolerance test on day 27 suggested myocardial ischemia, which was reported. A single-photon-emission-computed tomography scan with Tc99 MIBI revealed transient hypoperfusion in the inferior wall after exercise, an ejection fraction of 58% (normal >45%) and normal left ventricular global function at rest on day 29. The subject was hospitalized on day 77 for a cardiac catheterization which diagnosed coronary artery stenosis. Study drug was interrupted on day 73-80 due to myocardial ischemia, although the subject completed the study.

NDA 22-426. AEs in the ischemic heart disease cluster (Reproduced from the sponsor)

	Number of Subjects (%)		
Preferred Term (a)	ALO N=421	PIO N=550	ALO+PIO N=1107
Overall (any AE in cluster)	6 (1.4)	17 (3.1)	20 (1.8)
Angina pectoris	1 (0.2)	3 (0.5)	4 (0.4)
Myocardial ischemia	1 (0.2)	3 (0.5)	4 (0.4)
Musculoskeletal chest pain	0	2 (0.4)	3 (0.3)
Noncardiac chest pain	2 (0.5)	4 (0.7)	3 (0.3)
Chest pain	1 (0.2)	2 (0.4)	2 (0.2)
ECG ST segment depression	0	0	2 (0.2)
Myocardial infarction	1 (0.2)	1 (0.2)	2 (0.2)
Acute myocardial infarction	0	0	1 (0.1)
Angina unstable	1 (0.2)	1 (0.2)	1 (0.1)
Coronary artery stenosis	0	0	1 (0.1)
Coronary artery disease	1 (0.2)	1 (0.2)	0
ECG ST segment elevation	0	1 (0.2)	0
Ischemic cardiomyopathy	0	1 (0.2)	0

The overall incidence of AEs in the cardiac arrhythmia cluster was greatest in the pioglitazone group (pioglitazone 4.2%, A+P 3.6%, alogliptin 1.7%). The incidence of the most common AEs, palpitations and tachycardia, was higher however in the A+P group, although the percent incidence was low (0.5%). Four subjects had an SAE within this cluster (2 pioglitazone, 1 A+P, 1 alogliptin). The A+P subject was 002/040-2513; please refer to the narrative above. Among the arrhythmia cluster AEs, only 1 subject discontinued the study as a result of the AE. This was A+P subject 001/655-3005: 66 year old female with history of T2D, hyperlipidemia, hypertension, and depression who experienced palpitations, anorexia, dizziness, and hyperhydrosis on day 8. Concomitant medications included enalapril, doxazosin, pravastatin, brotizolam, and acetylsalicylic acid. The baseline ECG was normal. She discontinued the study on day 13 due to the AE, which resolved on day 15.

NDA 22-426. Summary of AEs in the cardiac arrhythmia cluster (≥2 subjects overall) (Reproduced from the sponsor)

	Number of Subjects (%)		
Preferred Term (a)	ALO N=421	PIO N=550	ALO+PIO N=1107
Overall (any AE in cluster)	7 (1.7%)	23 (4.2%)	40 (3.6%)
Palpitations	1 (0.2)	1 (0.2)	6 (0.5)
Tachycardia	0	1 (0.2)	6 (0.5)
Atrioventricular block first degree	0	1 (0.2)	4 (0.4)
Bundle branch block left	0	2 (0.4)	4 (0.4)
Bundle branch block right	0	3 (0.5)	3 (0.3)
Supraventricular extrasystoles	0	0	3 (0.3)
Syncope	2 (0.5)	1 (0.2)	3 (0.3)
Atrial fibrillation	0	0	2 (0.2)
ECG QT prolonged	1 (0.2)	0	2 (0.2)
ECG repolarization abnormality	2 (0.5)	0	2 (0.2)
Sinus bradycardia	0	3 (0.5)	2 (0.2)
Bundle branch block	0	1 (0.2)	1 (0.1)
ECG abnormal	0	1 (0.2)	1 (0.1)
Extrasystoles	0	1 (0.2)	1 (0.1)
Sinus tachycardia	1 (0.2)	0	1 (0.1)
Ventricular extrasystoles	0	4 (0.7)	1 (0.1)
Bradycardia	0	2 (0.4)	0

The incidence of angioedema events was highest in the pioglitazone group (4.2% vs. A+P 3.3% and alogliptin 2.4%). Edema peripheral, a known AE of pioglitazone, accounted for the majority of the agioedema cluster events. All but 2 remaining events (urticaria and swelling face) occurred in only 1-2 subjects. Urticaria occurred in 2 subjects in each grouping; swelling face occurred in 2 A+P subjects and 1 pioglitazone subject. Although there were no SAEs in the angioedema cluster, 3 subjects in each of the A+P and pioglitazone groups discontinued the study as a result of their AE. The 3 A+P subjects that discontinued the study were as follows:

- 001/756-3002: 50 year old female with history of T2D, CVA, asthma, hyperlipidemia, hypertension, multiple sclerosis, and multiple allergies experienced edema peripheral on day 11, which led to her discontinuation on day 39. No treatment was required.
- 001/738-3006: 56 year old female with a history of T2D, lipoma, increased cholesterol, hypertension, asthma, and history of smoking experienced edema peripheral on day 4, which led to study discontinuation on day 7. No treatment was given for the event, which was continuing at her last study visit on day 8.
- 002/643-2502: 44 year old woman with a history of T2D, atrial fibrillation, depression, hypertension, mitral valve incompetence/prolapse, and obesity experienced tachycardia, peripheral edema (legs), and localized edema (abdominal wall) on day 86. The edema events led to study drug discontinuation after week 16 and study withdrawal on day 163. Treatment included metoprolol and furosemide.

NDA 22-426. AEs in the angioedema cluster (Reproduced from the sponsor)

	Number of Subjects (%)		
Preferred Term (a)	ALO N=421	PIO N=550	ALO+PIO N=1107
Overall (any AE in cluster)	10 (2.4)	23 (4.2)	37 (3.3)
Edema peripheral	6 (1.4)	19 (3.5)	30 (2.7)
Face edema	0	0	2 (0.2)
Edema	0	0	2 (0.2)
Swelling face	0	1 (0.2)	2 (0.2)
Urticaria	2 (0.5)	2 (0.4)	2 (0.2)
Drug hypersensitivity	0	0	1 (0.1)
Localized edema	0	0	1 (0.1)
Urticaria localized	1 (0.2)	0	1 (0.1)
Wheezing	0	0	1 (0.1)
Angioedema	0	1 (0.2)	0
Eyelid edema	0	1 (0.2)	0
Generalized edema	1 (0.2)	0	0

In alogliptin NDA 22-271, 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.

In the 2 pivotal studies of A+P under NDA 22-426, the overall incidence of PCDR AEs was higher in the combination grouping (7.6%) than the pioglitazone and alogliptin groupings (6.5% and 6.2%, respectively). The most frequently reported AEs in this cluster were again pruritis and rash. There were no PCDR SAEs, although AEs led to discontinuation in 6 subjects (5 A+P, 1 pioglitazone). AEs which lead to discontinuation in A+P subjects were as follows:

- 001/770-3002: 45 year old male with history of T2D, shellfish allergy, depression, and anxiety experienced pruritis (upper torso) on day 2. He was treated with pimecrolimus on day 14 and discontinued the drug on day 130. The pruritis resolved on day 137. The subject also experienced a vesicular rash on his hands on day -1 and Campbell de Morgan spots (also known as cherry hemagniomas) on his arms and hands on day -7.
- 002/888-2505: 53 year old female with a history of T2D, dyslipidemia, hypertension, hyperthyroidism, ischemic cardiomyopathy, and obesity experienced generalized pruritis on day 3 which led to study withdrawal on day 12. She was treated with calcium chloride dehydrate from day 8-10. Symptoms resolved after the study drug was stopped.
- 002/097-2508: 55 year old male with T2D experienced papular rash on his neck and shoulders on day 130, which led to study withdrawal on day 155. The rash was treated with betamethasone from day 154-198. He also experienced chin erythema on day 120. Both the rash and erythema resolved.

- 002/011-2508: 41 year old female with a history of T2D and hyperlipidemia experienced a drug eruption on day 6, which led to study withdrawal. The subject had concurrent vaginal candidiasis on days 5-29 which was treated with fluconazole. The rash involved her left hand, ventral wrist, and inner thighs and was treated with diphenhydramine hydrochloride. Ciprofloxacin was also started on day 22 for the vaginal candidiasis. Study drug was interrupted, restarted, and subsequently discontinued due to the drug eruption on day 29. The eruption resolved on day 32.
- 001/304-3004: 63 year old male with a history of T2D, tobacco use, and leukocytosis experienced dermatitis on day 17, specifically erythematous, "inflammatory dermatitis with punctuate scabs on the ventral surfaces of the digits, sparing the palms." The subject self-treated with an ear and eye product containing neomycin, polymyxin B, and gramicidin on day 30. He discontinued study drug on day 28 due to the event, which resolved on day 51.

NDA 22-426. Summary of AEs in the potential cutaneous drug reaction cluster (≥2 subjects overall) (Reproduced from the sponsor)

	Number of Subjects (%)		
Preferred Term (a)	**ALO N=421**	**PIO N=550**	**ALO+PIO N=1107**
Overall (any AE in cluster)	26 (6.2)	36 (6.5)	84 (7.6)
Pruritus	3 (0.7)	1 (0.2)	13 (1.2)
Rash	4 (1.0)	5 (0.9)	12 (1.1)
Dry skin	3 (0.7)	0	8 (0.7)
Dermatitis	1 (0.2)	0	6 (0.5)
Dermatitis allergic	2 (0.5)	3 (0.5)	4 (0.4)
Eczema	0	4 (0.7)	4 (0.4)
Skin exfoliation	3 (0.7)	2 (0.4)	4 (0.4)
Dermatitis contact	2 (0.5)	3 (0.5)	3 (0.3)
Erythema	1 (0.2)	0	3 (0.3)
Pruritus generalized	0	0	3 (0.3)
Rash papular	0	1 (0.2)	3 (0.3)
Skin lesion	0	1 (0.2)	3 (0.3)
Dermatitis atopic	0	1 (0.2)	2 (0.2)
Face edema	0	0	2 (0.2)
Rash erythematous	0	1 (0.2)	2 (0.2)
Skin discoloration	1 (0.2)	1 (0.2)	2 (0.2)
Skin fissures	0	1 (0.2)	2 (0.2)
Swelling face	0	1 (0.2)	2 (0.2)
Urticaria	2 (0.5)	2 (0.4)	2 (0.2)
Vulvovaginal pruritus	0	0	2 (0.2)
Rash macular	1 (0.2)	0	1 (0.1)
Rash pruritic	0	1 (0.2)	1 (0.1)
Skin disorder	0	1 (0.2)	1 (0.1)
Urticaria localized	1 (0.2)	0	1 (0.1)
Asthma	1 (0.2)	1 (0.2)	0
Bronchospasm	2 (0.5)	1 (0.2)	0
Rash maculo-papular	0	2 (0.4)	0

As requested, on May 20, 2009, the sponsor provided an analysis of pancreatitis cases occurring with alogliptin and comparators in the controlled phase 2/3 clinical trials. The analysis was

performed by using the SMQ of "acute pancreatitis" in MedDRA version 10.0. This includes PTs that are categorized as PTs specific for acute drug associated pancreatitis (category A) PTs of elevated laboratory values (category B), and PTs of nonspecific signs and symptoms suggestive of acute pancreatitis (category C). The results of this search are shown below. Overall, the pancreatitis event rate as defined by this SMQ was similar to placebo (~5%).

NDA 220426. Subjects with ≥ 1 TEAE in the "acute pancreatitis" SMQ. Note: Overall tally includes studies 003, 007-011, OPI-001, and OPI-002

Study	Placebo	A 6.25	A 12.5	A 25	A > 25	All A
Overall	57/1213 (4.7)	3/42 (7.1)	81/1603 (5.1)	96/1757 (5.5)	7/87 (8.0)	187/3489 (5.4)
TZD-009	4/97 (4.1)	NA	18/198 (9.1)	10/199 (5.0)	NA	28/397 (7.1)
OPI-001	26/516 (5.0)	NA	27/518 (5.2)	29/519 (5.6)	NA	56/1037 (5.4)
OPI-002	8/163 (4.9)	NA	8/163 (4.9)	17/328 (5.2)	NA	25/491 (5.1)

To make a selection more specific and relevant for the detection of acute pancreatitis, the sponsor applied the following algorithm to this SMQ: Cases were selected if they contained

- At least 1 PT from category A

- OR -

- At least 1 PT from categories B and C

This search identified the following 4 cases in phase 2/3 alogliptin trials (i.e. studies 003, 007-011, OPI-001, and OPI-002). Narratives for the OPI-001 and OPI-002 cases are provided.

- OPI-002/750-2501 (alogliptin 25 mg + pioglitazone 30 mg): 60 year old female with a history of T2D, hypermetropia, codeine allergy, hypopharyngeal and vulvular cancer, insomnia, hypertonic bladder/stress incontinence, chronic obstructive pulmonary disease (COPD), emphysema, rhinitis, contact dermatitis, and hypertension experienced pancreatitis and cholecystitis on days 35 and 36, respectively. On day 27, the subject developed severe abdominal cramps, nausea, and vomiting. On day 31, a nurse practitioner diagnosed pancreatitis and the patient saw the investigator. On day 32, ultrasound was negative but laboratory results were consistent with pancreatitis. The subject was medically managed. On day 35, he was hospitalized for pancreatitis. CT scan showed pancreatic calcification consistent with chronic pancreatitis, nonspecific splenic calcifications, and sigmoid diverticulosis. The hospitalization was prolonged due to cholecystitis on day 36. The patient was medically managed and underwent laparoscopic cholescystectomy with intraoperative cholangiogram on day 38. Cholangiogram revealed normal caliber biliary system with no obstruction or retained stones or filling defects status post cholecystectomy. During surgery, there was a brief episode (2-3 minutes) of hypoxia likely due to COPD. On day 39, the pathology report revealed chronic inflammation of the gallbladder. On day 42, the AEs resolved and the patient was discharged. Study drug was interrupted on days 27-42; it was resumed after discharge.
  COMMENT: The CT and pathology findings suggest chronic pancreatitis; this is likely not study drug-related after 1 month's exposure.
- OPI-001/436-3004 (alogliptin 12.5 mg): 48 year old female with a history of T2D, cholecystectomy, pancreatitis, and hypertension experienced pancreatitis on day 113.

The subject was hospitalized with abdominal pain, nausea, vomiting, and thirst on day 113. Laboratories were as follows: WBC 14.7 (nl 8-11.0 x 10^9/L), ALT 37 U/l, calcium 2.14 mmol/l, lipase 4871 U/l (nl < 60 U/l), and creatinine 81 µmol/l (nl 40-80 µmol/l). She was medically managed and discharged on day 115 when the event resolved. Study drug was interrupted on days 113-122.

COMMENT: Due to the patient's history, this event was likely not study drug related.

NDA 22-426. TEAE events in the "acute pancreatitis" SMQ for subjects with events meeting SMQ algorithm in controlled phase 2/3 trials of alogliptin

Study	Subject	Treatment	PT	Start date	Category	Serious
OPI-001	436-3004	12.5	Pancreatitis	113	A	Yes
OPI-002	750-2501	25	Nausea	5	C	No
			Pancreatitis	27	A	No
			Pancreatitis	35	A	Yes
INS-011	256-5004	25	Pancreatitis acute	73	A	No
INS-011	269-5004	12.5	Nausea	64	C	No
			Pancreatitis	88	A	Yes

The sponsor analyzed the following AEs of interest for pioglitazone treatment in the 2 pivotal trials:

- Cardiac failure cluster: PTs in MedDRA SMQ "cardiac failure"
- Edema cluster: Standardized selected PTs that have been used in previous analyses of data with pioglitazone exposure.
- Weight gain cluster: Standardized selected PTs that have been used in previous analyses of data with pioglitazone exposure.
- Bone fracture cluster: PTs that map to the HLT "fractures" or "bone and joint injuries" in MedDRA v10.0 through a primary or nonprimary SOC. This approach is consistent with that taken previously for analysis of events with pioglitazone.
- Neoplasms benign, malignant, and unspecified SOC: All AEs that occurred in the SOC of neoplasms benign, malignant, and unspecified were reviewed and attention given to events associated with bladder neoplasm.

TZDs, including pioglitazone, can cause fluid retention which may lead to or exacerbate congestive heart failure. The incidence of cardiac failure cluster AEs in the pioglitazone group was greater than that of the A+P and alogliptin groups (4.0% vs. 3.4% and 1.4%, respectively). The most common AE in this cluster was edema peripheral, which was also greatest in the pioglitazone group.

One subject (001/860-3004; A+P group) experienced an SAE of pulmonary congestion in the cardiac failure cluster. This subject was a 74 year old female with history of T2D, anxiety, hyperlipidemia, hypertension, obesity, and rheumatic heart disease. The investigator reported that the AE was due to valve function failure caused by rheumacarditis during childhood.

Five subjects had AEs leading to discontinuation in the cardiac failure cluster; all were edema peripheral AEs and are discussed below.

NDA 22-426. AEs in the cardiac failure cluster (Reproduced from the sponsor)

	Number of Subjects (%)		
Preferred Term (a)	**ALO N=421**	**PIO N=550**	**ALO+PIO N=1107**
Overall (any AE in cluster)	6 (1.4)	22 (4.0)	38 (3.4)
Edema peripheral (b)	6 (1.4)	19 (3.5)	30 (2.7)
Pitting edema (b)	0	1 (0.2)	5 (0.5)
Edema (b)	0	0	2 (0.2)
Cardiac failure congestive	0	2 (0.4)	1 (0.1)
Pulmonary congestion	0	0	1 (0.1)
Cardiac failure chronic	0	1 (0.2)	0

According to the Actos label, in monotherapy studies with pioglitazone (7.5-45 mg), edema was reported for 4.8% of Actos patients and 1.2% of placebo patients. AEs in the edema cluster occurred more commonly in the pioglitazone group when compared to the A+P and alogliptin groups (3.8% vs. 3.3% and 1.7%, respectively). The most common AE was edema peripheral which also occurred more commonly in the pioglitazone group (3.5% vs. 2.7% and 1.4%, respectively). Pitting edema, however, occurred more commonly in the A+P group (A+P 0.5%; pioglitazone 0.2%), although none of the events were SAEs or lead to discontinuation.

Although there were no SAEs in the edema cluster, 5 subjects were discontinued due to events in the edema cluster. Two were pioglitazone subjects; 3 were A+P subjects (001/756-3002, 001/738-3006, and 002/643-2505: See above narratives).

NDA 22-426. AEs in the edema cluster (Reproduced from the sponsor)

	Number of Subjects (%)		
Preferred Term (a)	**ALO N=421**	**PIO N=550**	**ALO+PIO N=1107**
Overall (any AE in cluster)	7 (1.7)	21 (3.8)	37 (3.3)
Edema peripheral	6 (1.4)	19 (3.5)	30 (2.7)
Pitting edema	0	1 (0.2)	5 (0.5)
Edema	0	0	2 (0.2)
Fluid retention	0	1 (0.2)	1 (0.1)
Localized edema	0	0	1 (0.1)
Generalized edema	1 (0.2)	0	0

TZDs, including pioglitazone, are associated with weight gain, which is likely due to fluid retention and subcutaneous fat accumulation. Standardized selected PTs that had been used in previous analyses of pioglitazone data were used to search the database. The only AE that occurred was "weight increased". The incidence of weight increased was similar in the pioglitazone and A+P groups (2.5% and 2.4%, respectively, vs. 0.5% alogliptin). There were no SAEs in the weight gain cluster, although 2 subjects (both A+P) discontinued due to weight increased.

- 001/653-3003: 63 year old male with a BMI of 26.6 and history of T2D, smoking, 3 MIs, hyperlipidemia, hypertension, and coronary artery artherosclerosis experienced increased weight on day 155 and peripheral edema on day 161. The subject discontinued the study on day 160 and was treated with furosemide on day 161. The increase weight continued but the edema resolved on day 176.
- 001/944-3003: 61 year old female with history of T2D, gastric stapling, hypothyroidism, hypercholesterolemia, and hypertension experienced increased weight on day 8. Study drug was interrupted on days 29-41 and then permanently discontinued on day 42 due to this event. On day 48, the event was considered resolved.

The Actos label describes an increase in bone fractures that was observed with pioglitazone-treated subjects in the PROactive randomized trial. During a mean follow up of 34.5 months, 5.2% of pioglitazone subjects experienced bone fractures (most often nonvertebral) compared to 2.5% of placebo subjects.

The rate of bone fractures in the 2 pivotal trials was similar in the pioglitazone and A+P groups (2.0% and 1.8%, respectively, vs. 1.2% alogliptin). The most common AE in this cluster was limb injury which was greatest in the pioglitazone group (0.9% pioglitazone, 0.5% A+P, 0.2% alogliptin). However, joint injury, foot fracture, and radius fracture occurred slightly more often in the A+P than pioglitazone group. Overall, though, the incidence of AEs in the bone fracture cluster was low.

There was 1 subject with an SAE in the bone fracture cluster (001/826-3017; pioglitazone). No AEs in this cluster led to discontinuation.

NDA 22-426. AEs in the bone fracture cluster (Reproduced from the sponsor)

	Number of Subjects (%)		
Preferred Term (a)	**ALO N=421**	**PIO N=550**	**ALO+PIO N=1107**
Overall (any AE in cluster)	5 (1.2)	11 (2.0)	20 (1.8)
Limb injury	1 (0.2)	5 (0.9)	6 (0.5)
Joint injury	0	1 (0.2)	5 (0.5)
Foot fracture	1 (0.2)	0	3 (0.3)
Joint sprain	1 (0.2)	1 (0.2)	2 (0.2)
Radius fracture	0	0	2 (0.2)
Joint dislocation	0	0	1 (0.1)
Rotator cuff syndrome	1 (0.2)	0	1 (0.1)
Tibia fracture	0	0	1 (0.1)
Wrist fracture	0	0	1 (0.1)
Ankle fracture	0	2 (0.4)	0
Hand fracture	1 (0.2)	0	0
Lower limb fracture	0	1 (0.2)	0
Traumatic fracture	0	1 (0.2)	0

Benign and/or malignant transitional cell neoplasms were observed in male rats exposed to ≥4 mg/kg/d pioglitazone (approximately equal to the maximum recommended human oral dose based on mg/m^2). A 2-year carcinogenicity study of pioglitazone was conducted in male and

female mice at oral doses up to 100 mg/kg/d (approximately 11x the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed.

In two 3-year studies in which pioglitazone was compared to placebo or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom study drug exposure was <1 year at the time of bladder cancer diagnosis, there were 6 (0.16%) pioglitazone cases and 2 (0.05%) placebo cases.

Mechanistic studies in rats and an epidemiologic cohort and nested case control study are ongoing.

When AEs in the neoplasm benign, malignant, and unspecified SOC were reviewed, the incidence was highest in the A+P group, although it was similar to the pioglitazone group (A+P 0.9%, pioglitazone 0.7%, and alogliptin 0.2%). Most events which occurred more frequently in the A+P group were isolated events, although skin papilloma and seborrheic keratosis occurred at 0.3% and 0.2% respectively. Overall, the incidence of AEs in this SOC were low. The only AEs which were serious or led to discontinuation occurred in the pioglitazone group (1 and 2 events, respectively). There were no reports of bladder cancer.

NDA 22-426. AEs in the neoplasms benign, malignant, and unspecified SOC cluster (Reproduced from the sponsor)

	Number of Subjects (%)		
Preferred Term (a)	**ALO N=421**	**PIO N=550**	**ALO+PIO N=1107**
Overall (any AE in SOC)	1 (0.2)	4 (0.7)	10 (0.9)
Skin papilloma	0	0	3 (0.3)
Seborrhoeic keratosis	0	0	2 (0.2)
Acrochordon	0	0	1 (0.1)
Basal cell carcinoma	0	0	1 (0.1)
Hemangioma	0	0	1 (0.1)
Prostate cancer	0	0	1 (0.1)
Squamous cell carcinoma	0	0	1 (0.1)
Uterine leiomyoma	0	2 (0.4)	1 (0.1)
Colon cancer	0	1 (0.2)	0
Squamous cell carcinoma of skin	0	1 (0.2)	0
Thyroid neoplasm	1 (0.2)	0	0

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The incidence rates of TEAEs in the controlled pivotal and supportive phase 3 studies were reviewed. Events which occurred in ≥ 1% of the A+P or alogliptin dose group are listed by SOC and preferred term below. In pivotal studies OPI-002 and OPI-001, 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 nasopharnygitis (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%), hypertension (3.3% vs. 3.3% vs. 2.7%), abdominal pain upper (2.1% vs. 1.8% vs. 0.5%), and dyspepsia (1.0% vs. 1.2% vs. 0.2%). (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 (≥ 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
Parasthesia	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 supportive study TZD-009, cardiac disorders occurred more often in the alogliptin 12.5 and 25 mg groups when compared to placebo (3.0% and 6.5% vs. 1.0%). The most common events in the cardiac disorder SOC were atrial fibrillation, cardiac failure, MI, coronary artery disease, and ventricular extrasystoles. Nervous system events occurred more often in the alogliptin groups in TZD-009 (15.2% and 16.6% vs. 10.3%). The most common nervous system events were headache and dizziness. Respiratory, thoracic, and mediastinal events occurred more often in the alogliptin groups (8.1% and 9.5% vs. 5.2%); cough and epistaxis were the most common AEs. Adverse events in the blood & lymphatic, ear & labyrinth, and immune system SOCs were also

more common the alogliptin groups; anemia and vertigo were the most common AEs in these SOCs.

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. In the pivotal studies, infection and infestation events occurred more often in the A+P group than the alogliptin and pioglitazone groups (27.5% vs. 25.2% and 25.1%). Upper respiratory infection, pharyngitis, bronchitis, and sinusitis all occurred more often in the A+P and/or alogliptin group than the pioglitazone group. However, in supportive study TZD-009, infections and infestations were more common the placebo group when compared to alogliptin 12.5 and 25 mg (37.1% vs. 34.8% and 33.7%).

NDA 22-426. Percent incidence of TEAEs in supportive, controlled phase 3 study TZD-009 (≥ 1% alogliptin group) (Safety set). Source: Table 15.3.1.2 (p. 721)

System organ class – Preferred term	**Placebo**	**A12.5**	**A25**
Total number of TEAE	**198**	**389**	**420**
% of subjects ≥ 1 TEAE	**64.9**	**69.7**	**72.4**
Blood & lymphatic	**0**	**1.5**	**3.5**
Anemia	0	1.0	3.0
Cardiac	**1.0**	**3.0**	**6.5**
Atrial fibrillation	0	0.5	1.0
Cardiac failure	0	0	1.5
Myocardial infarction	0	0.5	1.0
Coronary artery disease	0	1.0	0
Ventricular extrasystoles	0	0	1.0
Ear & labyrinth	**0**	**1.0**	**2.5**
Vertigo	0	0.5	1.0
Endocrine	**0**	**1.0**	**0**
Eye	**4.1**	**2.0**	**3.5**
Conjunctivitis	1.0	0	1.0
Gastrointestinal	**13.4**	**16.7**	**11.1**
Nausea	2.1	4.5	3.0
Diarrhea	3.1	3.0	0.5
Constipation	1.0	1.5	1.5
Dyspepsia	0	2.0	1.5
Vomiting	0	2.0	1.5
Flatulence	1.0	0.5	1.5
Toothache	1.0	1.0	1.0
Abdominal pain	0	1.5	0.5
Abdominal pain upper	0	1.0	0.5
Abdominal pain lower	0	0	1.0
Peptic ulcer	0	1.0	0
General disorders	**13.4**	**11.1**	**11.6**
Edema peripheral	7.2	6.1	5.5
Fatigue	3.1	2.0	2.0
Pyrexia	1.0	1.0	0.5
Pitting edema	0	1.0	0.5
Malaise	0	1.0	0

Hepatobiliary	**1.0**	**1.5**	**0**
Cholelithiasis	0	1.0	0
Immune system	**0**	**0.5**	**2.0**
Infections & infestations	**37.1**	**34.8**	**33.7**
Nasopharyngitis	6.2	4.0	7.0
Urinary tract infection	1.0	4.5	2.0
Upper respiratory infection	5.2	5.6	5.0
Bronchitis	5.2	2.0	1.5
Sinusitis	6.2	2.5	2.0
Cellulitis	0	0.5	3.0
Viral infection	2.1	1.5	1.0
Laryngitis	1.0	1.5	1.0
Rhinitis	0	2.5	0.5
Tinea pedis	2.1	1.0	1.0
Fungal skin infections	2.1	1.0	0.5
Pneumonia	1.0	0.5	1.5
Ear infection	1.0	0.5	1.0
Gastroenteritis	0	0.5	1.0
Lower respiratory tract infection	0	1.0	0.5
Paronchia	0	0.5	1.0
Faruncle	0	1.0	0
Impetigo	0	0	1.0
Respiratory tract infection viral	0	1.0	0
Injury, poisoning, & procedural comp	**14.4**	**6.6**	**12.6**
Contusion	1.0	2.0	0.5
Fall	0	1.5	1.0
Skin laceration	2.1	0	1.5
Arthropod bite	1.0	0.5	1.0
Joint sprain	1.0	0	1.0
Road traffic accident	0	0.5	1.0
Concussion	0	1.0	0
Epicondylitis	0	0	1.0
Scratch	0	0	1.0
Wrist fracture	0	0	1.0
Investigations	**6.2**	**6.1**	**6.0**
Weight increased	1.0	2.0	1.0
Blood creatinine increased	0	0	1.5
Hepatic enzyme increased	0	0.5	1.0
Metabolism & nutrition	**5.2**	**3.0**	**6.0**
Dyslipidemia	0	0.5	1.5
Hypertriglyceridemia	0	0.5	1.5
Gout	1.0	0	1.0
Hyperlipidemia	1.0	1.0	0
Musculoskeletal & connective tissue	**18.6**	**14.1**	**13.6**
Arthralgia	2.1	1.5	4.0
Back pain	3.1	2.5	2.5
Pain in extremity	1.0	1.5	2.5
Muscular pain	2.1	1.0	0.5
Tendonitis	0	2.0	1.5
Muscle spasms	4.1	1.0	1.0
Myalgia	2.1	3.0	1.5

Neoplasms benign, malig, & unspec	**4.1**	**1.5**	**0.5**
Nervous system	**10.3**	**15.2**	**16.6**
Headache	4.1	4.0	5.0
Dizziness	2.1	3.5	1.5
Hypoaesthesia	1.0	1.5	1.0
Neuropathy	1.0	1.0	0.5
Tremor	1.0	0.5	1.0
Carpal tunnel syndrome	0	1.0	0.5
Paraesthesia	0	0.5	1.0
Sinus headache	0	1.0	0.5
Tension headache	0	0.5	1.0
Sciatica	0	1.0	0
Psychiatric	**2.1**	**3.0**	**2.5**
Insomnia	0	1.5	1.0
Anxiety	1.0	1.0	0.5
Depression	0	0.5	1.0
Renal & urinary	**2.1**	**2.0**	**2.5**
Hematuria	0	0	1.5
Nephrolithiasis	0	1.0	0.5
Reproductive	**2.1**	**0.5**	**0.5**
Respiratory, thoracic, & mediastinal	**5.2**	**8.1**	**9.5**
Cough	1.0	1.5	2.0
Epistaxis	1.0	2.0	1.5
Pharyngolaryngeal pain	1.0	0.5	1.0
Rhinitis allergic	1.0	0.5	1.0
Wheezing	0	1.5	0.5
Dyspnea	0	0	1.5
Sleep apnea syndrome	0	1.0	0.5
Skin & subcutaneous tissue	**15.5**	**11.6**	**12.1**
Pruritis	1.0	1.0	2.5
Dry skin	3.1	1.0	0.5
Dermatitis contact	1.0	1.0	1.0
Rash	1.0	1.0	1.0
Skin lesion	2.1	1.0	0.5
Dermatitis	0	1.5	0.5
Blister	0	0.5	1.0
Hyperkeratosis	0	1.5	0
Ingrown nail	0	0	1.5
Skin exfoliation	0	0	1.0
Surgical & medical procedures	**1.0**	**1.0**	**0**
Vascular	**2.1**	**4.0**	**4.5**
Hypertension	2.1	3.0	4.0

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 predominately discussed in the safety sections above.

NDA 22-426. Safety laboratory evaluations in pivotal phase 3 studies		
Hematology	**Biochemistry**	**Urine measurements**
White blood cell count	Albumin	*Qualitative:*
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	*Quantitative:*
	Potassium	Albumin/creatinine ratio
	Sodium	
	Total bilirubin	
	Total protein	
	Uric acid	
	γ-Glutamyl-transferase	
	Lipid panel	

NDA 22-426. Frequency of safety laboratory evaluations in pivotal phase 3 studies	
Hematology and biochemistry	Screening & weeks -1, 0, 1, 2, 4, 8, 12, 16, 20, & 26[a]
Serum TSH	Screening
Serum pregnancy test	Screening & weeks 0, 4, 8, 12, 16, 20, and 26
Urinanalysis	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, 10x ULN OR >3x ULN & total bilirubin > 2 mg/dl
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 pivotal phase 3 studies, OPI-002 and OPI-001, which evaluated the safety and efficacy of the to-be-marketed dose combinations of alogliptin and pioglitazone. The laboratory results of supportive study TZD-009 were reviewed in my clinical review of alogliptin NDA 22-271.

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 3 studies. Pioglitazone has been associated with dose-related decreases in hemoglobin and hematocrit, which are likely related to increased plasma volume. As expected, small decreases in the pioglitazone and A+P groups' hematocrit and hemoglobin were seen (hematocrit: -1.61% and -1.61% vs. -0.87%; hemoglobin: -0.30 and -0.41 g/dl vs. -0.08 g/dl). Lymphocytes and platelets decreased slightly (lymphocytes: A+P -1.1%, Pio 0.5%, Alo -1.7 %; platelets: A+P -6.2, Pio -5.7, Alo -5.0). Monocytes increased slightly (A+P 1.1%, Pio 0.8%, Alo 0.5%). Overall, the mean changes from baseline to endpoint in hematology results were minor and not clinically meaningful.

NDA 22-426. Change from baseline to endpoint according to hematology parameter and treatment group in pivotal, controlled phase 3 studies. Note: Plus-minus values are mean±SD; values with parentheses are median (min, max). Source: Integrated Analysis of Safety Table 8.5.1.1 (p. 2784)

Hematology laboratory	Alogliptin (n=421)	Pioglitazone (n=550)	A+P (n=1107)
Basophils (%)	0±0.58 0 (-1,1)	0±0.61 0 (-1,2)	0±0.61 0 (-2, 2)
Eosinophils (%)	-0.1±2.52 0 (-19, 9)	0.2±2.90 0 (-18, 15)	0.2±2.61 0 (-16, 25)
Hematocrit (%)	-0.87±2.486 -0.9 (-9.6, 8.2)	-1.61±2.642 -1.3 (-18.5, 8.0)	-1.61±2.850 -1.5 (-16.6, 8.1)
Hemoglobin (g/dl)	-0.08±0.768 -0.10 (-2.2, 3.0)	-0.36±0.812 -0.30 (-5.6, 2.8)	-0.41±0.863 -0.30 (-5.8, 2.9)
Lymphocytes (%)	-1.7±9.45 -2.0 (-29, 51)	0.5±9.26 0 (-45, 42)	-1.1±10.01 -2.0 (-44, 43)
Monocytes	0.5±4.99 0 (-50, 56)	0.8±4.64 0 (-33, 50)	1.1±5.16 1.0 (-42, 57)
Neutrophils (%)	1.3±11.67 1.0 (-62, 54)	-1.4±12.10 -1.0 (-64, 49)	-0.2±13.08 1.0 (-62, 54)
Platelet count ($10^3/mm^3$)	-5.0±37.34 -4.0 (-187, 137)	-5.7±36.29 -4.0 (-155, 164)	-6.2±37.50 -6.0 (-206, 242)
WBCs ($10^3/mm^3$)	0.15±1.458 0.20 (-4.4, 8.7)	-0.40±1.459 -0.40 (-9.1, 5.4)	-0.23±1.565 -0.20 (-6.6, 8.8)

In the pivotal, controlled phase 3 studies, subjects were required to have ALT <2.5x ULN (OPI-002) or ≤2.5x ULN (OPI-001), and creatinine < 2.0 mg/dl (males and females in OPI-002) or < 1.5 mg/dl (males in OPI-001) or < 1.4 mg/dl (females in OPI-001). The mean change from baseline to endpoint in serum BUN and creatinine increased slightly more in the A+P group when compared to the alogliptin and pioglitazone groups (BUN: 1.4 vs. 0.7 and 0.2 mg/dl; creatinine: 0.04 vs. 0.02 and 0.02 mg/dl, respectively). However, AST and ALT improved (i.e. decreased) on average in the A+P group (-2.1 and -4.1 mU/ml). The mean change from baseline to endpoint in sodium and LDH was greatest in the A+P group, although values were similar to comparators. Alkaline phosphatase decreased the most in the A+P group (-7.0 mU/ml).

NDA 22-426. Change from baseline to endpoint according to chemistry parameter and treatment group in pivotal,

controlled phase 3 studies. Note: Plus-minus values are mean±SD; values with parentheses are median (min, max). Source: Integrated Analysis of Safety Table 8.5.1.2 (p. 2843)			
Chemistry laboratory	**Alogliptin (n=421)**	**Pioglitazone (n=550)**	**A+P (n=1107)**
Alkaline phosphatase (mU/ml)	-2.2±11.71 -2.0 (-44, 80)	-4.7±17.37 -5.0 (-64, 300)	-7.0±13.06 -7.0 (-59, 94)
Bicarbonate	0.7±3.02 1.0 (-8, 11)	1.3±2.86 1.0 (-10, 11)	1.2±3.00 1.0 (-11, 15)
BUN (mg/dl)	0.7±3.46 1.0 (-10, 18)	1.2±3.64 1.0 (-13, 14)	1.4±4.19 1.0 (-16, 27)
Creatinine (mg/dl)	0.02±0.108 0 (-0.5, 0.5)	0.02±0.97 0 (-0.3, 0.3)	0.04±0.122 0 (-0.9, 1.4)
Potassium	-0.04±0.453 0 (-1.5, 2.1)	0.01±0.44 0 (-1.5, 1.8)	0.01±0.469 0 (-2.1, 2.1)
SGOT (AST; mU/ml)	1.9±65.87 -1.0 (-57, 1320)	-1.3±7.14 -1.0 (-34, 80)	-2.1±7.06 -1.0 (-42, 54)
SGPT (ALT; mU/ml)	3.2±87.00 -1.0 (-48, 1745)	-2.7±10.61 -2.0 (-57, 85)	-4.1±9.53 -3.0 (-62, 71)
Sodium	0.4±2.63 1.0 (-10, 11)	0.4±2.90 1.0 (-27, 8)	0.8±2.64 1.0 (-12, 12)
Total bilirubin (mg/dl)	-0.026±0.1633 -0.030 (-0.58, 0.61)	-0.30±0.1955 -0.035 (-1.04, 1.92)	-0.056±0.1798 -0.050 (-1.17, 0.80)
Uric acid	0.12±0.977 0 (-3.1, 4.7)	-0.16±0.893 -0.20 (-3.7, 4.5)	-0.05±0.988 0 (-6.6, 5.9)
LDH (mU/ml)	1.8±20.72 2.0 (-68, 255)	5.9±16.39 5.5 (-55, 96)	6.7±15.99 7.0 (-82, 106)

Subjects with a urine albumin/creatinine ratio of >1000 mcg/mg (>113 mg/mol) were excluded from the pivotal, controlled phase 3 studies. The mean changes from baseline for pH and specific gravity were small. For the albumin/creatinine ratio, baseline means were elevated in all groups (71.8-79.5 µg/mg; normal 0-20 µg/mg). However, baseline medians were only slightly elevated (23-26 µg/mg). The mean change in albumin/creatinine ratios from baseline to endpoint increased in the A+P and pioglitazone groups when compared to alogliptin (24.3 and 12.0 vs. -2.6 µg/mg), although median change was more similar (-6 and -6 vs. -4) Endpoint albumin/creatinine ratio means were significantly higher than the normal range, but the medians were closer to normal for all groups (20-22 µg/mg). Sample sizes for this measurement were small, due to the number of subjects who had detectable levels.

NDA 22-426. Change from baseline to endpoint according to urinalysis parameter and treatment group in pivotal controlled phase 3 studies. Note: Plus-minus values are mean±SD; values with parentheses are median (min, max). Source: Integrated Analysis of Safety Table 8.5.1.3 (p. 2908)			
Urinalysis laboratory	**Alogliptin (n=421)**	**Pioglitazone (n=550)**	**A+P (n=1107)**
Albumin/cr ratio (mcg/mg)	-2.6±132.36 -4.0 (-702, 933)	12.0±179.33 -6.0 (-542, 1506)	24.3±545.86 -6.0 (-927, 9608)
pH	0.10±0.511 0 (-2.0, 1.5)	0.09±0.608 0 (-3.0, 2.5)	0.15±0.610 0 (-3.0, 4.0)
Specific gravity	-0.0010±0.00741 -0.0010 (-0.033, 0.029)	-0.0019±0.0080 -0.0020 (-0.045, 0.026)	-0.0020±0.00751 -0.0020 (-0.038, 0.029)

7.4.2.3.2 Analyses focused on outliers or shifts from normal to abnormal

The incidence of markedly abnormal hematology results was highest in the A+P group when compared to the alogliptin and pioglitazone groups, except for low platelet count and high white blood cell count. The incidence of A+P subjects with low hemoglobin, hematocrit, and red blood cells was 1.4, 2.3, and 2.4%, respectively.

NDA 22-426. Number and percentage of subjects with markedly abnormal hematology results in pivotal, controlled phase 3 studies. Source: Integrated Analysis of Safety Table 3.c (p. 58)

Variable, n (%)	**Alogliptin**	**Pioglitazone**	**A+P**
Hemoglobin			
Baseline low abnl	N/A	N/A	N/A
Postbaseline low abnl	2 (0.5)	5 (0.9)	15 (1.4)
Hematocrit			
Baseline low abnl	N/A	N/A	N/A
Postbaseline low abnl	2 (0.5)	8 (1.5)	25 (2.3)
RBCs			
Baseline low abnl	N/A	N/A	N/A
Postbaseline low abnl	3 (0.7)	9 (1.7)	26 (2.4)
WBCs			
Baseline high abnl	0	0	0
Baseline low abnl	0	0	1 (0.1)
Postbaseline high abnl	1 (0.2)	0	0
Postbaseline low abnl	0	0	1 (0.1)
Platelet count			
Baseline high abnl	0/416	0/548	0/1104
Baseline low abnl	0/416	0/548	0/1104
Postbaseline high abnl	0	0	3 (0.3)
Postbaseline low abnl	0	1 (0.2)	0

Few shifts among low, normal, and high categories from baseline to endpoint were observed for most variables across groupings. Exceptions included hemoglobin, hematocrit, lymphocytes, and monocytes, which are described below. As explained above, the hemoglobin and hematocrit shifts were expected in the groups taking pioglitazone. The shift towards an increased lymphocyte percentage is not consistent with the mean change from baseline to endpoint which was negative.

NDA 22-426. Summary of shifts of selected hematology variables. Source: Integrated Analysis of Safety Table 3.b

	Alogliptin	**Pioglitazone**	**A+P**
Hemoglobin (nl to low)	5 (1.3) / 388	13 (2.6) / 501	53 (5.1) / 1030
Hematocrit (nl to low)	6 (1.5) / 388	20 (4.0) / 498	53 (5.2) / 1029
Lymphocyte (nl to high)	16 (4.2) / 381	32 (6.4) / 501	65 (6.4) / 1017
Monocyte (nl to high)	9 (2.3) / 400	25 (4.8) / 520	65 (6.1) / 1064

The incidence of markedly abnormal chemistry results in the pivotal phase 3 studies in the A+P group were similar or less than comparators, except for serum creatinine (A+P 1.6% vs. alogliptin 1.2% and pioglitazone 0.7%). In total, 26 subjects had creatinine levels >1.5x baseline during treatment. Only 3 of the 26 subjects, all in the A+P group, had creatinine levels that also exceeded the ULN. Uric acid also increased in the A+P and alogliptin groups (1.8% and 2.7%

vs. 0.6%), although the incidence of gout AEs was similar across study groups in the pivotal phase 3 trials (0-0.2%).

NDA 22-426. Number and percentage of subjects with markedly abnormal chemistry results in pivotal, controlled phase 3 studies. Source: Integrated Analysis of Safety Tables 3.h and 3.j (p. 64 and 66)

Variable, n (%)	Alogliptin	Pioglitazone	A+P
SGPT (ALT) > 3x ULN & Total bili > 2 mg/dl			
Baseline high abnl	0	0	0
Postbaseline high abnl	0	2 (0.4)	0
SGPT (ALT) > 3x ULN			
Baseline high abnl	2 (0.5)	1 (0.2)	2 (0.2)
Postbaseline high abnl	3 (0.7)	11 (2.0)	10 (0.9)
SGPT (ALT) > 5x ULN			
Baseline high abnl	0	0	0
Postbaseline high abnl	2 (0.5)	2 (0.4)	1 (0.1)
SGPT (ALT) > 10x ULN			
Baseline high abnl	0	0	0
Postbaseline high abnl	2 (0.5)	0	0
SGOT (AST) > 3x ULN			
Baseline high abnl	1 (0.2)	1 (0.2)	2 (0.2)
Postbaseline high abnl	3 (0.7)	8 (1.5)	8 (0.7)
SGOT (AST) > 5x ULN			
Baseline high abnl	0	0	0
Postbaseline high abnl	3 (0.7)	2 (0.4)	2 (0.2)
SGOT (AST) > 10x ULN			
Baseline high abnl	0	0	0
Postbaseline high abnl	1 (0.2)	1 (0.2)	1 (0.1)
Total bilirubin			
Baseline high abnl	0	2 (0.4)	2 (0.2)
Postbaseline high abnl	0	7 (1.3)	3 (0.3)
Alkaline phosphatase			
Baseline high abnl	0	0	1 (0.1)
Postbaseline high abnl	0	2 (0.4)	3 (0.3)
Gamma GT			
Baseline high abnl	12 (2.9)	20 (3.6)	33 (3.0)
Postbaseline high abnl	26 (6.3)	28 (5.2)	42 (3.8)
BUN			
Baseline high abnl	0	0	0
Postbaseline high abnl	0	0	1 (0.1)
Creatinine			
Baseline high abnl	N/A	N/A	N/A
Postbaseline high abnl	5 (1.2)	4 (0.7)	17 (1.6)
Uric acid			
Baseline high abnl	4 (1.0)	5 (0.9)	14 (1.3)
Postbaseline high abnl	11 (2.7)	3 (0.6)	20 (1.8)
Potassium			
Baseline high abnl	2 (0.5)/415	0/546	7 (0.6)/1091
Baseline low abnl	0/415	0/546	1 (0.1)/1091
Postbaseline high abnl	14 (3.4)	24 (4.5)/536	40 (3.7)/1091

Postbaseline low abnl	0	0/536	0/1091
Sodium			
Baseline high abnl	0	1 (0.2)	1 (0.1)
Baseline low abnl	0	0	1 (0.1)
Postbaseline high abnl	4 (1.0)	2 (0.4)	11 (1.0)
Postbaseline low abnl	2 (0.5)	2 (0.4)	7 (0.6)

When shifts in chemistry values were reviewed, more A+P subjects experienced normalization of AST, ALT, and alkaline phosphatase (A+P: 67.2, 69.3, and 62.0%; alogliptin: 45.7, 47.3, 36.9%, pioglitazone: 56.8, 65.3, 49.3%, respectively). However, more A+P subjects also experienced increases in BUN and magnesium (A+P: 9.3 and 7.2%; alogliptin: 6.4 and 6.5%; pioglitazone: 8.9 and 5.9%, respectively). A total of 15.7% of A+P subjects experienced increased LDH, although this was less than the percentage of pioglitazone subjects (16.5%).

NDA 22-426. Summary of shifts of selected chemistry variables. Source: Integrated Analysis of Safety Table 3 f

	Alogliptin	**Pioglitazone**	**A+P**
AST (high to nl)	32 (45.7) / 70	46 (56.8) / 81	125 (67.2) / 186
ALT (high to nl)	43 (47.3) / 91	77 (65.3) / 118	165 (69.3) / 238
Alkaline phosphatase (high to nl)	41 (36.9) / 111	66 (49.3) / 134	158 (62.0) / 255
BUN (nl to high)	24 (6.4) / 375	44 (8.9) / 494	91 (9.3) / 983
Magnesium (nl to high)	25 (6.5) / 385	30 (5.9) / 505	75 (7.2) / 1038
LDH (nl to high)	31 (8.6) / 362	79 (16.5) / 479	155 (15.7) / 988

To assess for potential effects on renal function, the sponsor calculated creatinine clearance by the Cockcroft-Gault (CG) and MDRD formulas, as shown below. The change from baseline was low in all groups and varied on the formula used (CG: -0.84 to -2.98 ml/min; MDRD: -1.53 to -3.91 ml/min).

NDA 22-426. Change from baseline to endpoint in creatinine clearance (ml/min). Source: Integrated Analysis of Safety Table 3.g

	Alogliptin (n=407)	**Pioglitazone (n=534)**	**A+P (n=1091)**
Mean (SD)			
CG	-2.98 (14.20)	-0.84 (13.80)	-2.58 (15.71)
MDRD	-1.53 (11.37)	-2.02 (11.11)	-3.91 (12.26)
Median (min, max)			
CG	-2.11 (-87.7, 39.3)	0 (-57.7, 53.9)	-1.84 (-103.8, 77.4)
MDRD	0 (-55.1, 45.2)	0 (-70.9, 38.8)	0 (-96.5, 67.0)

Slightly more subjects in the A+P group experienced a shift from normal to mild or moderate renal impairment when compared to the alogliptin and pioglitazone groups using both CG and MDRD formulas. Approximately 7.1-7.5% of A+P mild renal impairment subjects shifted to moderate renal impairment using the MDRD and CG formulas. This shift was less than that seen with pioglitazone when the CG formula was used but nearly 2x the shift seen with the pioglitazone group when the MDRD formula was used. No subjects had a postbaseline value in the severe renal impairment category.

NDA 22-426. Summary of abnormal creatinine clearance results. Source: Sponsor, Integrated Analysis of Safety Table 3.i

Baseline Classification Postbaseline Abnormality Criteria	Number of Subjects (%) With ≥1 Abnormality During Treatment ALO	PIO	ALO+PIO
No Renal Impairment (Cockcroft-Gault)	n=335	n=437	n=884
≥50 and ≤80 mL/min (mild)	38 (11.3)	57 (13.0)	152 (17.2)
≥30 and <50 mL/min (moderate)	0	0	2 (0.2)
<30 mL/min (severe)	0	0	0
No Renal Impairment (MDRD)	n=196	n=267	n=559
≥50 and ≤80 mL/min (mild)	107 (54.6)	132 (49.4)	314 (56.2)
≥30 and <50 mL/min (moderate)	1 (0.5)	0	5 (0.9)
<30 mL/min (severe)	0	0	0
Mild Renal Impairment (Cockcroft-Gault)	n=69	n=94	n=199
≥30 and <50 mL/min (moderate)	5 (7.2)	9 (9.6)	15 (7.5)
<30 mL/min (severe)	0	0	0
Mild Renal Impairment (MDRD)	n=205	n=261	n=518
≥30 and <50 mL/min (moderate)	10 (4.9)	10 (3.8)	37 (7.1)
<30 mL/min (severe)	0	0	0

The percentage of subjects with elevated albumin/creatinine ratios was similar between treatment groups. Shifts in the albumin/creatinine ratio from normal at baseline to high at endpoint occurred in a similar proportion of subjects in the 3 treatment groups (37/148 [25.0%] A+P, 15/77 [19.5%] pioglitazone, 14/59 [23.7%] alogliptin).

NDA 22-426. Summary of abnormal urine albumin/creatinine ratio results

	Alogliptin (n=171)	Pioglitazone (n=224)	A+P (n=429)
>1.5x baseline	24.0	19.6	21.0
>2x baseline	13.5	13.8	13.5
>3x baseline	6.4	6.3	8.2

7.4.2.3.3 Marked outliers and dropouts for laboratory abnormalities

The incidence of hematology results reported as AEs (≥ 2 subjects in any group) is shown below. Anemia was most common in the A+P group (2.3%). There were no anemia SAEs or AEs leading to discontinuation. Monocytosis, leucopenia, and lymphocytosis also occurred more often in the A+P group (0.5, 0.5, and 0.4%, respectively). Overall, however, the incidence of hematology results reported as AEs was low. No hematology-related SAEs or AEs leading to discontinuation occurred.

NDA 22-426. Percent incidence of hematology results reported as AEs (≥ 2 subjects in any group). Source: Integrated Analysis of Safety Table 3.d

	Alogliptin (n=421)	Pioglitazone (n=550)	A+P (n=1107)
Anemia	0.2	1.5	2.3
Neutropenia	1.7	2.0	1.5
Eosinophilia	0.7	1.6	1.4
Monocytosis	0	0.2	0.5
Leukopenia	0	0.5	0.5
Lymphocytosis	0	0.2	0.4
Neutrophil count decreased	0.2	0.5	0.3
Iron deficiency anemia	0.2	0	0.2
Thrombocythemia	0	0	0.2
Hemoglobin decreased	0	0.2	0.2

Plasminogen activator inhibitor increased	0.5	0	0.2
Anemia megaloblastic	0	0	0.2
Eosinophil count increased	0	0.4	0.1

No trends in chemistry-related AEs were seen. With the exception of lipid-related events, the incidence of events in the A+P group was low (0-0.5%). There was 1 chemistry-related SAE and 4 subjects with AEs leading to discontinuation. The SAE of hypertriglyceridemia (002/686/2507) was likely due to disease progression and not study drug. The AEs leading to discontinuation were as follows:

- 002/313-2509 (A+P): Blood urea increased
- 002/055-2516 (A+P): Liver function test abnormal
- 002/057-2503 (pioglitazone): Liver function test abnormal
- 001/412-3101 (pioglitazone): Hepatic enzyme increased

Two pioglitazone subjects had ALT >3x ULN with total bilirubin >2.0 mg/dl. Four subjects (1 A+P, 2 pioglitazone, 2 alogliptin) had ALT or AST > 10x ULN. The narratives for the A+P and alogliptin subjects are as follows:

- 001/889-3002 (A+P): The subject had normal baseline ALT, AST, and bilirubin values. Day 85 values were ALT 43 mU/ml, AST 260 mU/ml (>10x ULN), and bilirubin 1.32 mg/dl. All three values were normal at visits before (day 58) and after (day 91). The investigator reported it as laboratory error. The subject had no AEs and completed the study with normal ALT, AST, and bilirubin values.
- 002/831-2508 (alogliptin): The subject had baseline ALT and AST values within normal limits and a medical history of hypoacusis and umbilical hernia. On day 64, the subject had an AE of hepatitis B, diagnosed by serology, which resulted in study discontinuation. A sexual mode of transmission of hepatitis B was suspected. On day 86, approximately 3 weeks after discontinuation, the subject had ALT and AST values >10x ULN (689 and 515 mU/ml, respectively); bilirubin was normal. Approximately 1 month after discontinuation, a follow up test showed improved liver function with ALT and AST values of 23 and 31 mU/ml, respectively.
- 001/395-3054 (alogliptin): The subject had ALT and AST elevations during the study, but bilirubin was within normal limits at all visits. At baseline, ALT and AST were slightly elevated (26 and 26 mU/ml, respectively). On day 84, ALT and AST were 15 mU/ml. On day 112, ALT rose to 257 mU/ml (>10x ULN) and AST rose to 118 mU/ml (>5x ULN). This was reported as an AE of increased hepatic enzymes, considered not related to study drug, and resolved on day 140.

The sponsor evaluated subjects with ≥75 ml/min creatinine clearance reductions from baseline. Seven subjects (all from OPI-001) were identified using either the CG or MDRD formula (3 alogliptin, 2 pioglitazone, and 2 A+P). Of these 7 subjects, 5 were males and 2 were females; the mean age and baseline serum creatinine were 55.1 years and 0.6 mg/dl, respectively. Four of the 7 subjects had serum creatinine below the LLN (< 0.7 mg/dl) at baseline. None had an SAE.

A total of 26 subjects had creatinine levels >1.5x baseline during treatment (17 [0.6%] A+P, 4 [0.7%] pioglitazone, and 5 [1.2%] alogliptin). Only 3 of the 26 subjects, all in the A+P group, had creatinine that was also greater than the upper limit of normal:

- 001/735-3003 (A+P): Baseline creatinine and BUN were normal (1.1 and 18 mg/dl, respectively). On day 19, values rose to 1.9 and 39 mg/dl where they remained throughout the study and then decreased to normal limits when the subject completed the study on day 181 (1.1 and 20 mg/dl, respectively).
- 001/961-3009 (A+P): Baseline creatinine was normal (0.7 mg/dl) but it rose to 1.5 mg/dl on day 126, decreased to 1.0 mg/dl on day 140, and rose to 1.5 mg/dl on day 179. All BUN values were normal. The subject completed the study on day 189.
- 002/313-2509 (A+P): A 75 year old female, with bronchial hyperreactivity, cardiomegaly, hyperlipidemia, hypertension, and peripheral vascular disease, was enrolled with elevated baseline creatinine and BUN values (1.9 and 57 mg/dl, respectively). Levels remained elevated throughout the study. On days 57, 85, and 113, creatinine/BUN values were as follows: 2.1/49, 2.2/65, and 3.3/72 mg/dl, respectively. The day 1 BUN and day 57 creatinine values were reported as AEs, as was edema peripheral on day 103. The subject was discontinued on day 113 due to the AE of BUN increased on day 1. This subject was the only subject classified in the severe renal impairment category at study entry.
    - **COMMENT: The reason for study discontinuation on day 113 (i.e. AE of BUN increased on day 1) was miscoded. Creatinine at the time of discontinuation on day 113 was 3.3 mg/dl; this was more likely the reason for discontinuation. Furthermore, as this subject had severe renal impairment, 6.25 mg alogliptin once daily would have been a more appropriate dose than the 25 mg alogliptin that she received.**

Few urinalysis results were reported as AEs. There was 1 A+P subject (002/487-2512) who experienced an SAE of hematuria which led to discontinuation but was judged not related to study drug.

Hypoglycemic events were classified as severe (blood glucose <60 mg/dl requiring assistance), mild/moderate with or without symptoms (blood glucose <50 mg/dl), and symptomatic mild/moderate (blood glucose < 60 mg/dl with symptoms). The pioglitazone group had the greatest incidence of severe hypoglycemia (pioglitazone 2.0%, A+P 0.1%, and alogliptin 0%). The greatest incidence of blood glucose <50 mg/dl with or without symptoms occurred in the A+P group (0.8% vs. pioglitazone 0.4% and alogliptin 0.2%). The frequency of symptomatic blood glucose <60 mg/dl was similar between groups but greatest in the A+P group (0.7-1.2%). (Please refer to section 7.3.2 Nonfatal Serious Adverse Events for hypoglycemia narratives.)

7.4.2.4 Special assessments: Renal toxicity and hepatotoxicity

Very large alogliptin 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 (≥ 200x 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 pioglitazone does not require adjustment for renal impairment. 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 the pivotal phase 3 studies, the mean change from baseline to endpoint in serum BUN and creatinine increased slightly more in the A+P group when compared to the alogliptin and pioglitazone groups (BUN: 1.4 vs. 0.7 and 0.2 mg/dl; creatinine: 0.04 vs. 0.02 and 0.02 mg/dl, respectively). The incidence of markedly abnormal chemistry results in the pivotal phase 3 studies in the A+P group were similar or less than comparators, except for serum creatinine (A+P 1.6% vs. alogliptin 1.2% and pioglitazone 0.7%). Of the 26 subjects with creatinine levels >1.5x baseline during treatment, only 3 had creatinine levels that also exceeded the ULN; all were in the A+P group, Uric acid also increased in the A+P and alogliptin groups (1.8% and 2.7% vs. 0.6%), although the incidence of gout AEs was similar across study groups in the pivotal phase trials (0-0.2%).

Sample sizes for the albumin/creatinine ratio were small, due to the number of subject who had detectable values. The mean change in albumin/creatinine ratios from baseline to endpoint increased in the A+P and pioglitazone groups when compared to alogliptin (24.3 and 12.0 vs. -2.6 µg/mg), although median change was more similar (-6 and -6 vs. -4). Endpoint albumin/creatinine ratio means were significantly higher than the normal range, but the medians were closer to normal for all groups (20-22 µg/mg). Shifts in the albumin/creatinine ratio from normal at baseline to high at endpoint occurred in a similar proportion of subjects in the 3 treatment groups (37/148 [25.0%] A+P, 15/77 [19.5%] pioglitazone, 14/59 [23.7%] alogliptin).

To assess for potential effects on renal function, the sponsor calculated creatinine clearance by the Cockcroft-Gault (CG) and MDRD formulas. The change from baseline was low in all groups and varied on the formula used (CG: -0.84 to -2.98 ml/min; MDRD: -1.53 to -3.91 ml/min).

Slightly more subjects in the A+P group experienced a shift from normal to mild or moderate renal impairment when compared to the alogliptin and pioglitazone groups using both CG and MDRD formulas. Approximately 7.1-7.5% of A+P mild renal impairment subjects shifted to moderate renal impairment using the MDRD and CG formulas. This shift was less than that seen with pioglitazone when the CG formula was used but nearly 2x the shift seen with the

pioglitazone group when the MDRD formula was used. No subjects had a postbaseline value in the severe renal impairment category.

Use of pioglitazone should be avoided in cases of active liver disease or ALT >2.5 ULN. Although marketed sitagliptin is not associated with hepatoxicity, the nonmarketed DPP-4 inhibitor vildagliptin may be. In the pivotal phase 3 studies, AST and ALT improved (i.e. decreased) on average in the A+P group (-2.1 and -4.1 mU/ml). When shifts in chemistry values were reviewed, more A+P subjects experienced normalization of AST, ALT, and alkaline phosphatase (A+P: 67.2, 69.3, and 62.0%; alogliptin: 45.7, 47.3, 36.9%, pioglitazone: 56.8, 65.3, 49.3%, respectively).

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 22-426. Criteria for abnormal vital signs

Vital sign	**Low abnormal value**	**High abnormal value**
Heart rate	<50 bpm & CFB decrease ≥15 bpm	>120 bpm & CF B increase ≥15 bpm
Systolic blood pressure	<90 mmHg & CFB decrease ≥20 mmHg	>160 mmHg & CFB increase ≥20 mmHg
Diastolic blood pressure	<50 mmHg & CFB decrease ≥15 mmHg	>95 mmHg & CFB increase ≥15 mmHg
CFB=Change from baseline		

The changes from baseline to endpoint in blood pressure and heart rate were similar between treatment groups. A+P has neutral effects on blood pressure and heart rate.

NDA 22-426. Change from baseline to endpoint according to vital sign parameter and treatment group in pivotal, controlled phase 3 studies. Note: Plus-minus values are mean±SD; values with parentheses are median (min, max). Source: Integrated Analysis of Safety Table 8.6.1.1 (p. 3156)

	Alogliptin (n=421)	**Pioglitazone (n=550)**	**A+P (n=1107)**
Systolic BP (mmHg)	0.4±13.43 0 (-45, 45)	1.1±13.86 0 (-42, 46)	0.4±13.24 0 (-50, 48)
Diastolic BP (mmHg)	0.2±9.30 0 (-25, 41)	0±9.19 0 (-35, 33)	-0.4±8.63 0 (-40, 30)
Heart rate (bpm)	0.7±9.25 0 (-24, 32)	-0.7±9.27 0 (-28, 32)	-0.2±8.97 0 (-34, 32)

The percentage of subjects with abnormal vital sign measurements postbaseline were similar between the treatment groups, although slightly more A+P and pioglitazone subjects experienced increased systolic and diastolic blood pressure when compared to the alogliptin group (systolic: 3.4 and 4.2 vs. 2.2%; diastolic: 4.5 and 5.5 vs. 3.6%).

NDA 22-426. Number and percentage of subjects with abnormal vital signs in the pivotal, controlled phase 3 study groups. Source: Integrated Analysis of Safety Table 4.b (p.73)

	Alogliptin (n=413)	**Pioglitazone (n=543)**	**A+P (n=1099)**
Systolic BP			

High abnl	9 (2.2)	23 (4.2)	37 (3.4)
Low abnl	3 (0.7)	1 (0.2)	2 (0.2)
Diastolic BP			
High abnl	15 (3.6)	30 (5.5)	49 (4.5)
Low abnl	1 (0.2)	1 (0.2)	1 (0.1)
Heart rate			
High abnl	0	0	0
Low abnl	0	1 (0.2)	0

There were 3 vital sign SAEs; 1 SAE of syncope occurred in each treatment group (subjects: A+P 002/040-2513; pioglitazone 002/012-2524; alogliptin 001/393-3030). Two subjects experienced AEs which led to discontinuation (A+P 001/655-3005 palpitations and alogliptin 001/901-3007 hypertension).

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 pivotal, controlled phase 3 studies. 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 <5 msec for all groups and near zero in the A+P group. Therefore, A+P has minor effects, if any, on ECG parameters using central tendency analysis.

NDA 22-426. Change from baseline to endpoint in ECG parameters in the pivotal, controlled phase 3 study groups. Source: Integrated Analysis of Safety Table 4.e (p. 76)

	Alogliptin (n=421)	Pioglitazone (n=550)	A+P (n=1107)
Ventricular rate (bpm)			
Baseline mean (SD)	71.9 (11.03)	72.4 (10.85)	72.0 (10.85)
Mean CFB (SD)	1.5 (10.13)	0.4 (10.06)	0.1 (9.61)
PR interval (msec)			
Baseline mean (SD)	158.1 (24.999)/419	159.6 (25.14)/549	157.6 (24.69)/1104
Mean CFB (SD)	-1.1 (17.97)	-1.8 (23.54)	0.1 (20.18)
QRS duration (msec)			
Baseline mean (SD)	89.8 (21.15)	89.2 (16.60)	89.5 (18.04)
Mean CFB (SD)	0 (19.10)	0.4 (14.21)	0.2 (15.79)
QT interval (msec)			
Baseline mean (SD)	381.8 (31.16)	382.0 (31.86)	383.5 (33.08)/1106
Mean CFB (SD)	1.2 (31.26)	0.3 (28.88)	-0.1 (28.90)
QTcF interval (msec)			
Baseline mean (SD)	403.50 (26.128)	404.79 (27.870)	405.42 (28.021)/1106
Mean CFB (SD)	4.02 (28.681)	0.89 (28.605)	0.21 (26.731)

CFB = Change from baseline
The QTc interval was calculated using the Fridericia correction ($QTcF = QT/((60/\text{Ventricular Heart Rate})^{1/3})$).

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 pivotal controlled phase 3 studies.

NDA 22-426. 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 22-426. Summary of abnormal ECG measurements (≥2 subjects any group). Source: Sponsor, Integrated Analysis of Safety Table 4 f (p. 77).

	Number of Subjects (%) With ≥1 Abnormal Measurement (a)					
	Baseline			During Treatment		
Variable (Criteria)	**ALO n=421**	**PIO n=550**	**ALO+PIO n=1107**	**ALO n=405**	**PIO n=522**	**ALO+PIO n=1066**
PR Interval low (<120 msec)	18 (4.3) /419	16 (2.9) /549	35 (3.2) /1104	23 (5.7) /403	32 (6.1) /521	59 (5.6) /1061
PR Interval high (>200 msec)	17 (4.1) /419	15 (2.7) /549	36 (3.3) /1104	17 (4.2) /403	18 (3.5) /521	44 (4.1) /1061
QRS Interval low (<40 msec)	0	0	0	0	0	1 (0.1)
QRS Interval high (>120 msec)	16 (3.8)	21 (3.8)	39 (3.5)	18 (4.4)	30 (5.7)	45 (4.2)
QTcF Interval (450 to 480 msec)	10 (2.4)	21 (3.8)	34 (3.1) /1106	25 (6.2)	39 (7.5)	61 (5.7)
QTcF Interval (>480 to 500 msec)	0	2 (0.4)	5 (0.5) /1106	5 (1.2)	5 (1.0)	6 (0.6)
QTcF Interval (>500 msec)	1 (0.2)	3 (0.5)	4 (0.4) /1106	1 (0.2)	4 (0.8)	5 (0.5)
QTcF Interval (30-<60 msec increase from Baseline)	N/A	N/A	N/A	65 (16.0)	63 (12.1)	117 (11.0)
QTcF Interval (≥60 msec increase from Baseline)	N/A	N/A	N/A	14 (3.5)	18 (3.4)	30 (2.8)
QTcF Interval (>500 msec and ≥60 msec increase from Baseline)	N/A	N/A	N/A	0	2 (0.4)	1 (0.1)
Ventricular rate low (<50 bpm and 15 bpm decrease from Baseline)	N/A	N/A	N/A	0	1 (0.2)	1 (0.1)
Ventricular rate high (>120 bpm and 15 bpm increase from Baseline)	N/A	N/A	N/A	2 (0.5)	1 (0.2)	0

There were 3 subjects (2 A+P, 1 alogliptin) who had a QTcF value reported as an AE of ECG QT prolonged. Only 1 of the A+P subjects (001/809-3021) had a QTcF value that met the

predefined abnormality criteria (30 to <60 msec increase from baseline). Three subjects (1 A+P, 2 pioglitazone) had a QTcF value that met the abnormality criterion of >500 msec and ≥60msec increase from baseline, but these abnormalities were not reported as AEs:

- 001/704-3019 (A+P): 68 year old male with a baseline QTcF of 417.4 msec. At week 26, QTcF interval was 547.4 msec and QT interval was 520 msec. The change was not considered clinically significant by the investigator. No cardiac AEs were reported. The subject completed the study.
- 001/621-3005 (pioglitazone): 62 year old female with T2D, dyslipidemia, obesity, and hypertension who had a baseline QTcF of 422.3 msec. At week 26, the QTcF interval was 510.9 msec and the QT interval was 490 msec; these changes were thought to be due to left bundle branch block. Neither change was reported as an AE, although the subject experienced an AEs of left ventricular hypertrophy, cardiac failure chronic, and ischemic cardiomyopathy. Trimetazidine and isosorbide dinitrate were given for the ischemic cardiomyopathy. The subject completed the study.
- 002/067-2510 (pioglitazone): 62 year old male with T2D, hypertension, hyperlipidemia who had a baseline QTcF of 427.4 msec. At weeks 12 and 26, QTcF intervals were 493.5 and 519.3 msec and QT intervals were 436 and 452 msec, respectively. No cardiac AEs were reported. The subject competed the study.

The ECG measurements reported as AEs (≥2 subjects in any group) are shown below. The incidence of AV block first degree, supraventricular extrasystoles, atrial fibrillation, left atrial hypertrophy, and ECG ST segment depression were greatest in the A+P group, although the overall incidence of ECG AEs was low. Three subjects experienced SAEs related to ECG measurements: 002/665-2509 (A+P, MI), 001/296-3007 (A+P, myocardial ischemia), and 001/632-3003 (pioglitazone, MI); the last subject (001/632-3003, pioglitazone) was discontinued due to the AE of MI.

NDA 22-426. ECG measurements reported as AEs (≥2 subjects in any grouping) (Reproduced from the sponsor)

SOC Preferred Term (a)	Number of Subjects (%) ALO N=421	 PIO N=550	 ALO+PIO N=1107
Cardiac disorders			
Atrioventricular block first degree	0	1 (0.2)	4 (0.4)
Bundle branch block left	0	2 (0.4)	4 (0.4)
Myocardial ischemia	1 (0.2)	3 (0.5)	4 (0.4)
Bundle branch block right	0	3 (0.5)	3 (0.3)
Supraventricular extrasystoles	0	0	3 (0.3)
Atrial fibrillation	0	0	2 (0.2)
Left atrial hypertrophy	0	0	2 (0.2)
Myocardial infarction	1 (0.2)	1 (0.2)	2 (0.2)
Ventricular extrasystoles	0	4 (0.7)	1 (0.1)
Investigations			
ECG QT prolonged	1 (0.2)	0	2 (0.2)
ECG ST segment depression	0	0	2 (0.2)
ECG repolarization abnormality	2 (0.5)	0	2 (0.2)

7.4.5 Special Safety Studies

The effect of renal impairment; hepatic impairment; and age, gender, and race were investigated in special safety studies under alogliptin IND 69,707. (Please refer to the clinical pharmacology and clinical review of alogliptin NDA 22-271.)

The safety of A+P in special populations was not investigated in phase 3 studies, although the sponsor analyzed the pivotal phase 3 studies by gender, age, race, BMI, and renal impairment. Please refer to sections 7.5.3 – 7.5.5 for more information.

7.4.6 Immunogenicity

No immunogenicity studies were completed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Pioglitazone is associated with dose-related increases in weight and decreases in hemoglobin and hematocrit. No dose-related trend was seen in pivotal studies OPI-002 and OPI-001 with respect to death or study withdrawal (i.e. voluntary or AE discontinuation).

In study OPI-002, a slight dose-related trend was seen in the incidence of SAEs and AEs (60.1% vs. 65.2% and 0.6% vs. 4.9% in the A12.5+P30 and A25+P30 groups, respectively). The difference in SAE was due to isolated events in the SOCs, except for 2 events in the Gastrointestinal disorders SOC. A >3% difference in AE incidence was observed between the A25+P30 and A12.5+P30 treatment groups in the General disorders, Metabolism and nutrition, Musculoskeletal and connective tissue, and Nervous system SOCs. The most frequently reported AEs (>3%) in each group is shown below.

OPI-002. The most frequently reported AEs in each group (>3%).

	A12.5+P30 (n=163)	**A25+P30 (n=164)**
Headache	8.6	12.2
Hypertension	3.7	3.7
Urinary tract infection	3.7	5.5
Bronchitits	3.7	
Diarrhea	3.1	
Dizziness	3.1	4.3
Back pain		6.1
Arthralgia		4.3
Weight increased		4.3
Upper respiratory tract infection		3.7
Dyslipidemia		3.7

No significant changes were observed among the treatment groups in mean change from baseline for serum chemistry or hematology results. There were sporadic shifts from a result in the normal reference range at baseline to an abnormal result at other study visits, but these shifts were similar across treatment groups. Hyperlipidemia was the only serum chemistry AE that occurred in ≥3% of subjects and showed a differential incidence across treatment groups (3.1% P30, 1.2% A12.5+P30, 3.0% A25+P30, and 0% A25). No significant difference was seen in the incidence of ALT >3x ULN between treatment groups. Slightly more A25+P30 subjects had creatinine levels 1.5x baseline during the study (3 A25+P30 subjects vs. 1 each in other groups).

In study OPI-001, multiple treatment groups were pooled into pioglitazone, A12.5+P, and A25+P groups for analysis. No significant, dose-related difference was seen in the incidence of SAE and AEs. When the incidence of AEs was reviewed by SOC, a slight increase in infection & infestation and musculoskeletal & connective tissue disorder AEs was seen in the A25+P group compared to the A12.5+P group (30.5% vs. 25.1% and 16.4% vs. 13.6%, respectively). Influenza was reported slightly more often in the A25+P group when compared to the A12.5+P group (4.6% vs. 2.3%).

OPI-001. Overview of adverse events. Source: OPI-001 report, Table 12.b

	Pio (n=387)	**A12.5+P (n=390)**	**A25+P (n=390)**
AE leading to discontinuation	2.8	2.1	1.5
Death	0.3	0	0
SAE	3.4	1.8	3.1
AE	61.0	61.0	64.4

No significant changes were observed among the treatment groups in mean change from baseline for serum chemistry or hematology results. There were sporadic shifts from a result in the normal reference range at baseline to an abnormal result at other study visits, but these shifts were similar across treatment groups. Hypertriglyceridemia was reported in a higher percentage of subjects receiving alogliptin alone compared with the other groups (5.5% A12.5, 4.7% A25, 2.3% placebo, 2.3-3.9% pioglitazone alone, 1.5-2.3% A12.5+P, 0.8-3.1% A25+P). Dyslipidemia was reported in a higher percentage of subjects in the A25+P30 or P45 alone groups compared with the other groups (3.1% and 5.4% vs. <2% to 2.3% other groups).

Similar to study OPI-002, no dose-related trend in increased ALT was seen but more A25+P subjects had creatinine 1.5x baseline when compared to A12.5+P.

OPI-001. Markedly abnormal serum chemistry values of interest (%). Source: OPI-002 report, Table 12.l.

	ALT				**AST**			**Creatinine**
	>3x ULN	**>5x ULN**	**>10x ULN**	**>3x ULN & bili >2 mg/dl**	**>3x ULN**	**>5x ULN**	**>10x ULN**	**>1.5x baseline**
Pio	1.9	0.3	0	0.3	1.6	0.5	0.3	0.8
A12.5+P	0.8	0.3	0	0	0.8	0.3	0	1.0
A25+P	1.0	0	0	0	1.0	0.3	0.3	2.4

Anemia was reported in a higher percentage of subjects receiving either A25+P30 or A25+P45 compared with the other groups (5.4% and 3.8% vs. <2% to 2.3% other groups). Pioglitazone may cause decreases in hemoglobin and hematocrit due to increased plasma volume.

7.5.2 Time Dependency for Adverse Events

No significant difference was seen between the alogliptin, pioglitazone, and A+P groups in time to onset of AEs.

NDA 22-426. Adverse event summary by time to onset. Source: Integrated Analysis of Safety, Table 2.f

	Alogliptin	Pioglitazone	A+P
≤1 day	9.3	9.3	8.9
≥1 to <7 days	8.1	7.8	10.2
≥7 to <30 days	25.2	24.2	24.4
≥30 to 165 days (<6 months)	45.2	48.4	49.4
≥166 days (≥6 months)	13.8	15.7	13.0

7.5.3 Drug-Demographic Interactions

The pivotal A+P phase 3 studies were analyzed with respect to gender, age, race, and BMI. I have confined my subgroup analyses of AEs to the following:

- Cardiovascular events: including ischemic heart disease, arrhythmias, and cardiac failure
- Gastrointestinal events: abdominal pain, pancreatitis, nausea/vomiting, constipation, diarrhea
- General disorders: edema, asthenia
- Infections: nasopharyngitis, upper respiratory tract infections, bronchitis
- Investigations: hypoglycemic events, weight increased
- Neurologic: headache, dizziness, paresthesia
- Musculoskeletal: back pain, arthralgia, fracture
- Renal and urinary: neoplasms
- Skin and subcutaneous tissue: angioedema, potential cutaneous drug reaction events

Cardiovascular events and hypoglycemic events are important considerations for any anti-diabetic agent. The other AEs were chosen because they are AEs of interest or common AEs.

Slightly more than half of all subjects were female (51.6-55.2%). Adverse events more commonly occurred in females (63.3-65.4% vs. 54.4-61.9%). Within the male subgroup, AEs occurred more often in the A+P group (61.9% vs. 54.4-56.4%), although this difference was not due to a particular SOC or AE. In the A+P group, the incidences of edema peripheral, urinary tract infection, and headache were ≥2% greater in females than males.

NDA 22-426. AEs of interest (%) by gender (≥3% incidence in any group)

	Males			**Females**		
	Alo (n=193)	**Pio (n=266)**	**A+P (n=496)**	**Alo (n=228)**	**Pio (n=284)**	**A+P (n=611)**
Any AE	54.4	56.4	61.9	65.4	64.4	63.3

Anemia	0	0	1.2	0.4	2.8	3.1
Abdominal pain upper	1.0	0.4	0.8	3.1	0.7	2.6
Diarrhea	2.1	2.6	3.4	1.3	3.9	3.3
Edema peripheral	1.0	1.9	1.0	1.8	4.9	4.1
Nasopharnygitis	3.1	2.6	4.6	4.4	3.2	3.4
Upper resp. tract infection	3.6	1.1	3.8	5.3	2.5	2.5
Urinary tract infection	2.1	1.5	1.2	5.3	8.1	6.2
Weight increased	0.5	3.4	2.6	0.4	1.8	2.3
Arthralgia	0.5	1.5	2.4	2.6	3.5	3.4
Back pain	1.6	3.4	4.4	2.6	2.1	4.4
Headache	1.6	4.5	4.2	9.6	7.7	6.5
Dizziness	2.6	3.0	2.8	1.3	3.5	3.9

The majority of subjects were < 65 years old (84.1-88.4%); this complicates age and treatment group comparison due to samples sizes as low as 49 in the ≥65 year alogliptin group. AEs occurred, on average, slightly more often in the < 65 year old group (60.7-62.6% vs. 44.9-63.1%). Within the ≥65 years group, AEs occurred more often in the A+P group (63.1%). The difference in the incidence of AEs of interest between the 2 age groups was <2%. Headache was the most common AE of interest in the <65 year group (5.7%), whereas back pain was most common in the ≥65 year group (6.3%). However, one AE (not of interest), anemia, occurred noticeably more often in the ≥65 years A+P group (see below).

NDA 22-426. AEs of interest, including anemia, (%) by age (≥3% incidence in any group)						
	<65 years			**≥65 years**		
	Alo (n=372)	**Pio (n=468)**	**A+P (n=931)**	**Alo (n=49)**	**Pio (n=82)**	**A+P (n=176)**
Any AE	62.4	60.7	62.6	44.9	59.8	63.1
Anemia	0.3	1.5	1.7	0	1.2	5.1
Ventricular extrasystoles	0	0.2	0.1	0	3.7	0
Diarrhea	1.6	3.2	3.3	2.0	3.7	3.4
Edema peripheral	1.3	3.0	2.7	2.0	6.1	2.8
Nasopharnygitis	4.0	3.0	4.0	2.0	2.4	4.0
Upper resp. tract infection	4.6	2.1	2.9	4.1	0	4.0
Weight increased	0.5	3.0	2.7	0	0	1.1
Arthralgia	1.9	2.6	2.9	0	2.4	3.4
Back pain	1.9	2.6	4.1	4.1	3.7	6.3
Headache	6.5	7.3	5.7	2.0	0	4.5
Dizziness	1.9	3.2	3.4	2.0	3.7	3.4

The majority of subjects in the pivotal studies were Caucasian (>70%). Asian subjects represented 7.3-10.2% of the treatment group population; Blacks represented 4.2-5.8% of the

studied population. For this reason, different selection criteria were used when presenting the AEs of interest below (i.e. ≥5% incidence and ≥2 subjects in any group). AEs occurred more often in the Asian and Black groups. The percentage incidences of AEs of interest varied between groups, probably in part due to the variation in sample size. Asians were at slightly higher risk for AEs in the blood and lymphatic system disorder SOC.

NDA 22-426. AEs of interest, including the blood and lymphatic system disorders SOC, (%) by race (≥5% incidence and ≥2 subjects in any group)

	Asian			**Black**			**Caucasian**		
	A (n=43)	**P (n=48)**	**A+P (n=81)**	**A (n=19)**	**P (n=32)**	**A+P (n=46)**	**A (n=304)**	**P (n=395)**	**A+P (n=829)**
Any AE	65.1	60.4	66.7	89.5	62.5	78.3	55.3	58.0	58.3
Eosinophilia	7.0	10.4	12.3	0	0	0	0	0.3	0.4
Neutropenia	2.3	6.3	3.7	10.5	6.3	4.3	0.7	1.3	1.3
Anemia	0	6.3	2.5	0	0	0	0.3	0.8	1.8
Edema peripheral	0	8.3	1.2	5.3	0	4.3	1.3	3.3	2.3
URI	4.7	2.1	9.9	21.1	3.1	6.5	3.3	1.8	2.7
Weight increased	0	4.2	1.2	5.3	3.1	6.5	0.3	2.8	2.8
Arthralgia	4.7	2.1	11.1	5.3	9.4	2.2	1.0	2.0	2.4
Headache	2.3	0	2.5	5.3	12.5	15.2	5.9	5.8	4.8
Rash	2.3	0	0	10.5	0	2.2	0.3	1.0	1.3

AEs occurred in a similar percentage of nonobese and obese subjects (58.3-64.4%). The difference in the AE event rate between the A+P nonobese and obese subjects was ≤2% for AEs of interest, except for nasopharyngitis (2.7% vs. 5.1%) and back pain (2.9% vs. 5.8%). Within the nonobese group, AEs of interest occurred at a similar rate except for headache which occurred in 9% of alogliptin subjects versus approximately 6% of pioglitazone and A+P subjects. Within the obese group, AEs of interest occurred at a similar rate except for upper respiratory tract infection which occurred in 6.3% of alogliptin subjects versus approximately 2.5% of pioglitazone and A+P subjects

NDA 22-426. AEs of interest (%) by BMI (≥3% incidence in any group)

	<30			**≥30**		
	Alo (n=199)	**Pio (n=266)**	**A+P (n=517)**	**Alo (n=222)**	**Pio (n=284)**	**A+P (n=590)**
Any AE	58.3	62.4	60.7	62.2	58.8	64.4
Diarrhea	2.5	2.6	3.9	0.9	3.9	2.9
Edema peripheral	0.5	1.9	2.3	2.3	4.9	3.1
Nasopharnygitis	4.0	2.6	2.7	3.6	3.2	5.1
Upper resp. tract infection	2.5	1.1	3.9	6.3	2.5	2.4
Weight increased	0.5	2.6	1.7	0.5	2.5	3.1
Arthralgia	1.5	1.5	2.9	1.8	3.5	3.1
Back pain	0.5	3.8	2.9	3.6	1.8	5.8
Headache	9.0	6.0	6.2	3.2	6.3	4.9

Dizziness	4.0	3.4	3.3	0	3.2	3.6

7.5.4 Drug-Disease Interactions

The sponsor tallied AEs by summary baseline renal impairment category. Using the MDRD formula, approximately 50% of subjects had no renal impairment and 50% had mild impairment. Using the CG formula, >80% subjects had no renal impairment and 18% had mild impairment. The incidence of AEs was similar between treatment groups within renal impairment categories, except for moderate renal impairment. More AEs occurred in A+P treated subjects with baseline moderate renal impairment (CG and MDRD formulas: 85.7% and 76.9%, respectively). However, the small sample size in the moderate renal impairment group limits conclusions.

On subject (002/313-2509) had severe renal impairment at study entry. The subject had a baseline creatinine of 1.9 mg/dl, which met study entry criteria (<2 mg/dl). On day 113, the subject was discontinued from the study due to an AE of BUN increased. Please refer to section 7.4.2.3.3 Marked Outliers and Dropouts for Laboratory Abnormalities for full details.

NDA 22-426. AE summary by baseline renal impairment category. Source: Sponsor, Integrated Analysis of Safety, Table 5.e

	Number of Subjects With ≥1 AE/ Number of Subjects in Impairment Category (%)		
Baseline Renal Impairment Category	**ALO**	**PIO**	**ALO+PIO**
Cockcroft-Gault			
None	208/344 (60.5)	266/451 (59.0)	559/897 (62.3)
Mild	45/74 (60.8)	65/96 (67.7)	128/202 (63.4)
Moderate	1/3 (33.3)	2/3 (66.7)	6/7 (85.7)
Severe	0/0	0/0	1/1 (100.0)
MDRD			
None	132/204 (64.7)	156/273 (57.1)	360/566 (63.6)
Mild	119/211 (56.4)	174/271 (64.2)	323/527 (61.3)
Moderate	3/6 (50.0)	3/6 (50.0)	10/13 (76.9)
Severe	0/0	0/0	1/1 (100.0)

The sponsor did not analyze the pivotal phase 3 A+P studies by hepatic impairment, although study SYR-322-023 assessed the single dose PK of alogliptin 25 mg in subjects with and without hepatic impairment. (Please refer to the clinical pharmacology and clinical reviews of alogliptin NDA 22-271.) Alogliptin exposure was decreased by 10% and 9% for AUC_{0-t} and Cmax, 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.

Compared with normal controls, subjects with Child-Pugh Grade B/C hepatic impairment have approximately a 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values. Pioglitazone should not be initiated if a patient has clinical evidence of active liver disease or serum transaminase levels (ALT) >2.5x ULN.

7.5.5 Drug-Drug Interactions

No A+P drug-drug interaction studies were conducted.

Thirteen drug- and drug-drug interaction studies were conducted under the alogliptin IND 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 the clinical pharmacology and clinical reviews of alogliptin NDA 22-271 (clinical section 4.4.3 Pharmacokinetics).

Please refer to the pioglitazone label for full pioglitazone drug-drug interaction details.

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 (≥ 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.

In a 2-year carcinogenicity study of pioglitazone in male and female rats, benign and/or malignant urinary bladder transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). A 2-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11x the maximum recommended human oral dose based on mg/m^2); no drug-induced tumors were observed in any organ.

No new cases of bladder tumor were identified during a prospective evaluation of urinary cytology in >1,800 patients who received pioglitazone for up to 1 year. In two 3-year studies comparing pioglitazone to placebo or glyburide, there were 16/3656 (0.44%) report of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was < 1 year at the time of bladder cancer diagnosis, there were 5 (0.16%) cases on pioglitazone and 2 (0.05%) on placebo.

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 with alogliptin. In rats, the concentration of alogliptin in milk is 2x maternal plasma concentration, thus fetal exposure with breastfeeding is expected in humans.

Pioglitazone is pregnancy category C; it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17x and 40x the maximum recommended human oral dose based on mg/m^2). Delayed parturition and embryotoxicity (e.g. increased postimplantation losses, delayed development, and reduced fetal weights were observed in rats at oral doses ≥40 mg/kg/day (approximately 10x the maximum recommended human oral dose based on mg/m^2). In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40x the maximum recommended human oral dose based on mg/m^2). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses ≥10 mg/kg during late gestation and lactation (approximately 2x the maximum recommended human oral dose based on mg/m^2).

Pioglitazone is secreted in the milk of lactating rats; it is not known if pioglitazone is secreted in human milk.

Two pregnancies were reported in the alogliptin 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 pivotal phase 3 A+P program in subjects who received alogliptin:

- 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. βHCG 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. In NDA 22-271, 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. Consistent with this, on May 18, 2009, the sponsor submitted a protocol to alogliptin IND 69,707 for a phase 1, comparative, randomized, open-label, single-dose PK/PD and safety study of alogliptin (12.5 and 25 mg) between children and adolescents with T2D. Following completion of the phase 1 study, the sponsor will conduct an international, multicenter, randomized, double blind, placebo controlled phase 3 study to evaluate the efficacy and safety of alogliptin in adolescents with T2D.

Prior to initiating the pediatric program for alogliptin, the sponsor intends to conduct the following nonclinical studies:

- A 4 week oral toxicity study in male and female Sprague-Dawley rats to evaluate potential toxicity of alogliptin in juvenile rats
- An 8 week oral toxicity study in male Sprague-Dawley rats to evaluate potential alogliptin-related effects on the male reproductive organs

In both studies, the rats will be 4 weeks of age at initiation of dosing so as to correspond to adolescent development. These studies will be completed before the initiation of dose administration to subjects in the pediatric phase 3 efficacy and safety study noted above.

As part of the clinical development of pioglitazone, a PK study was conducted in T2D adolescents (12 to < 17 years). Pioglitazone (15, 30, and 45 mg) was administered orally in the fasting state. However, 2 concerns about the use of pioglitazone in children < 18 years exist.

(b) (4)

(b) (4)

On May 26, 2009, the sponsor proposed a pediatric development plan for A+P. (b) (4)

COMMENT: If the sponsor submits a protocol studying A+P in children < 18 years, it may be placed on partial clinical hold for the above reasons. The division may recommend a full waiver of the pediatric research requirement in the next NDA review cycle.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of A+P 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.

During controlled clinical trials, 1 case of pioglitazone overdose was reported. A male patient took 120 mg daily for 4 days, then 180 mg daily for 7 days. The patient denied any clinical symptoms during this period.

In the event of pioglitazone overdosage, supportive treatment should be initiated.

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
7/1/2009 03:26:34 PM
MEDICAL OFFICER

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Please see the CDTL memorandum.