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RESEARCH**

APPLICATION NUMBER:

203414Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	203-414
Priority or Standard	Standard

Submit Date(s)	11-22-11
Received Date(s)	11-22-11
PDUFA Goal Date	12-22-12
Division / Office	DMEP/ODEII/OND

Reviewer Name(s)	Valerie S.W. Pratt, M.D.
Review Completion Date	01-17-13

Established Name	Alogliptin/metformin FDC
(Proposed) Trade Name	Kazano
Therapeutic Class	DPP4 inhibitor/biguanide FDC
Applicant	Takeda

Formulation(s)	12.5/500 and 12.5/1000 mg
Dosing Regimen	Twice daily
Indication(s)	Type 2 diabetes mellitus
Intended Population(s)	Adult type 2 diabetics

Template Version: March 6, 2009

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Abbreviations

ADA	Antidiabetic agent
AE	Adverse event
Alo or A	Alogliptin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AP	Alkaline phosphatase
AUC	Area under the curve
BE	Bioequivalence
BID	Twice daily
Bili	Bilirubin
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
CV	Cardiovascular
DBP	Diastolic blood pressure
DMC	Data monitoring committee
DDI	Drug-drug interaction
DMEP	Division of Metabolism and Endocrinology Products
DMF	Drug master file
DPP-4	Dipeptidyl peptidase 4
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FDC	Fixed dose combination
FPG	Fasting plasma glucose
GGT	γ -glutamyl-transferase
GIP	Glucose-dependent insulintropic polypeptide
GLP-1	Glucagon-like polypeptide-1
HCl	Hydrochloride
Hct	Hematocrit
HDL	High-density lipoproteins
Hgb	Hemoglobin
HgA1c	Hemoglobin A1c
HOMA-BCF	Homeostasis model assessment – beta cell function
HTN	Hypertension

IND	Investigational new drug
IRB	Institutional review board
IV	Intravenous
LDL	Low-density lipoproteins
LOCF	Last observation carried forward
LS	Least squares
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
Met or M	Metformin
NAI	No action indicated
MI	Myocardial infarction
NDA	New drug application
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
PeRC	Pediatric Review Committee
PI	Prescribing information
PK	Pharmacokinetics
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
SMQ	Standardized MedDRA query
SOC	Systems organ class
Study MET-302	Study SYR-322-MET-302
Study 402	CV study SYR-322_402
SU	Sulfonylurea
T1/2	Half-life
T2DM	Type 2 diabetes mellitus
Tg	Triglycerides
Tmax	Time to peak plasma concentration
TZD	Thiazolidinedione

Clinical Review
Valerie S. W. Pratt, M.D.
NDA 203-414
Alogliptin/metformin FDC

(b) (4)

ULN	Upper limit of normal
US	United States
VAI	Voluntary action indicated
WBC	White blood cells

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of new drug application 203-414 for alogliptin/metformin FDC, which was proposed as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

1.2 Risk Benefit Assessment

The applicant proposes 12.5/500 and 12.5/1000 mg alogliptin/metformin FDC tablet strengths for use twice daily with food in patients with normal renal function.

The applicant submitted three completed, phase 3, placebo- or active-controlled studies.

- In the 26-week trial MET-008, which compared alogliptin administered with metformin to metformin alone, the difference in adjusted mean change in HbA1c was -0.5% (95% CI: -0.7, -0.3).
- In the 52-week trial OPI-004, which compared the addition of alogliptin 25 mg versus dose titration from 30 mg to 45 mg pioglitazone in subjects who were inadequately controlled on metformin and pioglitazone 30 mg, the LS mean treatment difference between the metformin + alogliptin 25 mg + pioglitazone 30 mg and metformin + pioglitazone 45 mg groups was -0.4% (97.5% CI: -0.3). 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.
- In 26-week trial MET-302, which compared placebo, alogliptin, metformin, and alogliptin + metformin, the LS mean change from baseline was significantly greater with both coadministration regimens (-1.2% and -1.6% with A12.5+M500 BID and A12.5+M1000 BID, respectively) when compared to alogliptin (-0.5% with A12.5 BID) and metformin (-0.7% and -1.1% with M500 and M1000 BID, respectively).

As described in section 2.4 Important Safety Issues With Consideration to Related Drugs and my review of the second alogliptin resubmission, alogliptin and metformin are associated with the following safety issues. (The CV safety of alogliptin was demonstrated in the company's submission to a Complete Response letter issued on June 26, 2009.)

- 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 alogliptin 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 with alogliptin 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 $\leq$ 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, the current clinical database supports approval of alogliptin. As co-administration with metformin is not expected to alter the liver safety of alogliptin and review of the alogliptin + metformin data did not reveal a signal for hepatotoxicity, I recommend approval of the alogliptin/metformin FDC. I recommend the applicant include hepatic enzyme elevation text in the labeling sections 6.2 Postmarketing Experience and 5 Warnings and Precautions. Hepatotoxicity should be monitored as an adverse event (AE) of special interest in the controlled CV study 402, the PSURs, and by an enhanced pharmacovigilance PMR.

- Hypersensitivity: Hypersensitivity has been associated with DPP-4 inhibitors, such as sitagliptin, saxagliptin, vildagliptin, and alogliptin. The percentage of alogliptin + metformin subjects with AEs in the angioedema SMQ ranged from 0% (A12.5+M in study MET-302) to 5.2% (A25+M+P30 in study OPI-004). Edema peripheral was the most common event, although it is a broad search term and may not be indicative of a true case of angioedema. This is consistent with other DPP-4 inhibitors and is not an approvability issue but would need to be adequately labeled when approved. I recommend that use be contraindicated in subjects with a history of serious reaction to alogliptin. I also recommend a warning and description of events. Hypersensitivity should be monitored as an AE of special interest in the controlled CV study 402, the PSURs, and an enhanced pharmacovigilance PMR.
- Skin lesions: Necrotizing skin lesions, which have been observed in monkeys given other DPP-4 inhibitors, were not seen in alogliptin studies in mice, rats, dogs, or monkeys. However, the percentage of alogliptin + metformin subjects with any potential cutaneous drug reaction (PCDR) event in completed studies MET-302, MET-008, and OPI-004 ranged from 0% (A12.5+M in study MET-302) to 14.1% (A25+M+P30 in OPI-004). The incidence of PCDR events was higher in studies MET-008 and OPI-004, probably because they included an

examination of the skin and digits at every study visit whereas study MET-302 did not. Events in these studies as well as ongoing study 305 included pruritis, dermatitis, rash, and skin lesions. This is not an approvability issue but would need to be adequately labeled when approved.

- Pancreatitis: Using MedDRA's SMQ criteria, three subjects with acute pancreatitis were identified in study MET-302 (one each in A12.5+M500BID [pancreatitis acute], A12.5+M1000BID [pancreatitis], and M1000BID groups). In ongoing study 305, two alogliptin 25 mg + metformin subjects met the pancreatitis SMQ criteria. These findings are consistent with other DPP-4 inhibitor-containing products and are not an approvability issue but would need to be adequately labeled when 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: DPP-4 inhibition may increase the risk for infections because DPP-4 is expressed on a subset of CD4+ and CD8+ T-cells and natural killer cells. The percentage of alogliptin + metformin subjects with Infections and Infestations AEs in completed, placebo-controlled phase 3 studies ranged from 21.9 – 31.9% versus 18.9 – 26.9% in placebo subjects. Common AEs (≥5%) included upper respiratory tract infection, nasopharyngitis, and urinary tract infection. This is consistent with other DPP-4 inhibitor-containing products and is not an approvability issue but would need to be adequately labeled when approved.
- Hypo- and hyperglycemia: The incidence of hypoglycemia in completed and ongoing phase 3 studies was low; the majority of events were mild to moderate severity. The percentage of alogliptin + metformin subjects who required hyperglycemic rescue in phase 3 studies ranged from 2.6 - 12.3%; this was less than the percentage of placebo and comparator subjects.
- Lactic acidosis: Metformin is associated with the risk of lactic acidosis, which increases with sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. No cases of lactic acidosis were identified in the Summary of Clinical Safety (SCS), Four-Month Safety Update, or Interim CSR 305.
- Decrease in vitamin B12 levels and Anemia: Metformin is associated with a decrease in vitamin B12 levels and associated anemia. Although B12 was not routinely drawn in phase 3 studies, no cases of B12 deficiency were identified in the SCS, Four-Month Safety Update, or Interim CSR 305. No clinically significant hematologic laboratory abnormalities which would preclude approval were identified. The proposed label warns of the risks of decreased vitamin B12 levels and anemia.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Although I do not recommend a REMS, I recommend a MG which includes information about alogliptin's risks of hepatotoxicity and pancreatitis.

1.4 Recommendations for Postmarket Requirements and Commitments

I recommend the following 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:
 - o 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*
 - o 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*
 - o 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 also recommend the PSURs summarize the following AEs special interest: hepatotoxicity, hypersensitivity (including skin lesions), pancreatitis, pancreatic malignancy, infections, hypo- and hyperglycemia, and lactic acidosis.

2 Introduction and Regulatory Background

2.1 Product Information

Takeda submitted this 505(b)(2) NDA for the use of alogliptin/metformin FDC as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. It cross-references Glucophage (metformin HCl) NDA 20-357.

Alogliptin inhibits DPP-4, an enzyme that rapidly degrades incretin hormones such as GLP-1 and GIP. Incretin hormones stimulate insulin synthesis and glucose-dependent insulin secretion. GLP-1 suppresses glucagon secretion, which leads to decreased hepatic glucose production, delayed gastric emptying, and increased satiety.

Glucophage (metformin HCl, NDA 20-357) was first approved in the US on March 3, 1995. It decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. It does not produce hypoglycemia or hyperinsulinemia.

The applicant proposes 12.5/500 and 12.5/1000 mg alogliptin/metformin FDC tablet strengths for use twice daily with food in subjects with normal renal function. See also section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations.

2.2 Tables of Currently Available Treatments for Proposed Indications

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

- Insulin
- Sulfonylureas (SUs)
 - o Tolazamide (Tolinase)
 - o Chlopropramide (Diabinese)
 - o Glyburide (Micronase)
 - o Glipizide (Glucotrol and Glucotrol XL)
 - o Glimepiride (Amaryl)
- Glinides: Repaglinide (Prandin) and Nateglinide (Starlix)
- Biguanides: Metformin (e.g., Glucophage and Glucophage XR)
- Thiazolidinediones
 - o Rosiglitazone (Avandia)
 - o Pioglitazone (Actos)
- α -Glucosidase inhibitors
 - o Acarbose (Precose)
 - o Miglitol (Glyset)
- GLP-1 receptor agonists
 - o Exenatide (Byetta)
 - o Liraglutide (Victoza)
- Amylinomimetics
 - o Pramlintide (Symlin)

- Dipeptidyl peptidase 4 inhibitors
 - o Sitagliptin (Januvia)
 - o Saxagliptin (Onglyza)
 - o Linagliptin (Tradjenta)
- Bile acid sequestrants
 - o Colesevelam (WelChol)
- Dopamine receptor agonists
 - o Bromocriptine mesylate (Cycloset)
- FDCs of the various oral medications listed above

2.3 Availability of Proposed Active Ingredient in the United States

Alogliptin was approved for use in Japan on April 16, 2010. However, alogliptin is not currently approved for use in the US. CR letters were issued for alogliptin NDA 22-271 on June 26, 2009 and April 25, 2012. The second CR letter was issued due to a concerning signal for drug-induced liver injury. The second alogliptin CR is currently under review.

Glucophage (metformin HCl, NDA 20-357) was first approved in the US on March 3, 1995. The first DPP4 inhibitor/metformin FDC was sitagliptin/metformin FDC (Janumet). It was approved for use in the US on March 30, 2007.

2.4 Important Safety Issues With Consideration to Related Drugs

As described in my February 29, 2012 alogliptin CR review, alogliptin is associated with the following safety concerns:

- **Hepatotoxicity:** A signal for hepatotoxicity was seen in the first alogliptin CR. Specifically, there were numerical imbalances not favoring alogliptin for serum ALT elevations >5x, >10x, and >20x ULN compared to control and five probable cases of alogliptin hepatotoxicity among the estimated 219,000 patient-years of postmarketing experience in Japan. The sponsor addressed this issue in the second alogliptin CR (dated July 26, 2012), which contained clinical trial safety data from 9857 subjects exposed to alogliptin. **See my review of the second alogliptin resubmission. The second alogliptin resubmission is currently under review by the Agency.**
- **Hypersensitivity:** Hypersensitivity has been associated with other DPP-4 inhibitors, such as sitagliptin, saxagliptin, and vildagliptin. Narrow Anaphylactic Reaction, Angioedema, and Severe Cutaneous Adverse Reactions (SCAR) SMQ searches do not suggest alogliptin subjects are at increased risk for hypersensitivity events. However, two angioedema, four Stevens-Johnson syndrome (SJS), and five erythema multiforma serious Japanese postmarketing reports were identified in the alogliptin and alogliptin/pioglitazone FDC CR, 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.

- Skin lesions: Necrotizing skin lesions, which have been observed in monkeys given other DPP-4 inhibitors, were not seen in alogliptin studies in mice, rats, dogs, or monkeys. However, the percentage of subjects reporting at least one 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 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 DPP-4 inhibitors, they suggest that sensitive individuals may be hypersensitive to alogliptin. The incidence of PCDR 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: DPP-4 inhibition may increase the risk for infections because DPP-4 is expressed on a subset of CD4+ and CD8+ T-cells and natural killer cells. Therefore, the pooled clinical trial safety data was searched for events in the Infections and Infestations 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.
- 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.

Labeled safety concerns with metformin include the following:

- Risk of lactic acidosis, which increases with sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure
- Contraindication in patients with renal dysfunction (e.g. serum creatinine ≥ 1.5 mg/dl [males], ≥ 1.4 mg/dl [females] or abnormal creatinine clearance)
- Use with intravascular iodinated contrast materials, when hypoxic, when undergoing surgery, use with excessive alcohol intake, or if impaired hepatic function

- Hypersensitivity
- Decrease in vitamin B12 levels and associated anemia
- Hypoglycemia, especially in the elderly and debilitated patients when caloric intake is deficient or during concomitant use of other glucose-lowering agents (e.g. SU and insulin) or alcohol
- Hyperglycemia, during times of stress

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The alogliptin/metformin FDC IND 101,628 was opened on April 2, 2009. On December 3, 2009 and February 11 and March 9, 2010, comments were conveyed on protocol MET-302, *A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of alogliptin plus metformin, alogliptin alone, or metformin alone in subjects with type 2 diabetes.*

On April 5, 2011, the following key clinical points were conveyed in response to the applicant's pre-NDA meeting document. (See also section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations.)

- The agency agreed with the plan to present Phase 1 studies MET-101, MET-102, 322-005, 322-101 and Phase 3 studies MET-302, 322-008, and OPI-004 separately and without integration or pooling for a safety analysis, due to differences in treatment populations and durations.
- The 120-day Safety Update should include the results from ongoing trials of alogliptin under other INDs (e.g., alogliptin IND 69,707 for alogliptin and alogliptin/pioglitazone FDC IND 73,193), post-marketing experience with alogliptin in other countries, results from animal toxicity studies, and safety issues published in the literature.
- The agency agreed to the proposal to provide complete study reports, including the synopses for the two phase 3, non-IND (Japanese) studies that were conducted, to evaluate the safety and efficacy of alogliptin in combination with metformin and to not summarize the data from these studies within the NDA.
- The agency generally agreed to the plan to cross-reference information from alogliptin NDA 22-271, although we asked that new information be clearly labeled, summaries regarding the use of alogliptin with metformin be included, and provided additional general cross-referencing information.
- The agency recommended the applicant seek a PREA waiver for 0-9 year olds and deferral for 10-16 year olds.
- The agency recommended BE study SYR-322-MET-101 evaluate the final, to-be-marketed FDC formulation.
- The agency recommended US-approved metformin products be used in the BE study and phase 3 studies.

On August 11 and September 21, 2011, the agency agreed that the following alogliptin+metformin information would be resubmitted:

- US Phase 1 studies: MET-101, MET-102, SYR-322-005 (submitted to alogliptin NDA 22-271), and SYR-311-101 (submitted to NDA 22-271)

- US Phase 3 studies: SYR-322-MET-302, SYR-322-008 (submitted to alogliptin NDA 22-271), and OPI-004 (submitted to NDAs 22-271 and alogliptin/pioglitazone FDC NDA 22-426)
- Japanese phase 3 studies: OCT-005 and CCT-005 (submitted to alogliptin NDA 22-271)

On September 21 and November 17, 2011, the agency also clarified the following regarding the 120-day Safety Update:

- CV study 402 need not be included in the 120-day Safety Update.
- Studies SYR-322-OLE-12 and SYR-322_305 should not be pooled
 - Only an analysis of Hy's law and hypersensitivity cases, focusing on new data since the alogliptin November 7, 2011 submission, should be submitted for uncontrolled, open-label study SYR-322-OLE-012
 - An analysis of relevant safety findings should be included for study SYR-322_305.
- The Japanese PSUR (cut off date October 15, 2011) should analyze AEs of special interest (i.e., hepatotoxicity, renal failure, hypersensitivity, and pancreatitis)
- There are no ongoing or complete phase 2 or 3 studies in Japan that were not included in the alogliptin and alogliptin/pioglitazone FDC CRs.

On November 2, 2011, to answer the applicant's question regarding whether to use the Glucophage or Glumetza label as the basis for drafting the NDA 203-414 PI, the agency recommended that proposed labeling show the source of the data and language.

2.6 Other Relevant Background Information

On January 13, 2012, the applicant was asked to submit to this NDA all future alogliptin liver events and information that would ordinarily only come in to the IND. Subsequent submissions were made on the following dates:

- Submissions prior to second alogliptin CR on April 25, 2012 (see CR reviews for a discussion of these cases):
 - January 20, 23, and 24, 2012
 - February 1, 9, 14, and 22, 2012
 - March 8, 22, and 27, 2012
 - April 2, 4, 5, and 19, 2012
- Submissions after second alogliptin CR:
 - May 7, 2012: Follow up report TCI2011A06369
 - May 16, 2012: Follow up report ERD2010A00037
 - May 29, 2012: Initial reports TCI2012A02494 and TCI2012A02523
 - June 4, 2012: Follow up report TCI2012A01573
 - June 7, 2012: Follow up report TCI2012A02494
 - June 12, 2012: Initial report TCI2012A02933
 - June 19, 2012: Follow up report TCI2012A02523
 - June 27, 2012: Follow up reports TCI2012A02523 and TCI2012A02933

- July 10, 2012: Initial report TCI2012A03395 and follow up report TCI2011A06369
- July 19, 2012: Follow up report TCI2011A06369
- August 2, 2012: Follow up report TCI2011A02933
- August 14, 2012: Follow up report TCI2011A02933
- September 13, 2012: Follow up report TPG2012A01058
- September 25, 2012: Initial report TCI2012A05429
- November 15, 2012: Follow up report TCI2012A05586
- November 30, 2012: Initial report TCI2012A06036

On January 18, 2012, the applicant changed the proposed name (b) (4)

On January 20, 2012, the applicant submitted revised pediatric plan in response to our December 20, 2011 information request to alogliptin NDA 22-271.

On March 20, 2012, the applicant submitted the 120-day Safety Update, which included an interim analysis of study SYR-322_305 (305) and data from completed, open-label extension study SYR-322-OLE_012 (OLE-1012). Japanese Periodic Safety Update Report 3 (April 16, 2011 – October 15, 2011) and revised labeling (which included interim safety data from study 305) were also submitted, as were analyses of postmarketing events of interest (hepatotoxicity, pancreatitis, hypersensitivity, and renal failure) which were previously reviewed under the alogliptin CR.

(b) (4)

On April 23, 2012, the applicant submitted a second proposed trade name (Kazano) for review.

On April 25, 2012, a CR letter was issued for the alogliptin and alogliptin/pioglitazone CRs due to numerical imbalances not favoring alogliptin for serum alanine aminotransferase elevations and five probable cases of alogliptin hepatotoxicity among the estimated 219,000 patient-years of postmarketing experience in Japan.

On May 25, 2012, the applicant submitted a response to our information request regarding replicate subjects in CV study 402. (See section 3.1 Submission Quality and Integrity.)

On June 13, 2012, the applicant submitted a response to our information request regarding the interim subject discontinuation data from study 305.

On July 26, 2012, the applicant submitted a second resubmission to alogliptin NDA 22-271 and alogliptin/pioglitazone FDC NDA 22-426. The resubmission addressed

concerns regarding possible alogliptin hepatotoxicity. See also my review of the second alogliptin resubmission.

On August 16, 2012, the applicant submitted the updated clinical and postmarketing liver safety data that was submitted in alogliptin NDA 22-271 submission on July 26, 2012. This was a Major Amendment, which changed the PDUFA date to December 22, 2012. However, in order to coordinate review of this NDA with that of the alogliptin and alogliptin/pioglitazone NDAs, the action goal date was revised to January 26, 2013. See my review of the second alogliptin FDC resubmission for a discussion of this safety data.

On August 16, 2012, the applicant submitted an updated pediatric deferral request. It contained revised study dates and protocol SY-322_104 Amendment 8 (which was submitted to alogliptin IND 69-707 in SDN 729 on March 22, 2012).

On October 5, 2012, the applicant submitted a response to our September 24 and 26, 2012 liver information requests. See my review of the second alogliptin resubmission and section 7.3.5 Submission Specific Primary Safety Concerns.

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 plan.

On November 9, 2012, the applicant submitted a response to our October 19, 2012 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 submission was well organized and of appropriate quality, with the following two caveats:

- (b) (4) See section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations.
- In clinical study report MET-302, the applicant identified 13 subjects who enrolled at two or more study sites and ten subjects who enrolled both in study MET-302 and ongoing study 305

The replicate subjects were identified by PPD via comparing demographic data of all enrolled subjects in study MET-302, verified by PPD's project management, and reported by the applicant in Part 10.2 of the study report and Appendix 16.2.4.5. The treatment blind was maintained while making the determination as to whether or not the duplicate subjects should be included in the efficacy and safety analyses.

The Division concurs with the determinations made by the applicant concerning the status of each replicate enrollment in the FAS, PPS, and safety set, as documented in Appendix 16.2.4.5. However, as conveyed to the applicant on May 16, 2012, it raised the possibility that there may be replicate enrollments in CV study 402. As the integrity of study 402 is key to demonstrating the CV safety of alogliptin, the applicant was asked to search study 402's database for subjects who either enrolled at multiple sites or participated in other alogliptin studies. The applicant responded, as follows, to this request. The response is acceptable.

- Reports are run on a monthly basis to identify potential duplicate subjects in study 402 based on demographic data. Checks identify both subjects who have enrolled at more than one site within study 402 as well as subjects who may have been participating in another ongoing alogliptin study while also enrolled in study 402.
- As of May 25, 2012, two subjects have been confirmed as duplicate subjects. One subject (8294002/8287001) enrolled at two different sites in Peru. The other (8926001/8928001) enrolled at two different sites in the Philippines. Study drug was discontinued for both subjects, although the applicant will follow the subjects to assess for potential MACE events per the protocol.
- The applicant will continue to monitor for duplicate subjects and will discuss the handling of these subjects with the FDA prior to unblinding. The current plan is to include any subjects who enroll at multiple sites as a single subject in the final analysis. The subject would be included in the treatment group to which s/he was randomized. No per-protocol analysis is planned.

3.2 Compliance with Good Clinical Practices

The clinical study reviewed below, MET-302, was conducted in a manner consistent with the International Conference on Harmonisation Harmonised Tripartite Guidelines for Good Clinical Practices and all applicable US Food and Drug Administration regulations.

The methods for capturing reasons for study drug and visit discontinuation were revised in protocol Amendment 1. In the original protocol, all study drug discontinuations from hyperglycemic rescue were captured under “lack of efficacy”. In Amendment 1, “lack of efficacy” was removed from the list of reasons for study drug discontinuation. These changes were in part a response to an FDA request to incorporate hyperglycemic rescue procedures into the study design. The original nine reasons for study visit discontinuation were also changed to “lost to follow up”, “voluntary withdrawal”, “study termination”, and “pregnancy. See also 6.1.3 Subject Disposition.

The incidence of major protocol deviations was low (i.e. 0.0% - 2.7%) in both discontinuation groups. No meaningful differences in protocol deviations were observed between treatment groups. Fourteen subjects were excluded after it was discovered they were duplicate subjects (see above). The study blind was broken for two subjects (5138/008 and 5252/003 in the M500 BID group) who became pregnant while on study medication. Although treatment was stopped upon confirmation of third pregnancy (5017/019 in the A12.5+M500 BID group), study medication was not unblinded, per the subject’s request.

OSI inspected the following two studies:

- Clinical pharmacology study MET-101: PPD Phase I Clinic (Austin, Texas) (b) (4)
(b) (4) classified as VAI (b) (4)
- Clinical study MET-302: (Sites were chosen due a high number of subjects screened/randomized and lack of previous inspection history.)
 - Dr. Bandgar Tushar Ramkrishna’s site # 5254 in Mumbai, India screened 36 and randomized 20 subjects. On November 16, 2012, OSI classified the site as NAI.
 - Dr. Michael A. Szczesry’s site # 5301 in Boca Raton, Florida screened 50 and randomized 27 subjects. On August 2, 2012, OSI classified the site as NAI.

3.3 Financial Disclosures

All active clinical investigators, except the following three, certified no financial interests or arrangements existed during the conduct of the clinical studies MET-008, OPI-004, and MET-302. The investigators below 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 ”

(b) (4)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

This 505(b)(2) application cross-references alogliptin NDA 22-271 and Glucophage NDA 20-357. A letter of authorization is also provided to DMF (b) (4) for the CMC information on the drug substance metformin HCl.

The product is a fixed-dose combination, immediate-release tablet available in the strengths of 12.5/500 and 12.5/1000 mg/mg alogliptin (free base)/metformin hydrochloride. The excipients are mannitol, microcrystalline cellulose, povidone, crospovidone, and magnesium stearate, hypromellose 2910, talc, titanium dioxide, and ferric oxide yellow.

(b) (4)

(b) (4)

(b) (4)

The product will be packaged in bottles and in blisters, and will be stored at room temperature.

Please refer to Sheldon Markofsky's July 26 and December 21, 2012 CMC and Houda Mahayni's August 6, 2012 biopharmaceutics reviews, which recommend approval.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Early reproductive toxicity data suggested a potential interaction between DPP-4 inhibitor drugs and metformin leading to craniofacial malformations in rat fetuses exposed during development. As a result, an embryofetal development study in rats

that included separate alogliptin and metformin arms in addition to the combination groups was requested and submitted. The requested combination embryofetal rat study was submitted. As described in David Carlson's January 8, 2012 alogliptin CR review, the findings were not consistent with prior craniofacial malformation signals in the class. Please refer to David Carlson's July 23, 2012 PT review in which he recommends approval.

4.4 Clinical Pharmacology

The clinical pharmacology program consisted of two biopharmaceutic studies (pivotal BE study MET-101 and food-effect study MET-102) and two studies (PK/PD study 101 of alogliptin BID versus QD dosing and drug-interaction study 005 with metformin) that were conducted under alogliptin NDA 22-271. Please refer to Zhihong Li's July 27, 2012 clinical pharmacology review which recommends approval as well as relevant documents under alogliptin NDA 22-271 and Glucophage NDA 20-357.

4.4.1 Mechanism of Action

Alogliptin inhibits DPP-4, an enzyme that rapidly degrades incretin hormones such as GLP-1 and GIP. Incretin hormones stimulate insulin synthesis and glucose-dependent insulin secretion. GLP-1 suppresses glucagon secretion, which leads to decreased hepatic glucose production, delayed gastric emptying, and increased satiety.

Glucophage (metformin HCl, NDA 20-357) is a biguanide that decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. As a result, it lowers both basal and postprandial plasma glucose. It does not produce hyperinsulinemia or hypoglycemia.

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.

4.4.3 Pharmacokinetics

Alogliptin: 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. Renal clearance (170

ml/min) slightly exceeds the GFR of 120 ml/min in healthy adults, which suggests some active tubular secretion. The half-life of alogliptin is 21 hours.

Metformin: The absolute bioavailability of metformin is 50-60%. It is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

Following single IV doses of metformin to healthy subjects, metformin is excreted unchanged in the urine. Renal clearance is ~3.5 times greater than CrCl, which suggests tubular secretion is the major route of elimination.

Following oral administration, ~90% of absorbed metformin is eliminated via the renal route within the first 24 hours, with a half-life of ~6.2 hours in plasma. The elimination half-life in blood is approximately 17.6 hours, which suggests that the erythrocyte mass may be a compartment of distribution.

Alogliptin and Metformin: In summary, key clinical pharmacology studies demonstrated the following:

- Pivotal BE study MET-101: The AUC and C_{max} of both the alogliptin and metformin component following a single dose of the combination tablet were bioequivalent to the alogliptin 12.5 mg concomitantly administered with metformin HCl 500 or 100 mg tablets under fasted conditions in healthy subjects.
- Food-effect study MET-102: Administration of the FDC with food resulted in no change in AUC of alogliptin and metformin. Mean C_{max} of alogliptin and metformin were decreased by 13% and 28%, respectively, when administered with food. There was no change in T_{max} for alogliptin under fed conditions, although there was a delayed T_{max} for metformin of 1.5 hours. The applicant recommends dosing with food to reduce gastrointestinal AEs.
- PK/PD study 101 comparing alogliptin BID versus QD dosing: As expected, BID dosing had a lower C_{max} compared to QD dosing. The PD endpoint of DPP-4 inhibition (AUC_{0-24,ss}) was within the 80-125% range.
- Drug-interaction study 005: There was no significant interaction between alogliptin and metformin.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study	Study Design Primary Objective	Population No. and Type	Treatment Duration	Treatment (mg)
Phase1				
SYR-322-MET-101 (MET-101) BE	Randomized, open-label, 2-cohort, single-center, 4-sequence, 4-period crossover BE	96 healthy	4 single doses separated by 7-day washout	Cohort 1: FDC 6.25/500 BID Alo 6.25+Met 500 BID FDC 6.25/1000 BID Alo 6.25+Met 1000 BID Cohort 2: FDC 12.5/500 BID Alo 12.5+Met 500 BID FDC 12.5/1000 BID Alo 12.5+Met 1000 BID
SYR-322-MET-102 (MET-102) Food Effect	Randomized, open-label, single-site, 2-period crossover Food effect	24 healthy	1 day in each period with 7-day washout	FDC 12.5/1000 BID fasted FDC 12.5/1000 BID fed
SYR-322_101 PK of QD vs. BID dosing	Randomized, open-label, multiple dose, 2-period crossover PK of QD vs. BID dosing	28 healthy	7 days in each period with 7-day washout	Alo 12.5 BID and Alo 25 QD
SYR-322_005 Effect of food on PK and DDI: Met and cimetidine	Randomized, open-label, 2-phase, single-dose (2-period crossover), and multiple-dose (3-period crossover) Effect of food on PK and	36 healthy	1 day in each period for food effect with a 96-hour washout; 6 days in each period for DDI with a 96-hour washout	Food effect: Alo 100 fasted Alo 100 fed DDI (Met arm): Alo 100 QD, Met 1000 BID, and Alo 100

	DDI: Met and cimetidine			QD+Met 1000 BID DDI (cimetidine arm): Alo 100 QD, cimetidine 400 QD, and Alo 100 QD+cimetidine 400 QD
Phase 3				
SYR-322-MET-008 (MET-008) Add-on to Met	Randomized, double-blind, placebo-controlled, 3 treatment arm Efficacy (HbA1c)	527 T2DM on Met	26 weeks	Alogliptin 12.5 + Met Alogliptin 25 + Met Placebo + Met
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 weeks	Alogliptin 25 + pioglit 30 Pioglitazone 45
SYR-322-MET-302 (MET-302) Alo+Met vs. Alo or Met	Randomized, double-blind, placebo-controlled Efficacy (HbA1c)	784 T2DM	26 weeks	Placebo Alo 12.5 BID Alo 25 QD Met 500 BID Met 1000 BID Alo 12.5+Met 500 BID Alo 12.5+Met 1000 BID
Safety Update				
SYR-322-305 (305) Alo+Met Vs. Glipizide+Met Interim Report	Randomized, double-blind, active-controlled Efficacy (HbA1c)	2638 T2DM randomized	52 weeks	Alo 12.5+Met Alo 25+Met Glipizide+Met
SYR-322-OLE-012 (OLE-012) Uncontrolled extension	Open-label extension of 7 controlled phase 3 studies of 26 weeks duration Safety	3320 T2DM	4 years	Alo 12.5 Alo 25
Japanese				
SYR-322/CCT-006 Add-on to Met	Phase 2/3, randomized, double-blind, placebo-controlled, parallel-group Efficacy (HbA1c)	288 Japanese T2DM on Met	24 weeks	Met 250 BID or TID postprandial with: Alo 12.5 preprandial Alo 25 preprandial Placebo
SYR-322/OCT-005-MET	Phase 2/3, long-term,	287 Japanese T2DM who	40 weeks	Alo 12.5+Met 250 BID or

Clinical Review
Valerie S. W. Pratt, M.D.
NDA 203-414
Alogliptin/metformin FDC

(b) (4)

Long-term safety	open-label extension of CCT-005 and CCT-006 Long-term safety	were in CCT-005 or CCT- 006		TID Alo 25+MET 250 BID or TID MET 250 BID or TID→Alo 12.5+Met 250 BID or TID MET 250 BID or TID→Alo 25+MET 250 BID or TID
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5.2 Review Strategy

The applicant submitted the following three completed, phase 3, placebo- or active-controlled studies. I previously reviewed studies MET-008 and OPI-004 under the alogliptin NDA and CR, respectively.

- MET-008: *A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of SYR-322 when used in combination with metformin in subjects with T2DM*
- 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 pioglitazone HCl therapy*
- MET-302: *A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of alogliptin plus metformin, alogliptin alone, or metformin alone in subjects with T2DM*

A CV study was not submitted nor is required under alogliptin/metformin FDC NDA 203-414, although one is being conducted under alogliptin NDA 22-271. See my review of the alogliptin CR for a discussion of the interim results of CV study 402 as well as section 3.1 Submission Quality and Integrity.

As studies MET-008 and OPI-004 were previously reviewed, my efficacy review focuses on the HbA1c results of study MET-302.

Due to the differences in background therapies, treatment groups, and lengths of exposure in studies MET-008, OPI-004, and MET-302, the agency agreed with the applicant on April 5, 2011 that the safety data would not be pooled but summarized individually by study. As MET-008 and OPI-004 were previously reviewed under alogliptin NDA 22-271, my safety review focused on MET-302 as well as one-year interim data from study 305 and relevant postmarketing reports from the Four-Month Safety Update. I did not focus on the following two components of the Four-Month Safety Update for the reasons listed, although I described findings that were obscured by pooling and key safety information (e.g., liver events and hypoglycemia)

- Japanese PSUR 3 was previously reviewed under the alogliptin CR.
- Study OLE-012 was uncontrolled and evaluated the long-term safety of alogliptin 12.5 and 25 mg with or without concomitant antidiabetic agents (e.g. metformin).

See also my review alogliptin hepatotoxicity in the second alogliptin resubmission.

5.3 Discussion of Individual Studies/Clinical Trials

As phase 3 studies MET-008 and OPI-004 were previously reviewed under NDA 22-271, only study MET-302 is reviewed here.

SYR-322-MET-302: A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of alogliptin plus metformin, alogliptin alone, or metformin alone in subjects with T2DM (Amendment 1)

Study phase and dates conducted: This phase 3 study was conducted from November 16, 2009 through June 30, 2011.

Objectives:

Primary: To evaluate the efficacy of combination of alogliptin BID plus metformin BID as compared with alogliptin BID alone or metformin BID alone on HbA1c change from Baseline at Week 26 (or at time of discontinuation of double-blind study medication or hyperglycemic rescue).

Secondary:

- To evaluate the efficacy comparison between alogliptin BID alone and alogliptin QD alone on HbA1c change from Baseline at Week 26.
- To evaluate other measures of glycemic control including change from Baseline of fasting plasma glucose at all visits and HbA1c at visits other than Week 26.

Study design: This international, multicenter, randomized, double-blind, placebo-controlled, phase 3 study had a total of seven treatment arms, including placebo, alogliptin alone (12.5 mg BID and 25 mg QD), metformin alone (500 and 1000 mg BID), and the combination of alogliptin plus metformin (12.5 mg/500 mg BID and 12.5 mg/1000 mg BID). The study enrolled subjects with T2DM whose glycemia was inadequately controlled on diet and exercise alone for at least two months prior to Screening and who had an HbA1c concentration between 7.5% and 10.0%, inclusive, at Screening.

The total study duration was approximately 34 weeks, including a Screening Period (≤ 2 weeks), a Placebo Run-in/Stabilization Period (4 weeks), a Double-Blind Treatment Period (26 weeks), and a Follow-Up Period (2 weeks) after the End-of-Study or Early Termination Visit. After Screening, eligible subjects entered a 4-week Placebo Run-In/Stabilization Period during which they received dietary and exercise coaching and home glucose monitoring training along with placebo run-in study drug. Compliance with the study drug regimen was documented throughout the study. Subjects who were less than 75% or more than 125% compliant with the single-blind placebo regimen during the Placebo Run-in/Stabilization Period were not randomized.

Subjects were randomly assigned to one of the seven treatment arms described above and received double-blinded study medication from Day 1 through Week 26 (or Early Termination). Subjects who met protocol-defined rescue criteria for hyperglycemia

continued with assigned double-blind study medication, while sulfonylurea was added as a rescue therapy; the specific type and dose of sulfonylurea was determined by the investigator. These subjects continued in the study following hyperglycemic rescue and returned for all protocol-required study visits and procedures. For subjects who required hyperglycemic rescue but sulfonylurea was contraindicated and/or deemed as inappropriate by the investigator, double-blind study medication was discontinued, and rescue medications were prescribed at the investigator's discretion; these subjects also continued in the study and returned for all protocol-required study visits and procedures. An independent DMC periodically reviewed study safety data, and an independent CV event adjudication committee was established to blindly review and adjudicate all deaths, all serious and selected nonserious potential CV events.

Table 1. MET-302: Study design

	Screening Period	Placebo Run-in/ Stabilization Period		Double-blind Treatment Period (Weeks 1-26 After Randomization)								End-of-Study/ Early Termination	Follow-up Period
Week	-6 to -5	-4	-1	Baseline Visit (Day 1)	1	2	4	8	12	16	20	26	28
Beginning Day		-28	-7	1	8	15	29	57	85	113	141	183	197
Window		±2	±2		±2	±2	±2	±7	±7	±7	±7	±7	±7

Source: Protocol MET-302 Figure 6.a

Table 2. MET-302: Study schedule

	Screen- ing Period (a)	Placebo Run-in/ Stabilization (Weeks -4 to -1)		Double-blind Treatment Period (Weeks 1-26 After Randomization)								End-of- Study/ Early Termi- nation	Follow- up Period
Assessment	Week - 6 to -5	-4	-1	Baseline Visit (Day 1)	1	2	4	8	12	16	20	26	28
Beginning Day		-28	-7	1	8	15	29	57	85	113	141	183	197
Window		±2	±2		±2	±2	±2	±7	±7	±7	±7	±7	±7
Informed consent	X												
Inclusion/exclusion	X		X										
Demographics; Medical history (including medication history) concurrent medical conditions	X												
8-hour fast	X		X	X	X	X	X	X	X	X	X	X	
Diabetes education (b)		X	X	X	X								
Randomization				X									
Complete physical examination	X			X					X			X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and waist circumference	X (c)			X					X			X	
Height and BMI	X												
12-lead ECG	X			X					X			X	
Issue glucometer		X											
Issue subject diary		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	
Review concomitant medications and AEs		X	X	X	X	X	X	X	X	X	X	X	X
Hematology, serum chemistry (including fasting plasma glucose)	X		X(d)	X	X(e)	X	X	X	X	X	X	X	
Lipid panel	X			X			X	X	X	X	X	X	
Urinalysis	X			X					X			X	
Proinsulin				X					X			X	
Insulin				X					X			X	
HOMA BCF				X					X			X	
HbA1c	X		X(d)	X			X	X	X	X	X	X	
C-peptide	X												

	Screening Period (a)	Placebo Run-in/ Stabilization (Weeks -4 to -1)		Double-blind Treatment Period (Weeks 1-26 After Randomization)								End-of-Study/ Early Termination	Follow-up Period
Assessment	Week -6 to -5	-4	-1	Baseline Visit (Day 1)	1	2	4	8	12	16	20	26	28
Beginning Day		-28	-7	1	8	15	29	57	85	113	141	183	197
Window			±2		±2	±2	±2	±7	±7	±7	±7	±7	±7
hsCRP				X					X			X	
Serum pregnancy test (f)	X						X		X			X	
Urine pregnancy test (f)				X									
Access IVRS/TWRS	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense placebo run-in study drug via IVRS/TWRS		X	X(g)										
Dispense blinded medication drug via IVRS/TWRS				X	X (g)	X (g)	X	X	X	X	X		
Document drug accountability (h)			X	X	X	X	X	X	X	X	X	X	
2-hour PPG test (at selected sites)				X					X			X	
Serum amylase and lipase (i)				X									

(a) The screening visit will be scheduled within the 2 weeks prior to the start of the placebo run-in/stabilization period. During the placebo run-in / stabilization period, subjects will visit the study center weekly at the start of Weeks -4, and -1 prior to randomization. Subjects will be randomized on Day 1 (Baseline) of the 26-week treatment period.

(b) Subjects will be instructed on proper nutrition and exercise, how to recognize signs and symptoms of hypoglycemia, and the use of the glucometer. Each center should provide guidance in accordance with its standard of care for subjects with diabetes.

(c) Body weight assessment only.

(d) HbA1c and fasting plasma glucose only. HbA1c concentration should be between 7.5% and 10.0%, inclusive, and a fasting plasma glucose <310 mg/dL (17.5 mmol/L) at Week -1 to qualify for randomization. If this criterion is not met, the assessment may be repeated on a weekly basis, for a maximum of 2 additional weeks).

(e) Fasting plasma glucose only.

(f) Women of childbearing potential only.

(g) At Week -1, Week 1 and Week 2, drug will be re-dispensed.

(h) At Weeks -4 to Week -1, drug accountability will be performed for the placebo run-in medication. At Baseline, Week 1, 2, 4, 8, 12, 16, 20, and 26, drug accountability will be performed for the blinded study medication.

(i) Serum amylase and lipase should be measured for all subjects at baseline, and in subjects with persistent (>=3 days) nausea and/or vomiting with or without abdominal pain at unscheduled visits. If results are abnormal this testing should be repeated twice at a minimum.

Source: Protocol MET-302 Appendix A

Inclusion criteria:

1. Male or female subjects, 18 to 80 years of age, with a historical diagnosis of T2DM.
2. The subject has been treated with diet and exercise for at least 2 months prior to Screening and has an HbA1c concentration between 7.5% and 10.0%, inclusive at Screening.
3. The subject has received less than 7 days of any antidiabetic medication within 2 months prior to Screening.

4. Body mass index (BMI) $\geq 23 \text{ kg/m}^2$ and $\leq 45 \text{ kg/m}^2$ (except for Asian or Asian descendant subjects for whom the range is between 20 and 35 kg/m^2 , inclusive).
5. Fasting C-peptide concentration $\geq 0.8 \text{ ng/mL}$ ($\geq 0.26 \text{ nmol/L}$).
6. Subjects regularly using other, nonexcluded, medications must be on a stable dose for at least the 4 weeks prior to Screening; however, PRN (as needed) use of prescription or over-the-counter medications is allowed at the discretion of the investigator.
7. A female subject of childbearing potential and males who are sexually active agree to routinely use adequate contraception from Screening throughout the duration of the study. NOTE: Women NOT of childbearing potential are defined as those who have been surgically sterilized (i.e., hysterectomy, bilateral salpingo-oophorectomy, bilateral tubal ligation) or who are postmenopausal (defined as at least 45 years of age AND 1 year since last regular menses).
8. Subject is able and willing to monitor their own blood glucose concentrations with a home glucose monitor and complete subject diaries.
9. Subject is able and willing to provide written informed consent.
10. The subject is capable of understanding and complying with the protocol requirements, including scheduled clinic appointments.

Exclusion criteria:

1. Hemoglobin $\leq 12 \text{ g/dL}$ ($\leq 120 \text{ gm/L}$) for males and $\leq 10 \text{ g/dL}$ ($\leq 100 \text{ gm/L}$) for females at Screening Visit.
2. Subject has a history of any hemoglobinopathy that may affect determination of HbA1c.
3. Subject has a history of laser treatment for proliferative diabetic retinopathy within the 6 months prior to Screening.
4. Subject has a history of treatment for diabetic gastric paresis, gastric banding, or gastric bypass surgery.
5. Subject has a history of diabetic ketoacidosis or hyperosmolar non-ketotic coma.

6. Subject has systolic blood pressure ≥ 150 mmHg and /or diastolic pressure ≥ 90 mmHg at Screening visit.
7. Subject has New York Heart Association (NYHA) Class III to IV heart failure regardless of therapy. (Currently treated subjects who are stable at NYHA Class I or II are candidates for the study.)
8. Subject has a history of coronary angioplasty, coronary stent placement, coronary bypass surgery, or myocardial infarction within the 90 days prior to Screening.
9. Alanine aminotransferase (ALT) $> 3\times$ upper limit of normal at Screening.
10. Subject has a history of alcohol or substance abuse with the 2 years prior to Screening.
11. Serum creatinine ≥ 1.5 mg/dL for males or ≥ 1.4 mg/dL for females, or creatinine clearance < 60 mL/min based on calculation by central lab using the MDRD approximation at Screening.
12. Subject has 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 cervical intraepithelial neoplasia [CIN] I or CIN II is allowed.)
13. Subject has a history of infection with human immunodeficiency virus, hepatitis B virus, or hepatitis C virus.
14. Subject has any major illness or debility that in the investigator's opinion prohibits the subject from completing the study.
15. Subject has received any investigational drug within the 90 days prior to Screening.
16. Subject has a history of hypersensitivity or allergy to alogliptin, other DPP-4 inhibitors, metformin, or related compounds.
17. If female, the subject is pregnant or lactating or intending to become pregnant during or within 1 month after participating in this study.
18. The subject is unable to understand verbal or written English, or any other language for which a certified translation of the approved informed consent is available.

19. 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.

20. Subject has used oral or systemically injected glucocorticoids (including intra-articular injection) or use of weight-loss drugs within 2 months prior to screening. (Inhaled or topical corticosteroids are allowed.)

Treatments and management: The total study duration was ~34 weeks, including a ≤2 week Screening period, 4 week Placebo Run-in/Stabilization period, 26 week Double-blind Treatment period, and 2 week Follow-up period. Subjects were randomly assigned to one of the following seven oral treatments:

- Placebo
- Alogliptin 12.5 mg BID
- Alogliptin 25 mg QD
- Metformin 500 mg BID
- Metformin 1000 mg BID
- Alogliptin 12.5/metformin 500 mg BID
- Alogliptin 12.5/metformin 1000 mg BID

Treatment with any antidiabetic agents was not allowed within the two months prior to Screening, unless the treatment was received for less than seven days.

Hyperglycemic rescue criteria: Randomized subjects were rescued if any of the following criteria were met:

- After more than one week 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.

See Study Design (above) for a description of the hyperglycemic rescue therapy.

Hypoglycemic criteria: Hypoglycemia was defined as follows:

- Mild to moderate:
 - o Documented symptomatic hypoglycemia defined as plasma glucose <70 mg/dl in the presence of symptoms, or
 - o Asymptomatic hypoglycemia defined as plasma glucose <70 mg/dl without symptoms
- Severe: Any episode requiring the assistance of another person to actively administer carbohydrate, glucagons, 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)

Excluded medications: Treatment with any antidiabetic agents was not allowed within the two months prior to Screening, unless a subject received other diabetic therapy for less than seven days within the two months prior to Screening. No antidiabetic agent was allowed in the four-week placebo run-in period. Unless a subject discontinued double-blind study medication, no antidiabetic agent other than the study medications (i.e., alogliptin and metformin) and sulfonylurea (if the subject required hyperglycemic rescue) was allowed from randomization through the completion of the end-of-treatment/early termination procedures.

Treatment with weight-loss drugs, oral or systemically injected glucocorticoids (including intra-articular injection) was not allowed from two months prior to screening, during the placebo run-in period and through the completion of the end-of-treatment/early termination procedures. Inhaled or topical corticosteroids were not allowed.

Liver safety withdrawal criteria: Study medication was interrupted and an inquiry about symptoms made if the following occurred:

- ALT or AST >8x ULN, or
- ALT or AST ≥3x ULN in conjunction with total bilirubin >2x ULN

If the subject experienced symptoms or if the abnormal liver test was confirmed within seven days, study medication was discontinued.

Study medication was discontinued and appropriate clinical follow up initiated if the following occurred:

- ALT or AST >5x ULN for more than two weeks, or
- ALT or AST ≥3x ULN with fatigue, nausea, vomiting, upper right quadrant tenderness, fever, rash or eosinophilia

Renal safety withdrawal criteria: If a subject did not have renal impairment at screening and randomization, but later developed renal impairment that was confirmed by a second test by the central laboratory (i.e., serum creatinine ≥ 1.5 mg/dL for males or ≥ 1.4 mg/dL for females; AND creatinine clearance < 60 mL/min, based on calculation by the central laboratory using the MDRD approximation.), the subject discontinued study medication. The central laboratory calculated these values at the same visits when a full laboratory panel was performed. If a subject's calculated creatinine clearance indicated moderate or severe renal impairment, a laboratory alert notified the site to discontinue the double-blind study medication.

Pancreatitis monitoring and withdrawal criteria: Subjects were urged to make an appointment for an unscheduled visit if she or he experienced persistent nausea and/or vomiting for ≥ 3 days with or without abdominal pain. Investigations, including serum amylase and lipase, should have been performed in order to establish the diagnosis. Study drug should have been interrupted immediately if the following occurred:

- Pancreatitis was suspected, or
- Serum amylase ≥ 2 x ULN, or
- Serum lipase ≥ 2 x ULN

The enzyme tests should have been repeated within seven days after the first sample and appropriate imaging tests performed. Subjects should have been followed until resolution. If pancreatitis was confirmed, study drug should not have been restarted.

Discontinuation criteria: See also sections 3.2 Compliance with Good Clinical Practices and 6.1.3 Subject Disposition.

- Loss to follow up
- Voluntary withdrawal
- Study termination
- Pregnancy

Study sites including enrollment: A total of 198 study sites worldwide screened 2478 subjects. A total of 784 subjects were enrolled (FAS 768 subjects; PPS 586 subjects) in the seven treatment groups.

A total of 105 subjects per treatment group ensured at least 90% power to declare that either of the BID combinations of alogliptin and metformin was statistically superior to its constituent doses of alogliptin and metformin. This power calculation assumed a treatment effect of 0.55% between a BID combination and its constituent doses, an SD of 1.0%, and a 2-sided false-rejection rate of 2.5% for both comparisons between a BID combination and its constituent doses.

Alternatively, this sample size provided 90% power to detect a treatment effect of approximately 0.45% between any pair of treatment groups, assuming an SD of 1.0% and a 2-sided false-rejection rate of 5%.

Efficacy (exposure/response) assessments:

Primary: HbA1c change from Baseline at Week 26 (or at time of discontinuation of double-blind study medication or hyperglycemic rescue).

Secondary:

- Change from Baseline in HbA1c at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in fasting plasma glucose at Weeks 1, 2, 4, 8, 12, 16, 20, and 26.

Safety assessments: Safety variables included AEs, hypoglycemic events, clinical laboratory parameters, vital signs, physical examinations, and ECG readings.

6 Review of Efficacy

Efficacy Summary

The proposed indication is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

The applicant submitted the following three completed, phase 3, placebo- or active-controlled studies. As I previously reviewed studies MET-008 and OPI-004 under the alogliptin NDA and CR, respectively, this efficacy review focuses on MET-302.

- MET-008: *A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of SYR-322 when used in combination with metformin in subjects with T2DM*
- 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 pioglitazone HCl therapy*
- MET-302: *A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of alogliptin plus metformin, alogliptin alone, or metformin alone in subjects with T2DM*

In the 26-week trial MET-008, which compared alogliptin administered with metformin to metformin alone, the difference in adjusted mean change in HbA1c was -0.5% (95% CI: -0.7, -0.3).

In the 52-week trial OPI-004, which compared the addition of alogliptin 25 mg versus dose titration from 30 mg to 45 mg pioglitazone in subjects who were inadequately controlled on metformin and pioglitazone 30 mg, the LS mean treatment difference between the metformin + alogliptin 25 mg + pioglitazone 30 mg and metformin + pioglitazone 45 mg groups was -0.4% (97.5% CI: -0.3). 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.

In MET-302, the mean age of subjects was 53.5 years. The majority of subjects were female (52.3%), white (71.6%), had a mean BMI of 30.7, and a mean diabetes duration of 4 years. There was slight variability in the rates of study drug and visit discontinuation (and the associated reasons for discontinuation) between treatment groups. Although a clinically relevant trend in discontinuations was not observed, amendment 1's revisions to the reasons for study drug and visit discontinuation complicate this analysis.

The primary endpoint in trial MET-302 was the change from baseline in HbA1c at week 26 (or at time of discontinuation of study medication or hyperglycemic rescue). The baseline HbA1c was similar between the placebo, alogliptin, metformin, and A+M treatment groups (8.3 – 8.5%). At week 26, the LS mean change from baseline was significantly greater with both coadministration regimens (-1.2% and -1.6% with A12.5+M500 BID and A12.5+M1000 BID, respectively) when compared to alogliptin (-0.5% with A12.5 BID) and metformin (-0.7% and -1.1% with M500 and M1000 BID, respectively). Supportive analyses with the PPS and comparison to placebo were consistent with the FAS analysis, as were secondary analyses of the change in FPG and HbA1c from baseline over time.

As discussed in section 3.1 Submission Quality and Integrity, the applicant identified 13 subjects who enrolled at two or more study sites and ten subjects who enrolled both in study MET-302 and ongoing study 305. The Division concurs with the determinations made concerning the status of each replicate enrollment in the FAS, PPS, and safety set as documented by the applicant in Appendix 16.2.4.5.

6.1 Indication

The proposed indication is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

6.1.1 Methods

The applicant submitted the following three completed, phase 3, placebo- or active-controlled studies. As studies MET-008 and OPI-004 were previously reviewed under the alogliptin NDA and CR, respectively, this review focuses on the primary and key secondary endpoints of MET-302.

- MET-008: *A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of SYR-322 when used in combination with metformin in subjects with T2DM*
- 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 pioglitazone HCl therapy

- MET-302: A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of alogliptin plus metformin, alogliptin alone, or metformin alone in subjects with T2DM

6.1.2 Demographics

The demographics of the randomized population in study MET-302 are shown in Table 3. The mean age in the trial was 53.5 years. The majority of subjects were female (52.3%), white (71.6%), had a mean BMI of 30.7, and a mean diabetes duration of 4 years. The treatment groups were generally similar to each other in the distribution of these demographics. The study population was ethnically diverse, as 198 study sites were included worldwide.

Table 3. MET-302: Demographics (Randomized set)

Characteristic	P1b (n=109)	A25 QD (n=112)	A12.5 (n=113)	M500 BID (n=114)	M1000 BID (n=111)	A12.5+M 500 BID (n=111)	A12.5+M 1000 (n=114)
Age (mean years [SD])	53.1 (9.6)	52.6 (9.4)	53.7 (9.7)	54.6 (10.2)	52.6 (11.3)	53.7 (11.6)	54.6 (10.4)
Gender (male n [%])	55 (50.5)	48 (42.9)	63 (55.8)	47 (41.2)	51 (45.9)	48 (43.2)	62 (54.4)
BMI (mean [SD])	31.1 (5.3)	30.8 (5.2)	30.4 (5.6)	30.2 (4.8)	30.5 (5.0)	30.9 (5.4)	31.0 (5.4)
HbA1c (mean [SD])	8.5 (0.7)	8.3 (0.8)	8.4 (0.7)	8.5 (0.8)	8.4 (0.7)	8.5 (0.8)	8.4 (0.7)
Duration of DM (years mean [SD])	4.2 (4.8)	3.7 (4.1)	4.0 (4.8)	3.8 (3.9)	4.0 (4.6)	4.1 (4.8)	4.2 (5.0)
Race							
American Indian or Alaska Native	5 (4.6)	8 (7.1)	5 (4.4)	3 (2.6)	6 (5.4)	9 (8.1)	5 (4.4)
Asian	20 (18.3)	17 (15.2)	21 (18.6)	19 (16.7)	20 (18.0)	20 (18.0)	26 (22.8)
Black or African American	8 (7.3)	3 (2.7)	3 (2.7)	6 (5.3)	6 (5.4)	6 (5.4)	5 (4.4)
Native Hawaiian or Pacif Isl	0	0	1 (0.9)	0	0	0	0
White	76 (69.7)	84 (75.0)	83 (73.5)	85 (74.6)	79 (71.2)	76 (68.5)	78 (68.4)
Multiracial	0	0	0	1 (0.9)	0	0	0
Ethnicity (Hispanic n [%])	45 (41.3)	43 (38.4)	43 (38.1)	45 (39.5)	42 (37.8)	45 (40.5)	39 (34.2)

Source: CSR MET-302 Table 11.c

6.1.3 Subject Disposition

A total of 784 subjects were randomized in study MET-302; 609 (77.7%) completed the trial. The number of subjects in each of the seven treatment groups was similar (n=109-114), as was the percentage of subjects in each group that completed treatment (62.8-85.6%).

The reasons for study drug discontinuation were modified in protocol amendment 1, which incorporated hyperglycemic rescue criteria at the request of the Agency. In the original protocol, all study drug discontinuations that resulted from hyperglycemic rescue were captured under “lack of efficacy”. In Amendment 1, “lack of efficacy” was removed from the list of reasons for discontinuation.

The rate of discontinuation of study drug ranged from 14.4 - 37.2%. The rate of drug discontinuation in most alogliptin and metformin treatment groups was 14.4 - 22.3%, although the A12.5 BID group’s rate was 37.2%. This exceeded the placebo discontinuation rate (32.1%), which was mostly due to voluntary withdrawal (11.9%) and lack of efficacy (8.3). The rate of drug discontinuation due to AEs ranged from 1.8% (M1000 mg BID) to 9.6% (A12.5+M1000 mg BID).

The reasons for study visit discontinuation were also revised in Amendment 1. In the original protocol, there were 9 possible reasons for visit discontinuation. Amendment 1 limited the reasons to “lost to follow up”, “voluntary withdrawal”, “study termination”, and “pregnancy”.

The rates of study visit discontinuation were similar to the rates of drug discontinuation (i.e. 14.4% - 29.4%). The incidence of AEs which lead to visit discontinuation ranged from 0.0% (placebo) – 7.0% (A12.5+M1000 mg BID).

The incidence of major protocol deviations was low (i.e. 0.0% - 2.7%) in both discontinuation groups.

In summary, there was slight variability in the rates of study drug and visit discontinuation (and the associated reasons for discontinuation) between treatment groups. Although a clinically relevant trend in discontinuations was not observed, amendment 1’s revisions to the reasons for study drug and visit discontinuation complicate this analysis.

Table 4. MET-302: Subject disposition

	PIb (n=109)	A25 QD (n=112)	A12.5 (n=113)	M500 BID (n=114)	M1000 BID (n=111)	A12.5+M 500 BID (n=111)	A12.5+M 1000 (n=114)
Randomized (n)	784						
Total completed	609 (77.7)						

(n, %)							
Total discontinued (n, %)	175 (22.3)						
Received study medication (FAS n)	109	112	113	114	111	111	114
Completed (n, % of treated)	74 (67.9)	89 (79.5)	71 (62.8)	94 (82.5)	95 (85.6)	92 (82.9)	94 (82.5)
Discontinued study drug (n, % of treated)	35 (32.1)	23 (20.5)	42 (37.2)	20 (17.5)	16 (14.4)	19 (17.1)	20 (17.5)
Adverse event	4 (3.7)	4 (3.6)	7 (6.2)	3 (2.6)	2 (1.8)	5 (4.5)	11 (9.6)
Maj proto dev	2 (1.8)	0	3 (2.7)	0	0	0	0
Lost to follow up	4 (3.7)	8 (7.1)	7 (6.2)	2 (1.8)	5 (4.5)	2 (1.8)	2 (1.8)
Vol withdrawal	13 (11.9)	8 (7.1)	16 (14.2)	10 (8.8)	6 (5.4)	8 (7.2)	5 (4.4)
Study termin	0	0	0	0	0	0	0
Pregnancy	0	0	0	2 (1.8)	0	1 (0.9)	0
Lack of efficacy	9 (8.3)	3 (2.7)	6 (5.3)	2 (1.8)	1 (0.9)	2 (1.8)	1 (0.9)
PI discretion	2 (1.8)	0	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
Other	1 (0.9)	0	1 (0.9)	0	1 (0.9)	0	0
Discontinued visits (n, % of treated)	32 (29.4)	23 (20.5)	39 (34.5)	20 (17.5)	16 (14.4)	19 (17.1)	20 (17.5)
Adverse event	0	3 (2.7)	4 (3.5)	2 (1.8)	2 (1.8)	3 (2.7)	8 (7.0)
Maj proto dev	1 (0.9)	0	1 (0.9)	0	0	0	0
Lost to follow up	4 (3.7)	8 (7.1)	7 (6.2)	2 (1.8)	5 (4.5)	3 (2.7)	2 (1.8)
Vol withdrawal	17 (15.6)	9 (8.0)	18 (15.9)	11 (9.6)	6 (5.4)	9 (8.1)	8 (7.0)
Study termin	0	0	1 (0.9)	0	0	0	0
Pregnancy	0	0	0	2 (1.8)	0	1 (0.9)	0
Lack of efficacy	9 (8.3)	3 (2.7)	6 (5.3)	2 (1.8)	1 (0.9)	2 (1.8)	1 (0.9)
PI discretion	1 (0.9)	0	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
Other	0	0	1 (0.9)	0	1 (0.9)	0	0

Source: CSR MET-302 Figure 10.a and Table 10.a

6.1.4 Analysis of Primary Endpoint(s)

In the 26-week trial MET-008, which compared alogliptin administered with metformin to metformin alone, the difference in adjusted mean change in HbA1c was -0.5% (95% CI: -0.7, -0.3).

In the 52-week trial OPI-004, which compared the addition of alogliptin 25 mg versus dose titration from 30 mg to 45 mg pioglitazone in subjects who were inadequately controlled on metformin and pioglitazone 30 mg, the LS mean treatment difference between the metformin + alogliptin 25 mg + pioglitazone 30 mg and metformin + pioglitazone 45 mg groups was -0.4% (97.5% CI: -0.3).

The primary endpoint in trial MET-302 was the change from baseline in Hb1c at week 26 (or at time of discontinuation of study medication or hyperglycemic rescue). The primary analysis included the statistical comparison of the coadministration regimens to their individual components: A12.5+M500 BID vs. A12.5 BID alone and vs. M500 BID alone; and A12.5+M1000 BID vs. A12.5 BID alone and M1000 BID alone. The primary analysis was conducted using FAS data that was collected on or after baseline and within seven days after the last dose of double-blind study medication unless a subject was rescued for hyperglycemia, in which case only data collected on or prior to the date of rescue was used. At each visit, the endpoint was analyzed using the value collected at that visit or the last prior postbaseline value, if the value at that visit was unavailable (Analysis 1a).

The baseline HbA1c was similar between the placebo, alogliptin, metformin, and A+M treatment groups (8.3 – 8.5%). At week 26, the LS mean change from baseline was significantly greater with both coadministration regimens (-1.2% and -1.6% with A12.5+M500 BID and A12.5+M1000 BID, respectively) when compared to alogliptin (-0.5% with A12.5 BID) and metformin (-0.7% and -1.1% with M500 and M1000 BID, respectively). Supportive analysis with the PPS was consistent with the FAS analysis. See Table 5.

Another supportive analysis compared both coadministration regimens versus placebo. Both coadministration regimens resulted in significantly greater LS mean change from baseline in HbA1c at week 26 (-1.2% and -1.6% with A12.5+M500 BID and A12.5+M1000 BID, respectively) when compared with placebo (0.2%).

Table 5. ME-302: Primary analysis of HbA1c (%) changes from baseline at week 26 (FAS and PPS, Analysis 1a)

Treatment	N	Mean Baseline HbA1c (SD)	LS Mean Change (SE)	LS Mean Difference	1-sided 97.5% CI
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FAS					
Placebo	106	8.5 (0.7)	0.2 (0.1)		
A25 QD	112	8.3 (0.8)	-0.5 (0.1)		
A12.5 BID	110	8.4 (0.7)	-0.6 (0.1)	Versus A12.5+M500 BID: -0.7 Versus A12.5+M1000 BID: -1.0	Versus A12.5+M500 BID: (-0.96, -0.37) Versus A12.5+M1000 BID: (-1.29, -0.71)
M500 BID	109	8.5 (0.8)	-0.7 (0.1)	Versus A12.5+M500 BID: -0.6	Versus A12.5+M500 BID: (-0.87, -0.27)
M1000	111	8.4 (0.7)	-1.1 (0.1)	Versus A12.5+M1000 BID: -0.4	Versus A12.5+M1000 BID: (-0.73, -0.16)
A12.5+M500 BID	106	8.5 (0.8)	-1.2 (0.1)	Versus placebo: -1.4	Versus placebo: (-1.63, -1.11)
A12.5+M1000 BID	114	8.4 (0.7)	-1.6 (0.1)	Versus placebo: -1.7	Versus placebo: (-1.96, -1.45)
PPS					
Placebo	84	8.4 (0.7)			
A25 QD	85	8.3 (0.8)			
A12.5 BID	70	8.5 (0.7)	-0.5 (0.1)	Versus A12.5+M500 BID: -0.8 Versus A12.5+M1000 BID: -1.2	Versus A12.5+M500 BID: (-1.12, -0.41) Versus A12.5+M1000 BID: (-1.54, -0.83)
M500 BID	82	8.6 (0.8)	-0.8 (0.1)	Versus A12.5+M500 BID: -0.5	Versus A12.5+M500 BID: (-0.87, -0.19)
M1000	90	8.4 (0.7)	-1.1 (0.1)	Versus A12.5+M1000 BID: -0.6	Versus A12.5+M1000 BID: (-0.91, -0.25)
A12.5+M500 BID	84	8.6 (0.8)	-1.3 (0.1)		
A12.5+M1000 BID	88	8.5 (0.7)	-1.7 (0.1)		

Source: CSR ME-302 Table 11.h, Table 15.2.1.2.1, Table 15.2.1.6.1, and Table 11.i.

Please also refer to Janice Derr's July 17, 2012 review which describes superior efficacy of alogliptin co-administered with metformin compared to either alogliptin or metformin alone.

6.1.5 Analysis of Secondary Endpoints(s)

The only secondary endpoint in study MET-302 related to the effect of coadministration of alogliptin and metformin on glycemic control was the change from baseline in FPG at all visits and HbA1c at visits other than week 26.

The change from baseline in FPG was assessed at weeks 1, 2, 4, 8, 12, 16, 20, and 26. Baseline FPG was similar between treatment groups (176 – 187 mg/dl). The LS mean changes from baseline in FPG at weeks 26 were significantly greater with both coadministration regimens (-32 and -46 mg/dl with A12.5+M500 Bid and A12.5+M1000 BID, respectively) when compared to alogliptin (-10 mg/dl with A12.5 BID) or metformin (-12 and -32 mg/dl with M500 and M1000 BID, respectively) alone. Significant differences were also observed with coadministration regimens versus placebo (12 mg/dl). This trend was observed at all time points throughout the study, except for A12.5+M1000 BID versus M1000 BID at week 20 (p=0.114).

Table 6. MET-302: FPG (mg/dl) changes from baseline at week 26 (FAS, Analysis 1a)

Time Point Statistics	Treatment						
	Placebo (N=106)	A25 QD (N=112)	A12.5 BID (N=110)	M500 BID (N=109)	M1000 BID (N=111)	A12.5 + M500 BID (N=106)	A12.5 + M1000 BID (N=114)
Baseline, mg/dL							
n	105	112	106	106	110	106	112
Mean (SD)	186.5 (44.88)	177.6 (52.32)	177.0 (43.27)	180.4 (49.55)	181.3 (52.24)	175.8 (50.77)	184.5 (50.22)
Median (range)	183.0 (103-344)	169.5 (75-357)	170.0 (83-343)	175.5 (102-382)	169.0 (89-361)	161.0 (72-340)	181.5 (89-357)
Week 26 CFB, mg/dL							
n	105	112	106	106	110	106	112
LS mean (SE)	12.4 (4.52)	-6.1 (4.37)	-9.7 (4.49)	-11.5 (4.49)	-31.9 (4.41)	-31.7 (4.49)	-45.9 (4.37)
Coadministration regimens vs components							
Comparison vs A12.5 + M500 BID							
LS mean difference (95% CI) (a)			-22.1 (-34.5, -9.6)	-20.2 (-32.7, -7.7)			
p-value			<0.001	0.002			
Comparison vs A12.5 + M1000 BID							
LS mean difference (95% CI) (a)			-36.2 (-48.5, -23.9)		-14.0 (-26.2, -1.8)		
p-value			<0.001		0.025		

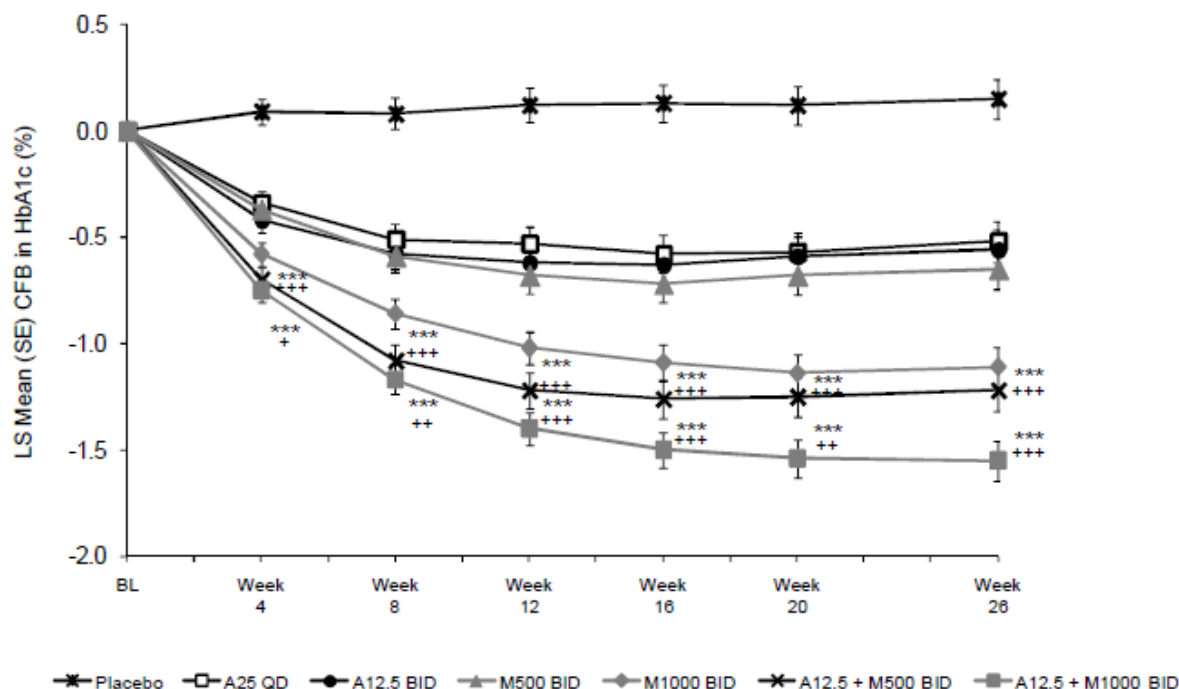
Source: Tables 15.2.2.1.1, 15.2.2.2.1, and 15.2.2.3.1.

Note: The LS means, SEs, and CIs are derived from an ANCOVA model with treatment and geographic region as fixed effects and baseline FPG as a covariate.

(a) The LS mean differences, CIs, and p-values presented are for comparisons between the coadministration regimen and its respective components.

Source: CSR MET-302 Table 11.k

In study MET-302, the change in HbA1c from baseline to weeks 4, 8, 12, 16, and 20 was also assessed. Significant differences were observed from week 4 and continued throughout the study.



Source: Tables 15.2.1.1.1, 15.2.1.3.1, and 15.2.1.4.1.

*** p<0.001 vs corresponding alogliptin dose.

+ p<0.05, ++ p<0.01, +++ p<0.001 vs corresponding metformin dose.

Figure 1. Study MET-302: HbA1c changes from baseline over time (FAS, Analysis 1a)

Source: CSR MET-302 Figure 11.b

6.1.6 Other Endpoints

In study MET-302, exploratory endpoints related to glycemic control included the following:

- To evaluate other measures of glycemic control including clinically meaningful levels of response in HbA1c and time to hyperglycemic rescue
- To evaluate changes in pancreatic beta cell function, measured by changes from baseline in fasting proinsulin, insulin, proinsulin/insulin ratio, and HOMA-BCF
- To evaluate changes from baseline in 2-hour PPG at selected sites only

As HOMA-BCF is not a well-validated surrogate for insulin beta-cell function and the 2-hour PPG was only evaluated in a subset of subjects, those data are not reviewed here.

A significantly greater percentage of subjects achieved HbA1c <7.0% at week 26 with coadministration regimens (47.1% with A12.5+M500 BID and 59.5% with A12.5+M1000 BID) compared with the individual alogliptin and metformin regimens. A higher

percentage of subjects also achieved HbA1c <6.5% by week 26 (20.6% and 32.4% with A12.5+M500 BID and A12.5+M1000 BID, respectively) when compared to alogliptin (13.5%) or metformin (6.8% and 18.5% with M500 and M1000 BID, respectively) alone. The differences in the incidence of HbA1c <6.5% were significant except for the comparison of A12.5+M500 BID versus A12.5 BID (20.6% and 13.5%, respectively).

The incidence of hyperglycemic rescue was lowest in the A12.5+M1000 BID group (2.6%) and highest in the placebo group (38.7%). Both coadministration groups had significantly lower hyperglycemic rescue when compared to their component regimens. See Table 7.

Table 7. MET-302: Time to hyperglycemic rescue (FAS)

	Treatment						
	Placebo (N=106)	A25 QD (N=112)	A12.5 BID (N=110)	M500 BID (N=109)	M1000 BID (N=111)	A12.5 + M500 BID (N=106)	A12.5 + M1000 BID (N=114)
Incidence of rescue							
Overall, n/N (%)	41/106 (38.7)	22/112 (19.6)	19/110 (17.3)	25/109 (22.9)	12/111 (10.8)	13/106 (12.3)	3/114 (2.6)
Coadministration regimens vs components							
Comparison vs A12.5 + M500 BID							
Cox proportional hazards (a)							
Hazard ratio			0.476	0.402			
(95% CI)			(0.233, 0.970)	(0.205, 0.789)			
p-value			0.041	0.008			
Comparison vs A12.5 + M1000 BID							
Cox proportional hazards (a)							
Hazard ratio			0.112		0.216		
(95% CI)			(0.033, 0.380)		(0.061, 0.766)		
p-value			<0.001		0.018		

Source: Tables 15.2.3.1, 15.2.3.2, and 15.2.3.3.

Note: The Cox proportional hazards model includes an effect for treatment, a stratification factor for geographic region, and a covariate for baseline HbA1c. Hazard ratio, 95% CI, and p-value are presented for comparison between coadministration regimen and its respective components.

Source: CSR MET-302 Table 11.m

6.1.7 Subpopulations

In study MET-302, the applicant evaluated the change in HbA1c from baseline in the following subgroups:

- Baseline HbA1c ($\leq 8.5\%$, $> 8.5\%$)
- Sex (male and female)
- Age (< 65 , ≥ 65)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiracial)

- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline BMI (<30, ≥30)

Although no formal statistical testing was conducted for these subgroups, the groups generally achieved greater reductions in HbA1c with the coadministration regimen when compared to individual alogliptin or metformin therapy. One exception to this was that the greatest HA1c reduction in Black or African Americans was observed with M1000 BID (-1.4%). See Table 8.

Table 8. MET-302: HbA1c changes from baseline to week 26 by subgroup (FAS, Analysis 1a)

Subgroup	Mean Changes From Baseline in HbA1c (%) at Week 26 (n)						
	Placebo (N=106)	A25 QD (N=112)	A12.5 BID (N=110)	M500 BID (N=109)	M1000 BID (N=111)	A12.5 + M500 BID (N=106)	A12.5 + M1000 BID (N=114)
Baseline HbA1c							
≤8.5%	-0.02 (n=59)	-0.33 (n=70)	-0.33 (n=61)	-0.54 (n=62)	-0.85 (n=64)	-0.96 (n=61)	-1.26 (n=70)
>8.5%	0.33 (n=43)	-0.74 (n=34)	-0.88 (n=43)	-0.91 (n=41)	-1.43 (n=44)	-1.69 (n=41)	-2.03 (n=41)
Sex							
Male	0.02 (n=51)	-0.44 (n=44)	-0.78 (n=56)	-0.65 (n=44)	-1.13 (n=50)	-0.96 (n=45)	-1.58 (n=60)
Female	0.24 (n=51)	-0.48 (n=60)	-0.30 (n=48)	-0.71 (n=59)	-1.05 (n=58)	-1.48 (n=57)	-1.51 (n=51)
Age							
<65 years	0.15 (n=94)	-0.45 (n=95)	-0.56 (n=89)	-0.60 (n=87)	-1.10 (n=92)	-1.20 (n=84)	-1.56 (n=93)
≥65 years	-0.19 (n=8)	-0.63 (n=9)	-0.55 (n=15)	-1.14 (n=16)	-1.03 (n=16)	-1.49 (n=18)	-1.46 (n=18)
Race							
American Indian or Alaska Native	-0.40 (n=5)	-0.63 (n=8)	-0.40 (n=5)	0.63 (n=3)	-0.90 (n=6)	-1.24 (n=9)	-1.76 (n=5)
Asian	0.21 (n=19)	-0.78 (n=17)	-0.53 (n=19)	-0.97 (n=18)	-1.21 (n=20)	-1.17 (n=20)	-1.57 (n=25)
Black or African American	0.68 (n=8)	0.77 (n=3)	-0.80 (n=2)	-0.75 (n=6)	-1.40 (n=6)	-1.18 (n=6)	-1.08 (n=5)
Native Hawaiian or Other Pacific Islander	0	0	-0.90 (n=1)	0	0	0	0
White	0.08 (n=70)	-0.43 (n=76)	-0.56 (n=77)	-0.66 (n=75)	-1.05 (n=76)	-1.28 (n=67)	-1.55 (n=76)
Multiracial	0	0	0	-1.00 (n=1)	0	0	0
Ethnicity							
Hispanic or Latino	0.10 (n=41)	-0.34 (n=38)	-0.62 (n=37)	-0.62 (n=37)	-0.93 (n=40)	-1.22 (n=40)	-1.61 (n=37)
Not Hispanic or Latino	0.15 (n=61)	-0.54 (n=66)	-0.52 (n=67)	-0.72 (n=66)	-1.18 (n=68)	-1.27 (n=62)	-1.51 (n=74)
Baseline BMI							
<30	0.27 (n=50)	-0.60 (n=43)	-0.68 (n=59)	-0.80 (n=59)	-1.17 (n=58)	-1.22 (n=44)	-1.59 (n=55)
≥30	-0.01 (n=52)	-0.37 (n=61)	-0.39 (n=45)	-0.54 (n=44)	-1.00 (n=50)	-1.27 (n=58)	-1.51 (n=56)

Source: Tables 15.2.1.7.1 through 15.2.1.12.4.

Source: CSR MET-302 Table 11.o

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

At the April 5, 2011 pre-NDA meeting, the applicant proposed marketing alogliptin/metformin FDC doses containing a total daily dose of alogliptin (b) (4) 25 mg (i.e. 12.5/500 and 12.5/1000 mg BID).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See section 6.1.5 Analysis of Secondary Endpoints(s).

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

Due to the differences in background therapies, treatment groups, and lengths of exposure in studies MET-008, OPI-004, and MET-302, the agency agreed with the applicant on April 5, 2011 that the safety data would not be pooled but summarized individually by study. As MET-008 and OPI-004 were previously reviewed under alogliptin NDA 22-271, my safety review at times focused on MET-302 as well as one-year interim data from study 305 and relevant postmarketing reports.

Including Four-Month Safety Update data from ongoing study 305, a total of 2244 subjects have been exposed to alogliptin + metformin for ≥ 26 weeks. A total of 1255 subjects have been exposed for ≥ 52 weeks.

Key safety findings were as follows:

- The concomitant administration of alogliptin and metformin is not associated with an increased risk of death.
- The percentage of subjects with SAEs in alogliptin + metformin groups ranged from 1.8% (A12.5+M1000BID in study MET-302) to 6.5% (A25+M in study 305).
- Discontinuation due to AEs with alogliptin + metformin occurred most often in the Investigations, Gastrointestinal, and Renal and Urinary SOC. Within these SOC, events related to changes in creatinine or renal function were most common. However, study MET-302 included protocol-defined renal safety monitoring criteria and study 305 included renal safety withdrawal criteria. Subjects could also be discontinued due to investigator discretion related to metformin use. These factors likely affected the overall discontinuation rate due to renal- and creatinine-related AEs.

As described in section 2.4 Important Safety Issues With Consideration to Related Drugs, alogliptin and metformin are associated with the following safety issues. (The CV safety of alogliptin was demonstrated in the company's submission to a Complete Response letter issued on June 26, 2009.

- 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 alogliptin 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 $\leq 3x$ 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, the current clinical database supports approval of alogliptin. As co-administration with metformin is not expected to alter the liver safety of alogliptin and review of the alogliptin + metformin data did not reveal a signal for hepatotoxicity, I recommend approval

of the alogliptin/metformin FDC. I recommend the applicant include hepatic enzyme elevations in the labeling section 6.2 Postmarketing Experience as well as section 5 Warnings and Precautions. 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: The percentage of alogliptin + metformin subjects with AEs in the angioedema SMQ ranged from 0% (A12.5+M in study MET-302) to 5.2% (A25+M+P30 in study OPI-004). Edema peripheral was the most common event, although it is a broad search term and may not be indicative of a true case of angioedema.
- Skin lesions: The percentage of alogliptin + metformin subjects with any PCDR event in completed studies MET-302, MET-008, and OPI-004 ranged from 0% (A12.5+M in study MET-302) to 14.1% (A25+M+P30 in OPI-004). The incidence of PCDR events was higher in studies MET-008 and OPI-004, probably because they included an examination of the skin and digits at every study visit whereas study MET-302 did not. Events in these studies as well as ongoing study 305 included pruritis, dermatitis, rash, and skin lesions.
- Pancreatitis: Using the SMQ criteria, there were 3 subjects with acute pancreatitis in study MET-302 (one each in A12.5+M500BID [pancreatitis acute], A12.5+M1000BID [pancreatitis], and M1000BID groups). In ongoing study 305, two alogliptin 25 mg + metformin subjects met the pancreatitis SMQ criteria. These findings are consistent with other DPP-4 inhibitor-containing products.
- Infection: The percentage of subjects with Infections and Infestations AEs in completed phase 3 studies ranged from 21.9 – 38.6%. This is consistent with other DPP-4 inhibitor-containing products.
- Hypo- and hyperglycemia: The incidence of hypoglycemia in completed and ongoing phase 3 studies was low; the majority of events were mild to moderate severity. The percentage of alogliptin + metformin subjects who required hyperglycemic rescue in phase 3 studies ranged from 2.6 - 12.3%; this was less than the percentage of placebo and comparator subjects.
- Lactic acidosis: No cases of lactic acidosis were identified in the SCS, Four-Month Safety Update, or Interim CSR 305.
- Decrease in vitamin B12 level: Although B12 was not routinely drawn in phase 3 studies, no cases of B12 deficiency were identified in the SCS, Four-Month Safety Update, or Interim CSR 305.
- Anemia: Although metformin is associated with a decrease in vitamin B12 levels which is very rarely associated with anemia and the proposed label includes this warning, no clinically significant hematologic laboratory abnormalities which would preclude approval were identified.

The percentage of alogliptin + metformin subjects with any AE in studies MET-302 and 305 ranged from 63.2-64.0% to 70.1-72.2%, respectively. These values were less than the placebo group (71.7%) or similar to glipizide comparator (71.1%), respectively. The

most common AEs ($\geq 5\%$) in the combination treatment groups were creatinine clearance decreased, diarrhea, dyslipidemia, dyspepsia, headache, hyperglycemia, hypertension, nasopharyngitis, nausea, and upper respiratory tract infection.

As the laboratory data from studies MET-008 and OPI-004 were previously reviewed as part of the alogliptin NDA and first CR, my review of the laboratory findings focused on phase 3 study MET-302. No clinically significant laboratory abnormalities which would preclude approval were identified.

The use of alogliptin with metformin does not appear to be associated with a clinically meaningful change in vital signs or ECG parameters. In addition, the CV safety of alogliptin was previously demonstrated by the interim analysis of CV study 402 in the first alogliptin CR. 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 was <1.8 , supporting approvability.

The safety of alogliptin + metformin in special groups was not investigated in the clinical program, because study 005 demonstrated no drug interaction between alogliptin and metformin. The safety profile of the FDC is expected to be similar to that of the individual components and as follows:

- Metformin is contraindicated in patients with renal dysfunction (e.g. serum creatinine ≥ 1.5 mg/dl in males, ≥ 1.4 mg/dl in females, or abnormal creatinine clearance).
- Metformin should be avoided in patients with hepatic insufficiency because of the risk of lactic acidosis.
- Patients should be cautioned against excessive alcohol intake when taking metformin, since alcohol potentiates its effects on lactate metabolism.
- Metformin should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.
- The small LS mean change from baseline at week 52 in study 303 suggests that alogliptin may not be very efficacious in adults 65 to 90 years over the long-term, although poor study design complicated the primary efficacy assessment. See also my review of the first alogliptin CR.

Alogliptin poses minimal carcinogenic risk to humans based on high exposure multiples at the NOAEL (32x) for rat thyroid C-cell tumors, very high exposure multiples ($\geq 288x$) at doses that caused increased combined thyroid C-cell adenomas and carcinomas in male rats, and absence of any other drug-related tumors in rats ($> 400x$ female MRHD) or mice (60x MRHD).

A rat embryofetal development study was conducted with the concomitant administration of alogliptin and metformin. No drug-related fetal abnormalities considered relevant to human subjects were identified in the study. No studies were

conducted to assess the effect of the alogliptin/metformin FDC on pregnancy and lactation. I agree with the applicant-proposed that labeling the alogliptin/metformin FDC be pregnancy category B. The text states that both alogliptin and metformin are secreted in the milk of lactating rats.

I agree with the applicant's request that pediatric studies in subjects 0-9 years be waived because studies are impossible or highly impractical due to the small number of these T2DM subjects.

I also agree with the applicant's proposal to conduct the following two deferred pediatric studies in T2DM subjects aged 10-17 years.

- SYR-322_104: *A Comparative, Randomized, Open-Label, Multi-Center, 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_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*

On August 22, 2012, PeRC agreed with the proposed waiver in T2DM subjects 0-9 years and deferral in T2DM subjects 10-17 years. (See section 7.6.3 Pediatrics and Assessment of Effects on Growth for full details.)

Although metformin is dialyzable, alogliptin is minimally dialyzable. In the event of an overdose, removal of the unabsorbed material from the gastrointestinal tract should be considered. Clinical monitoring and supportive therapy should be initiated. Alogliptin and metformin are not associated with drug abuse, withdrawal, or rebound.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Due to the differences in background therapies, treatment groups, and lengths of exposure in studies MET-008, OPI-004, and MET-302, the agency agreed with the applicant on April 5, 2011 that the safety data would not be pooled but summarized individually by study. As MET-008 and OPI-004 were previously reviewed under alogliptin NDA 22-271, my safety review at times focused on MET-302 as well as one-year interim data from study 305 and relevant postmarketing reports. I did not focus on the following two components of the Four-Month Safety Update for the reasons listed:

- Japanese PSUR 3 was previously reviewed under the alogliptin CR.
- Study OLE-012 was uncontrolled and evaluated the long-term safety of alogliptin 12.5 and 25 mg with or without concomitant antidiabetic agents (e.g. metformin).

See also my review of hepatotoxicity in the second alogliptin resubmission.

7.1.2 Categorization of Adverse Events

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

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

Due to the differences in background therapies, treatment groups, and lengths of exposure in studies MET-008, OPI-004, and MET-302, the agency agreed with the applicant on April 5, 2011 that the safety data would not be pooled but summarized individually by study. See also section 7.1.1 Studies/Clinical Trials Used to Evaluate Safety.

7.2 Adequacy of Safety Assessments

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

In the original submission, a total of 1044 T2DM subjects received at least one dose of alogliptin with metformin in the phase 3 studies and 137 healthy subjects received at least one dose of alogliptin with metformin in phase 1 studies. Most subjects were exposed for at least six months, and 18.7% in the combination group were exposed for one year. All one-year exposure came from study OPI-004, which did not include alogliptin only and placebo groups.

Table 10. Exposure by duration (phase 3 studies MET-008, OPI-004, and MET-302)

Exposure	Placebo N=106	Alogliptin N=222	Metformin N=723	Alogliptin+Metformin N=1044
Number (%) of subjects exposed for:				
<2 weeks	1 (0.9)	5 (2.3)	13 (1.8)	18 (1.7)
2 weeks to <4 weeks	2 (1.9)	11 (5.0)	10 (1.4)	14 (1.3)
4 weeks to <8 weeks	5 (4.7)	14 (6.3)	23 (3.2)	30 (2.9)
8 weeks to <12 weeks	4 (3.8)	6 (2.7)	25 (3.5)	26 (2.5)
12 weeks to <16 weeks	10 (9.4)	11 (5.0)	49 (6.8)	42 (4.0)
16 weeks to <20 weeks	7 (6.6)	10 (4.5)	31 (4.3)	29 (2.8)
20 weeks to <26 weeks	28 (26.4)	43 (19.4)	83 (11.5)	155 (14.8)
26 weeks to <34 weeks	49 (46.2)	122 (55.0)	216 (29.9)	412 (39.5)
34 weeks to <42 weeks	--	--	19 (2.6)	20 (1.9)
42 weeks to <52 weeks	--	--	84 (11.6)	103 (9.9)
≥52 weeks	--	--	170 (23.5)	195 (18.7)

Source: SCS Table 1.f

The Four-Month Safety Update increased overall exposure by its addition of interim data from study 305 and completed but uncontrolled data from study OLE-012. However, OLE-012 was a long-term safety study of alogliptin 12.5 and 25 mg with or without concomitant antidiabetic drugs. Thus, not all subjects were coadministered alogliptin and metformin. As a result, the applicant did not include this exposure data in the Four-Month Safety Update.

In study 305, a total of 1750 subjects have been exposed to alogliptin 12.5 or 25 mg + metformin; the majority (59.3-61.8%) have been exposed for ≥52 weeks. In uncontrolled study OLE-012, 3320 subjects received alogliptin 12.5 or 25 mg, although the number coadministered metformin was not specified.

Table 11. Study 305: Interim exposure (Safety set)

	Treatment			
	MET+A12.5 (N=873)	MET+A25 (N=877)	MET+Glipizide (N=869)	Total (N=2621)
Length of exposure (weeks)				
Mean (SD)	44.92 (14.115)	45.31 (14.141)	43.63 (15.481)	44.61 (14.607)
Median (range)	52.1 (0.1, 57.4)	52.1 (0.1, 55.3)	52.1 (0.6, 58.1)	52.1 (0.1, 58.1)
Number (%) of subjects exposed:				
<2 weeks	5 (0.6)	11 (1.3)	10 (1.2)	26 (1.0)
≥2 weeks	868 (99.4)	866 (98.7)	859 (98.8)	2595 (99.0)
≥4 weeks	857 (98.2)	856 (97.6)	840 (96.7)	2555 (97.5)
≥8 weeks	841 (96.3)	836 (95.3)	813 (93.6)	2492 (95.1)
≥12 weeks	819 (93.8)	822 (93.7)	800 (92.1)	2443 (93.2)
≥16 weeks	810 (92.8)	806 (91.9)	777 (89.4)	2395 (91.4)
≥20 weeks	791 (90.6)	792 (90.3)	765 (88.0)	2349 (89.6)
≥26 weeks	751 (86.0)	763 (87.0)	729 (83.9)	2244 (85.6)
≥39 weeks	691 (79.2)	711 (81.1)	665 (76.5)	2067 (78.9)
≥52 weeks	518 (59.3)	542 (61.8)	515 (59.3)	1575 (60.1)
≥335 days	653 (74.8)	672 (76.6)	619 (71.2)	1944 (74.2)

Source: Interim CSR 305 Table 12.a

Table 12. Exposure to alogliptin + metformin in controlled, phase 3 studies (including ongoing study 305)

Exposure	Original Submission (study MET-008, OPI-004, & MET-302)	Controlled Safety Data (study 305)	Total
≥26 weeks	730	1514	2244
≥52 weeks	195	1060	1255

Source: Table 10 and Table 11

Table 12 shows the exposure in controlled, phase 3 studies, including ongoing study 305. A total of 2244 subjects have been exposed to alogliptin + metformin for ≥26 weeks; 1255 subjects have been exposed for ≥52 weeks. Although this exposure 1) is not consistent with the ≥4,000 exposed subjects that applicants now submit in NME applications since the implementation of the CV outcomes trial requirement and 2) it is not consistent with the February 2008 Diabetes guidance recommendation that ≥300 subjects be exposed for 18+ months, I have determined that the current exposure levels are sufficient for the following reasons:

- This application bridges to alogliptin NDA 22-271. In the second alogliptin CR, which addressed the hepatotoxicity signal, total alogliptin exposure was 9857. (See also my review of that submission.).
- The relative safety of metformin has been demonstrated since its approval in 1995.

- Drug-interaction study 005 demonstrated that there is no significant interaction between alogliptin and metformin.

7.2.2 Explorations for Dose Response

As shown in section 5.1 Tables of Studies/Clinical Trials, the applicant explored the following doses in the four controlled phase 3 trials submitted. (PK study 101 previously demonstrated that alogliptin can be dosed once or twice daily.)

- NDA:
 - o MET-008: Alogliptin 12.5 or 25 mg + metformin
 - o OPI-004: Alogliptin 25 mg + pioglitazone 30 mg + metformin
 - o MET-302: Alogliptin 12.5 mg + metformin 500 or 1000 mg BID
- Four-Month Safety Update:
 - o 305 (interim report): Alogliptin 12.5 or 25 mg + metformin

However, the applicant proposed alogliptin/metformin FDC doses 12.5/500 and 12.5/1000 mg twice daily, which were reviewed. For my alogliptin dosing recommendations, see section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations.

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 alogliptin CR.

7.2.4 Routine Clinical Testing

The applicant obtained laboratory tests, vital signs, and ECGs at reasonable time points during the studies and under consistent settings, where applicable. I reviewed the timing of these assessments in studies MET-302, MET-008, and OPI-004 in section 5.3 Discussion of Individual Studies/Clinical Trials of this review and my alogliptin NDA and CR reviews, respectively.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to section 4.4.3 Pharmacokinetics.

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

As described in section 2.4 Important Safety Issues With Consideration to Related Drugs, alogliptin is associated with the following safety issues: hepatotoxicity, hypersensitivity, skin lesions, pancreatitis, infection, and hypoglycemia. (The CV safety of alogliptin was demonstrated in the CR; see also section 3.1.) Metformin is also

associated lactic acidosis, decrease in vitamin B12 level and anemia, and hyperglycemia.

The applicant analyzed hypersensitivity, acute pancreatitis, malignancies, infections, and CV safety as AEs of special interest in the SCS. The Four-Month Safety Update included study-specific information on hepatotoxicity, pancreatitis, hypersensitivity, and renal failure.

7.3 Major Safety Results

7.3.1 Deaths

In the four phase 3 studies of alogliptin + metformin (i.e. MET-008, OPI-004, MET-302, and ongoing 305), there were seven deaths in the following alogliptin + metformin subjects. (An additional A25+MET subject died from the pre-treatment AE of biliary cancer metastatic in study 305.)

- 008/520-8010 (alogliptin 12.5 mg daily + metformin 2500 mg/day): This 49 year old female with T2DM, bipolar disorder, seizures, and tobacco use died of hypertensive heart disease on day 45. Her blood pressure one month prior to her death was 153/76 mm Hg. On day 42, she was seen in the emergency room for viral gastroenteritis. On day 44, she was visited by a physician for vomiting and generalized aches. She had an irregular heart beat. Later that night, she was taken by ambulance to the hospital for shallow breathing and worsening abdominal symptoms. She was dead on arrival at the hospital. The death certificate noted the cause of death as hypertensive heart disease.
- 004/1230-4515 (alogliptin 25 mg daily + pioglitazone 30 mg daily + metformin): This 70 year old female with history of T2DM, hypertension, angina, MI, dyslipidemia, and arteriosclerosis died from a MI on day 62. She was on five concomitant medications. The week 1 ECG showed normal sinus rhythm, slight ventricular hypertrophy, and left atrial enlargement.
- 305/5053-009 (alogliptin 12.5 mg daily + metformin): This 59 year old male with history of T2DM, atrial fibrillation and flutter, cardiac aneurysm, cardiomyopathy, MI, cerebral hemorrhage, CVA, and coronary artery bypass died of hemorrhagic stroke on day 439. He was brought to the emergency room by ambulance but collapsed after walking in the door. The death certificate noted the cause of death as acute respiratory failure.
- 305/5090-010 (alogliptin 12.5 mg daily + metformin): This 58 year old, T2DM male died of non-small cell lung cancer stage IIIB on day 202. He was found unresponsive while hospitalized for acute renal failure. Although the advanced cardiac life support protocol was implemented, the subject was pronounced dead.

- 305/5007-045 (alogliptin 25 mg daily + metformin): This 49 year old, T2DM male died of a MI on day 49. The site reported the cause of death as “emphysema flare up and heart attack”. The autopsy report is pending.
- 305/5228-001 (alogliptin 25 mg daily + metformin): This 67 year old, T2DM male died of acute pulmonary edema on day 230.
- 305/5346-010 (alogliptin 25 mg daily + metformin): This 45 year old, T2DM, male died of sepsis. He was hospitalized due to fever and required a ventilator. He experienced cardiopulmonary arrest. Resuscitation was attempted but he was not revived. The death certificate notes the cause of death as toxic shock syndrome with multiorgan failure.

There were also three deaths in metformin + glipizide subjects in study 305. The causes of death were septic shock, antioventricular block complete, and MI.

The concomitant administration of alogliptin and metformin is not associated with an increased risk of death. The deaths reviewed appear to be due to the subjects' underlying medical conditions.

7.3.2 Nonfatal Serious Adverse Events

The number and frequency of SAEs by SOC in controlled, phase 3 trials of alogliptin + metformin are shown in Table 13 and Table 14. The percentage of subjects with SAEs in alogliptin + metformin groups ranged from 1.8% (A12.5+M1000BID in study MET-302) to 6.5% (A25+M in study 305). The percentage of alogliptin+ metformin subjects with SAEs was similar to the percentage of control subjects with SAEs in the four trials. The percentage of subjects with SAEs by SOC in each treatment group was $\leq 1.0\%$, with the exception of cardiac events (1.6% A25+M in study 305) and neoplasms (1.4% A12.5+M in study MET-008).

Table 13. Serious adverse events (n, %) in completed phase 3 studies

SOC	MET-302							MET-008			OPI-004	
	PLB	A25QD	A12.5BID	M500BID	M1000BID	A12.5+ M500BID	A12.5+ M1000BID	PLB+M	A12.5+M	A25+M	A25+M +P30	M+P45
N	106	112	110	109	111	106	114	104	213	207	404	399
Overall	3 (2.8)	1 (0.9)	4 (3.6)	2 (1.8)	2 (1.8)	2 (1.9)	2 (1.8)	4 (3.8)	6 (2.8)	8 (3.9)	20 (5.0)	20 (5.0)
Cardiac	1 (0.9)	0	0	1 (0.9)	1 (0.9)	0	0	1 (1.0)	2 (0.9)	1 (0.5)	3 (0.7)	4 (1.0)
Congenital	0	0	0	0	0	0	0	1 (1.0)	0	0	0	0
Ear	0	0	0	0	0	0	0	0	0	0	1 (0.2)	0
Eye	0	0	0	0	0	0	0	0	0	0	0	3 (0.8)
Gastrointestinal	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)
Infections	0	1 (0.9)	1 (0.9)	0	0	0	1 (0.9)	2 (1.9)	1 (0.5)	2 (1.0)	4 (1.0)	4 (1.0)
Nervous	1 (0.9)	0	2 (1.8)	0	0	0	0	0	0	0	2 (0.5)	1 (0.3)
Respiratory	0	0	0	2 (1.8)	0	0	0	0	0	1 (0.5)	1 (0.2)	1 (0.3)
General	0	0	0	0	0	1 (0.9)	0	0	0	2 (1.0)	2 (0.5)	0
Hepatobiliary	0	0	0	0	0	0	1 (0.9)	0	0	1 (0.5)	0	0
Injury	0	0	1 (0.9)	0	0	0	0	1 (1.0)	1 (0.5)	0	4 (1.0)	2 (0.5)
Metabolism	1 (0.9)	0	0	0	0	0	0	0	0	0	0	0
Musculoskeletal	0	0	0	0	0	0	0	0	0	1 (0.5)	2 (0.5)	2 (0.5)
Neoplasms	0	0	0	0	0	0	0	0	3 (1.4)	0	1 (0.2)	1 (0.3)
Psychiatric	0	0	0	0	0	1 (0.9)	0	0	0	0	1 (0.2)	0
Renal	0	0	0	0	1 (0.9)	0	0	0	0	0	1 (0.2)	1 (0.3)
Vascular	0	0	0	0	0	0	1 (0.9)	0	0	0	1 (0.2)	4 (1.0)

Source: SCS Tables 2.n, 2.o, and 2.p and Four-Month Safety Update Table

Table 14. Study 305: Treatment-emergent serious adverse events (n, %) reported by ≥2 subjects (Interim safety data)

SOC	A12.5+M (n=873)	A25+M (n=877)	Glipizide+M (n=869)
Overall	51 (5.8)	57 (6.5)	59 (6.8)
Cardiac	8 (0.9)	14 (1.6)	15 (1.7)
Gastrointestinal	4 (0.5)	6 (0.7)	7 (0.8)
Infections	9 (1.0)	9 (1.0)	14 (1.6)
Nervous	7 (0.8)	5 (0.6)	5 (0.6)
Respiratory	3 (0.3)	5 (0.6)	2 (0.2)
General	2 (0.2)	5 (0.6)	2 (0.2)
Injury	4 (0.5)	2 (0.2)	6 (0.7)
Musculoskeletal	4 (0.5)	4 (0.5)	4 (0.5)
Neoplasms	4 (0.5)	7 (0.8)	4 (0.5)
Renal	5 (0.6)	3 (0.3)	2 (0.2)
Reproductive	4 (0.5)	3 (0.3)	0
Vascular	2 (0.2)	4 (0.5)	2 (0.2)

Source: Interim CSR 305 Table 12.h

All SAE events were single events in alogliptin + metformin subjects in each of the trials except for the following events:

- Cardiac (n = 13):
 - o Coronary artery disease: 5 events in study 305 (2 A12.5+M and 3 A25+M)
 - o Angina unstable: 2 events in study 305 (A25+M)
 - o Atrial fibrillation: 2 events in study 305 (A25+M)
 - o Atrial flutter: 2 events in study 305 (A12.5+M)
 - o Cardiac failure congestive: 2 events in study 305 (1 each A12.5+M and A25+M)
- Infections and infestations (n = 13):
 - o Colitis: 4 events in study 305 (2 each A12.5+M and A25+M)
 - o Cellulitis: 3 events in study 305 (2 A12.5+M and 1 A25+M)
 - o Gastroenteritis: 4 events in study 305 (2 A12.5+M and 2 A25+M)
 - o Pneumonia: 2 events in study 305 (1 each A12.5+M and A25+M)
- General disorders and administration site conditions (n = 9):
 - o Non-cardiac chest pain: 2 events in MET-008 (A25+M), 2 events in OPI-004 (A25+M+P30), and 5 events in study 305 (2 A12.5+M and 3 A25+M)
- Musculoskeletal (n = 7):
 - o Osteoarthritis: 2 events in OPI-004 (A25+M+P30) and 3 events in study 305 (1 A12.5+M and 2 A25+M)
 - o Musculoskeletal chest pain: 2 events in study 305 (1 each A12.5+M and A25+M)
- Renal and urinary (n = 6):
 - o Renal failure acute: 2 events in study 305 (1 each A12.5+M and A25+M)
 - o Nephrolithiasis: 2 events in study 305 (A12.5+M)

- o Renal colic: 2 events in study 305 (1 each A12.5+M and A25+M)
- Vascular (n = 4):
 - o Deep vein thrombosis: 2 events in study 305 (1 each A12.5+M and A25+M)
 - o Hypertension: 2 events in study 305 (A25+M)
- Nervous (n = 4):
 - o Syncope: 2 events in study 305 (A12.5+M)
 - o Transient ischemic attack: 2 events in study 305 (A25+M)
- Injury, poisoning, and procedural (n=2):
 - o Ankle fracture: 2 events in study 305 (1 event each A12.5+M and A25+M)
- Neoplasms (n = 2):
 - o Basal cell carcinoma: 2 events in study 305 (1 each A12.5+M and A25+M)
- Reproductive (n = 2):
 - o Benign prostatic hyperplasia: 2 events in study 305 (1 each A12.5+M and A25+M)

DPP-4 inhibitors, including alogliptin, are associated with risk of infection. This is not an approvability issue, but one that would be addressed in safety labeling.

The CV safety of alogliptin was previously demonstrated in the alogliptin CR. This included a percentage of subjects who were coadministered metformin.

Other duplicate SAEs occurred infrequently and do not appear to be associated with the co-administration of alogliptin and metformin.

7.3.3 Dropouts and/or Discontinuations

The rate of discontinuation due to AEs in completed phase 3 studies was generally similar between treatment groups, except for the A12.5+M1000 BID group in study MET-302 (9.6%) (see Table 15). Events in this treatment group occurred mostly in the Investigations SOC (n=6, 5.3%) and Gastrointestinal SOC (n=3, 2.6%). Within these SOC, events were single events except for creatinine renal clearance decreased (n=4, 3.5%). In completed phase 3 studies (i.e. MET-302, MET-008, and OPI-004), the only other Investigations event to occur more than once was liver function test abnormal (n=2, 0.9%) in the A12.5+M group of study MET-008. However, in study MET-302, the A25QD, A12.5BID, and A12.5+M500BID groups each had two events of renal impairment (~1.8%). All other events in alogliptin + metformin treatment groups in studies MET-302, MET-008, and OPI-004 were single events.

Table 15. AEs leading to discontinuation in completed phase 3 trials

SOC	MET-302							MET-008			OPI-004	
	PLB	A25QD	A12.5BID	M500BID	M1000BID	A12.5+ M500BID	A12.5+ M1000BID	PLB+M	A12.5+M	A25+M	A25+M +P30	M+P45
N	106	112	110	109	111	106	114	104	213	207	404	399
Overall	5 (4.7)	4 (3.6)	7 (6.4)	3 (2.8)	2 (1.8)	5 (4.7)	11 (9.6)	1 (1.0)	7 (3.3)	4 (1.9)	12 (3.0)	16 (4.0)
Cardiac	0	0	0	0	0	0	0	0	1 (0.5)	1 (0.5)	3 (0.6)	4 (1.2)
Investigations	0	1 (0.9)	2 (1.8)	0	1 (0.9)	2 (1.9)	6 (5.3)	0	2 (0.9)	0	0	1 (0.3)
Ear	0	0	0	0	0	0	0	0	0	0	1 (0.2)	0
Gastrointestinal	1 (0.9)	0	0	1 (0.9)	1 (0.9)	0	3 (2.6)	0	0	0	1 (0.2)	1 (0.3)
Infections	0	0	0	0	0	0	1 (0.9)	0	0	0	0	1 (0.3)
Nervous	0	0	2 (1.8)	0	0	0	0	0	2 (1.0)	1 (0.5)	0	0
Respiratory	0	0	0	1 (0.9)	0	0	0	0	0	1 (0.5)	0	2 (0.6)
General	1 (0.9)	0	0	0	0	0	0	0	0	1 (0.5)	2 (0.4)	3 (0.8)
Hepatobiliary	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Injury	0	0	1 (0.9)	0	0	0	0	0	0	0	1 (0.2)	0
Metabolism	2 (1.9)	0	0	0	0	0	0	0	0	0	1 (0.2)	0
Musculoskeletal	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)
Neoplasms	0	0	0	0	0	0	0	0	2 (1.0)	0	1 (0.2)	1 (0.3)
Psychiatric	0	0	0	0	0	1 (0.9)	1 (0.9)	0	0	0	0	0
Renal	1 (0.9)	2 (1.8)	2 (1.8)	1 (0.9)	0	2 (1.9)	0	0	0	0	0	1 (0.3)
Blood & lymph	0	1 (0.9)	0	0	0	0	0	1 (1.0)	0	0	0	1 (0.3)
Skin	0	0	0	0	0	0	0	0	0	1 (0.5)	2 (0.4)	0

Source: SCS Table 2.q, 2.r, and 2.s

At the time of interim data cut for ongoing study 305, the reason for discontinuation from the study and adverse event data were not fully reconcilable. This is because discontinuations due to AEs were captured both as discontinuation due to an “adverse event” and “drug withdrawn” due to the AE. Table 16 illustrates the similarities and differences between both discontinuation datasets.

Table 16. Disposition data vs. treatment-emergent AEs that led to discontinuation in study 305 interim analysis (cutoff date November 10, 2011)

Disposition Data (Table 15.1.1) (Part A)			
	MET+A12.5 (N=880)	MET+A25 (N=885)	MET+Glipizide (N=873)
Prematurely discontinued study drug due to an AE	48 (5.5)	64 (7.2)	73 (8.4)
Overview of TEAEs (Table 15.3.1.5) (Part B)			
	MET+A12.5 (N=873)	MET+A25 (N=877)	MET+Glipizide (N=869)
TEAE leading to discontinuation	52 (6.0)	62 (7.1)	73 (8.4)
Comparison of AEs by Disposition (Table 15.3.2.1 and Appendix 16.2.1.2) (Part C)			
	MET+A12.5 <u>Disposition</u>	MET+A25 <u>Disposition</u>	MET+Glipizide <u>Disposition</u>
	Total Subject	Total Subjects	Total Subjects
<u>AE</u>	Yes No	Yes No	Yes No
Yes	47 5 52	60 2 62	67 6 73
No	1 ---	4 ---	6 ---
Total	48	64	73
Subjects			
Total Subjects with a Discrepancy:	6	6	12

Source: Study 305 Tables 15.1.1, 15.3.2.1, and 15.3.1.5 and Appendix 16.2.1.2.

Note: A “yes” for disposition indicates that the subject prematurely discontinued study due to an AE on the EOS CRF and a “no” indicates that the subject discontinued study drug due to a reason other than AE or the information was not provided. A “yes” for AE indicates that the subject had an AE that led to discontinuation from study drug in the AE CRF and a “no” indicates that the subject did not have an AE that led to discontinuation from study drug. Cells containing subjects with a discrepancy (ie, a “yes” in one table and a “no” in the other) are shaded in grey in Part C.

Source: June 11, 2011 submission Table 1

There were 24 subjects in ongoing study 305 for which there was a discrepancy between the disposition and AE data (6 A12.5+MET, 6 A25+MET, and 12 glipizide+MET) (see Table 17).

- Of the 11 subjects who discontinued study drug due to an AE:
 - Seven were discontinued due to pretreatment AEs (subjects 5117-004, 5416-021, 5439-009, 5468-011, 5470-007, 5516-001, and 5091-028).
 - Subject 5007-054 died during the study, although additional information was not available.

- o Subject 5018-006 discontinued per the protocol for hypoglycemia.
 - o Subject 5144-005 discontinued due to a protocol violation (non-study physician changed metformin to pioglitazone).
 - o Subject 5436-007 died on day 385 after the week 52 visit.
- Of the 13 subjects who discontinued due to an AE:
 - o Eight subjects reported an AE based upon a central laboratory result with an onset date at the week 52 visit (subjects 5021-002, 5084-001, 5091-011, 5091-012, 5150-005, 5159-005, 5304-026, and 5310-008).
 - o Four subjects had poor glycemic control (subjects 5117-013, 5139-003, 5159-07, and 5336-009)
 - o Subject 5204-045 had an AE of apathy, did not want to continue in the study, and hence voluntarily withdrew.

Table 17. Subjects in study 305 with differences in study discontinuation between disposition and AE tables

Subject ID	Treatment	Adverse Event Leading to Discontinuation on the AE CRF	Reason for Discontinuation on the EOS CRF
On the EOS CRF, Subjects with AE Reported as the Reason for Discontinuation Without a Corresponding AE that led to Discontinuation on the AE CRF			
5007/045	Alogliptin 25 mg	----	Adverse Event
5018/006	Glipizide	----	Adverse Event
5091/028	Alogliptin 25 mg	----	Adverse Event
5117/004	Glipizide	----	Adverse Event
5144/005	Glipizide	----	Adverse Event
5416/021	Glipizide	----	Adverse Event
5436/007	Glipizide	----	Adverse Event
5439/009	Alogliptin 12.5 mg	----	Adverse Event
5468/011	Glipizide	----	Adverse Event
5470/007	Alogliptin 25 mg	----	Adverse Event
5516/011	Alogliptin 25 mg	----	Adverse Event
On the AE CRF, subjects with an AE that led to Discontinuation that did not have AE Reported as the Reason for Discontinuation on the EOS CRF			
5021/002	Alogliptin 25 mg	Blood creatinine increased	----
5084/001	Alogliptin 12.5 mg	Renal impairment	----
5091/011	Alogliptin 12.5 mg	Hyperglycaemia	----
5091/012	Glipizide	Hyperglycaemia	----
5117/013	Glipizide	Diabetes mellitus inadequate control	Lack of Efficacy
5139/003	Alogliptin 12.5 mg	Glycosylated haemoglobin increased	Lack of Efficacy
5150/005	Glipizide	Lipase increased	----
5159/005	Glipizide	Glycosylated haemoglobin increased	----
5159/007	Glipizide	Hyperglycaemia	Lack of Efficacy
5204/045	Alogliptin 12.5 mg	Apathy	Voluntary Withdrawal
5304/026	Alogliptin 25 mg	Creatinine renal clearance decreased	----
5310/008	Glipizide	Creatinine renal clearance decreased	----
5336/009	Alogliptin 12.5 mg	Glycosylated haemoglobin increased	Lack of Efficacy

Source: Study 305 Tables 15.3.1.5 and Appendix 16.2.1.2.

Source: June 11, 2012 submission Table 2

When AEs that led to study drug discontinuation were analyzed by SOC, discontinuations again occurred most commonly in alogliptin + metformin groups in the Investigations (2.0-3.0%) and Gastrointestinal (0.6-1.1%) as well as Renal and Urinary (0.5-1.0%) SOCs (see Table 18). In alogliptin + metformin treatment groups, the following events occurred in more than one subject:

- Investigations:

- o Creatinine renal clearance decreased: 11 (1.3%) A12.5+M and 14 (1.6%) A25+M subjects
- o Blood creatinine increased: 7 (0.8%) A12.5+M and 6 (0.7%) A25+M subjects
- o Alanine aminotransferase increased: 2 (0.2%) A12.5+M and 1 (0.1%) A25+M subjects
- o Glycosylated hemoglobin increased: 2 (0.2%) A12.5+M subjects
- Gastrointestinal:
 - o Diarrhea: 3 (0.3%) A12.5+M subjects
 - o Vomiting: 4 (0.5%) A25+M subjects
 - o Constipation: 2 (0.2%) A25+M subjects
- Renal and Urinary:
 - o Renal failure: 4 (0.5%) A12.5+M and 2 (0.2%) A25+M subjects
 - o Renal impairment: 4 (0.5%) A12.5+M and 2 (0.2%) A25+M subjects

Table 18. Study 305: Treatment-emergent AEs leading to discontinuation reported by ≥2 subjects (Interim safety set)

SOC	A12.5+M (n=873)	A25+M (n=877)	Glipizide+M (n=869)
Total Subjects	52 (6.0)	62 (7.1)	73 (8.4)
Gastrointestinal	5 (0.6)	10 (1.1)	6 (0.7)
Infections	1 (0.1)	1 (0.1)	4 (0.5)
Investigations	25 (2.9)	26 (3.0)	17 (2.0)
Metabolism	2 (0.2)	1 (0.1)	28 (3.2)
General	1 (0.1)	1 (0.1)	4 (0.5)
Skin	2 (0.2)	3 (0.3)	2 (0.2)
Renal	9 (1.0)	4 (0.5)	6 (0.7)

Source: Interim CSR 305 Table 12.i (and Table 15.3.2.1)

In summary, discontinuation due to AEs with alogliptin + metformin occurred most often in the Investigations, Gastrointestinal, and Renal and Urinary SOC. Within these SOC, events related to changes in creatinine or renal function were most common. However, study MET-302 included protocol-defined renal safety monitoring criteria and study 305 included renal safety withdrawal criteria. Both criteria likely affected the overall discontinuation rate due to renal- and creatinine-related AEs. Furthermore, subjects could also be discontinued due to investigator discretion related to metformin use. Many discontinued subjects had impaired renal function at baseline and/or hypertension. Therefore, although a trend in increased discontinuation due to renal- and creatinine-related AEs was observed, it is not clear if this is due to study drug. See also 7.4.2 Laboratory Findings.

7.3.4 Significant Adverse Events

As described in section 2.4 Important Safety Issues With Consideration to Related Drugs, alogliptin is associated with the following safety issues: hepatotoxicity,

hypersensitivity, skin lesions, pancreatitis, infection, and hypoglycemia. (The CV safety of alogliptin was demonstrated in the first CR and is briefly discussed briefly in section 3.1 Submission Quality and Integrity.) Metformin is also associated lactic acidosis, decrease in vitamin B12 levels and anemia, and hyperglycemia.

Hepatic safety is discussed in section 7.3.5 Submission Specific Primary Safety Concerns and my review of the second alogliptin resubmission.

Hypersensitivity and Skin Lesions: PCDR and angioedema events were analyzed in the four controlled phase 3 studies. PCDR events were analyzed as agreed upon at the pre-NDA meeting (and consistent with the alogliptin and alogliptin/pioglitazone NDA resubmissions). The angioedema analysis utilized the SMQ, as previously agreed.

Potential Cutaneous Drug Reactions: A summary of PCDR events that occurred in ≥ 2 subjects overall in studies MET-302, MET-008, and OPI-004 is shown in Table 19; events which occurred in ≥ 3 subjects in ongoing study 305 are shown in Table 20.

The percentage of alogliptin + metformin subjects with any PCDR event in completed studies MET-302, MET-008, and OPI-004 ranged from 0% (A12.5+M in study MET-302) to 14.1% (A25+M+P30 in OPI-004). The incidence of PCDR events was higher in studies MET-008 and OPI-004, probably because they included an examination of the skin and digits at every study visit whereas study MET-302 did not. Events in these studies as well as ongoing study 305 included pruritis, dermatitis, rash, and skin lesions. However, the incidence of discontinuation due to PCDR events in alogliptin + metformin subjects was low (n=4) and as follows:

- MET-008: 1 drug eruption (A25+M group)
- OPI-004: 1 rash and 1 rash generalized (A25+M+P30 group)
- 305: 1 rash (A12.5+M group)

Table 19. Potential cutaneous drug reaction AEs that occurred in ≥2 subjects overall (Completed phase 3 studies) Source: SCS Tables 2.w, 2.x, and 2.y

SOC	MET-302							MET-008			OPI-004	
	PLB	A25QD	A12.5BID	M500BID	M1000BID	A12.5+ M500BID	A12.5+ M1000BID	PLB+M	A12.5+M	A25+M	A25+M +P30	M+P45
N	106	112	110	109	111	106	114	104	213	207	404	399
Any PCDR AE	0	3 (2.7)	2 (1.8)	4 (3.7)	3 (2.7)	2 (1.9)	0	7 (6.7)	25 (11.7)	21 (10.1)	57 (14.1)	42 (10.5)
Asthma	0	0	0	1 (0.9)	0	2 (1.9)	0	0	0	0	2 (0.5)	2 (0.5)
Pruritis	0	2 (1.8)	0	0	1 (0.9)	0	0	0	2 (0.9)	3 (1.4)	7 (1.7)	4 (1.0)
Pruritis generalized	0	0	0	0	0	0	0	0	0	0	1 (0.2)	1 (0.3)
Blister	0	0	0	0	0	0	0	1 (1.0)	2 (0.9)	0	1 (0.2)	1 (0.3)
Dermatitis	0	0	0	0	0	0	0	0	0	0	4 (1.0)	1 (0.3)
Dermatitis allergic	0	0	0	0	0	0	0	0	0	0	1 (0.2)	1 (0.3)
Dermatitis contact	0	0	0	0	0	0	0	1 (1.0)	0	3 (1.4)	2 (0.5)	1 (0.3)
Dry skin	0	0	0	0	0	0	0	0	3 (1.4)	2 (1.0)	3 (0.7)	4 (1.0)
Eczema	0	0	0	0	0	0	0	0	2 (0.9)	2 (1.0)	2 (0.5)	5 (1.3)
Erythema	0	0	0	0	0	0	0	1 (1.0)	0	1 (0.5)	0	0
Face edema	0	0	0	0	0	0	0	0	0	0	1 (0.2)	1 (0.3)
Hypersensitivity	0	0	0	0	0	0	0	0	2 (0.9)	1 (0.5)	2 (0.5)	0
Rash	0	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)	0	0	0	4 (1.9)	5 (2.4)	10 (2.5)	7 (1.8)
Rash generalized	0	0	0	0	0	0	0	0	0	0	2 (0.5)	0
Rash macular	0	0	0	0	0	0	0	1 (1.0)	2 (0.9)	0	2 (0.5)	0
Rash papular	0	0	0	0	0	0	0	2 (1.9)	1 (0.5)	1 (0.5)	2 (0.5)	1 (0.3)
Rash pruritic	0	0	0	0	0	0	0	0	0	0	1 (0.2)	2 (0.5)
Skin exfoliation	0	0	0	0	0	0	0	0	0	0	0	2 (0.5)
Skin ulcer	0	0	0	0	0	0	0	0	0	0	5 (1.2)	1 (0.3)
Skin fissures	0	0	0	0	0	0	0	2 (1.9)	0	0	3 (0.7)	0
Skin lesion	0	0	0	0	0	0	0	0	2 (0.9)	1 (0.5)	4 (1.0)	3 (0.8)

Table 20. Study 305: Potential cutaneous drug reaction AEs that occurred in ≥3 subjects total

Preferred Term	Number (%) of Subjects			
	MET+A12.5 (N=873)	MET+A25 (N=877)	MET+Glipizide (N=869)	Total (N=2621)
Asthma	2 (0.2)	2 (0.2)	4 (0.5)	8 (0.3)
Blister	3 (0.3)	1 (0.1)	0	4 (0.2)
Dermatitis	1 (0.1)	0	3 (0.3)	4 (0.2)
Dermatitis allergic	4 (0.5)	1 (0.1)	1 (0.1)	6 (0.2)
Dermatitis contact	3 (0.3)	3 (0.3)	4 (0.5)	10 (0.4)
Eczema	2 (0.2)	2 (0.2)	1 (0.1)	5 (0.2)
Erythema	1 (0.1)	0	2 (0.2)	3 (0.1)
Hypersensitivity	3 (0.3)	0	1 (0.1)	4 (0.2)
Pruritus	10 (1.1)	4 (0.5)	3 (0.3)	17 (0.6)
Rash	9 (1.0)	11 (1.3)	10 (1.2)	30 (1.1)
Rash papular	0	1 (0.1)	3 (0.3)	4 (0.2)
Rash pruritic	2 (0.2)	1 (0.1)	2 (0.2)	5 (0.2)
Skin lesion	1 (0.1)	4 (0.5)	2 (0.2)	7 (0.3)
Skin ulcer	2 (0.2)	2 (0.2)	1 (0.1)	5 (0.2)
Urticaria	3 (0.3)	4 (0.5)	1 (0.1)	8 (0.3)

Source: Interim CSR 305 Table 12.k

Angioedema: The percentage of alogliptin + metformin subjects with AEs in the angioedema SMQ was lower than the percentage of subjects with PDCR events (see Table 21 and Table 22). It ranged from 0% (A12.5+M in study MET-302) to 5.2% (A25+M+P30 in study OPI-004). Edema peripheral was the most common event, although it is a broad search term and may not be indicative of a true case of angioedema. Furthermore, my review of the AEs leading to discontinuation in the four controlled phase 3 studies identified only one event in alogliptin + metformin subjects in the angioedema SMQ, an event of edema peripheral in a A25+M+P30 subject in study OPI-004. This event may not be related to alogliptin as pioglitazone is associated with edema.

Table 21. Angioedema AEs (Completed phase 3 studies)

SOC	MET-302							MET-008			OPI-004	
	PLB	A25QD	A12.5BID	M500BID	M1000BID	A12.5+ M500BID	A12.5+ M1000BID	PLB+M	A12.5+M	A25+M	A25+M +P30	M+P45
N	106	112	110	109	111	106	114	104	213	207	404	399
Any AE of Angioedema	0	1 (0.9)	0	2 (1.8)	0	0	2 (1.8)	2 (1.9)	4 (1.9)	5 (2.4)	21 (5.2)	25 (6.3)
Edema peripheral	0	0	0	2 (1.8)	0	0	2 (1.8)	1 (1.0)	0	3 (1.4)	16 (4.0)	18 (4.5)
Pitting edema	0	0	0	0	0	0	0	0	1 (0.5)	1 (0.5)	1 (0.2)	7 (1.8)
Angioedema	0	0	0	0	0	0	0	0	0	0	1 (0.2)	0
Corneal edema	0	0	0	0	0	0	0	0	0	0	1 (0.2)	0
Periorbital edema	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)
Face edema	0	0	0	0	0	0	0	0	0	0	1 (0.2)	1 (0.3)
Generalized edema	0	0	0	0	0	0	0	0	0	0	1 (0.2)	0
Lip swelling	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)
Swelling face	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)
Wheezing	0	1 (0.9)	0	0	0	0	0	0	0	0	0	0
Drug hypersensitivity	0	0	0	0	0	0	0	0	1 (0.5)	0	0	0
Hypersensitivity	0	0	0	0	0	0	0	0	2 (0.9)	1 (0.5)	2 (0.5)	0
Urticaria	0	0	0	0	0	0	0	0	0	0		
Urticaria localized	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)

Source: SCS Table 2.z, 2.aa, and 2.bb

Table 22. Study 305: Angioedema AEs

Preferred Term	Number (%) of Subjects			
	MET+A12.5 (N=873)	MET+A25 (N=877)	MET+Glipizide (N=869)	Total (N=2621)
Angioedema	0	0	2 (0.2)	2 (0.1)
Drug hypersensitivity	1 (0.1)	0	1 (0.1)	2 (0.1)
Eyelid oedema	0	0	1 (0.1)	1 (<0.1)
Face oedema	0	0	1 (0.1)	1 (<0.1)
Generalised oedema	0	0	1 (0.1)	1 (<0.1)
Hypersensitivity	3 (0.3)	0	1 (0.1)	4 (0.2)
Lip swelling	1 (0.1)	0	0	1 (<0.1)
Local swelling	0	1 (0.1)	3 (0.3)	4 (0.2)
Oedema	2 (0.2)	1 (0.1)	2 (0.2)	5 (0.2)
Oedema peripheral	7 (0.8)	13 (1.5)	12 (1.4)	32 (1.2)
Swelling face	1 (0.1)	0	1 (0.1)	2 (0.1)
Urticaria	3 (0.3)	4 (0.5)	1 (0.1)	8 (0.3)
Wheezing	0	2 (0.2)	2 (0.2)	4 (0.2)

Source: Interim CSR 305 Table 12.1

Table 23. Study 305: Total angioedema events

	A12.5+M (N=873)	A25+M (N=877)	Glipizide+M (N=869)
Total angioedema events	18 (2.0%)	21 (2.4%)	28 (3.2%)

Source: Table 22

Consistent with my previous recommendation for alogliptin drug product labels if alogliptin was approved, I recommend that use be contraindicated in subjects with a history of serious hypersensitivity reaction to alogliptin. I also recommend a warning about the risk of hypersensitivity and that these events be monitored as an AE of special interest in the controlled CV study 402 and PSURs.

Pancreatitis: The MedDRA SMQ for acute pancreatitis was used to search for events in completed phase 3 studies MET-302, MET-008, and OPI-004 and ongoing study 305. The MedDRA SMQ for acute pancreatitis specifies both narrow scope terms (category “A”) 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” terms) and a symptom associated with pancreatitis (category “C” terms). However, amylase and lipase values were only measured in study MET-302 when subjects experienced persistent nausea and/or vomiting for ≥3 days with or without abdominal pain.

Using the SMQ criteria, there were 3 subjects with acute pancreatitis in study MET-302 (one each in A12.5+M500BID [pancreatitis acute], A12.5+M1000BID [pancreatitis], and

M1000BID groups). The A12.5+M1000BID subject was discontinued due to acute pancreatitis. Narratives for these alogliptin + metformin subjects are as follows:

- 302/5082-004 (A12.5+M1000BID): 77 year old male with a history of T2DM, hyperlipidemia, chronic obstructive pulmonary disease, psoriasis, HTN, gastroesophageal reflux disease, and season allergy who experienced pancreatitis on day 56. The event was of moderate intensity and resulted in study drug withdrawal. The event resolved on day 88. Amylase values were 48, 124, and 58 U/L at baseline, day 56, and day 88, respectively (reference range 35 – 121 U/L). Lipase values were 72, 192, and 59 U/L at baseline, day 56, and day 88, respectively (reference range 13 – 60 U/L).
- 302/5166-007 (A12.5+M500BID): 70 year old female with T2DM, hypertriglyceridemia, chronic pancreatitis, essential HTN, alimentary constitutive obesity, osteoarthritis, menopause, and cholecystectomy experienced acute pancreatitis on days 86 – 92. The event was mild. She had no signs and symptoms other than mildly elevated lipase and amylase values. Amylase values were 75, 240, 134, and 63 at baseline, day 86, day 113, and day 123, respectively. Lipase values were 46, 152, 97, and 26 U/L on the same days.

Table 24. Study MET-302: AEs in the acute pancreatitis MedDRA SMQ by criteria

Adverse Event Type	Number (%) of Subjects					
	Placebo N=106	A12.5 QD N=112	A12.5 BID N=110	M500 BID N=109	M1000 BID N=111	A12.5+M500 BID N=106
Criteria Met (a)						
AEs						
A or (B and C)	0	0	0	0	1 (0.9%)	1 (0.9%)
A	0	0	0	0	0	1 (0.9%)
B and C	0	0	0	0	1 (0.9%)	0
Serious AEs						
A or (B and C)	0	0	0	0	0	0
AEs that led to discontinuation						
A or (B and C)	0	0	0	0	0	1 (0.9%)
A	0	0	0	0	0	1 (0.9%)
B and C	0	0	0	0	0	0

Source: IAS Table 2.1.1.2.1.

Note: Includes data collected on or after the date of first dose of double-blind study medication and within 14 days after the date of last dose of double-blind study medication (or on or prior to the date of hyperglycemic rescue, if applicable).

(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.

Source: SCS Table 2.dd

No subjects in MET-008 or OPI-004 reported a narrow-scope term within the acute pancreatitis SMQ or had laboratory values or signs and symptoms that met the SMQ criteria. One glipizide + metformin subject experienced a SAE of pancreatitis in study 305.

In ongoing study 305, the following two alogliptin 25 mg + metformin subjects met the pancreatitis SMQ criteria (see Table 25):

- 305/5032-008 (A25+M): 65 year old male with a history of T2DM, Guillain Barre, and cholelithiasis was discontinued due to nausea on day 344. Amylase and lipase on day 281 were 287 U/L (normal 35-121 U/L) and 711 U/L (normal 13-60 U/L), respectively. On days 344, 358 (early termination), and 372 (unscheduled visit), amylase was 103, 236, and 109 U/L, respectively. Lipase values on the same days were 140, 548, and 169 U/L, respectively.
- 305/5005-022 (A25+M): This subject had abdominal pain on days 20-28 and increased lipase (day 20-23), although the only reported lipase level was normal (37 U/L). The events resolved. The subject continued in the study.

Table 25. Study 305: Summary of acute pancreatitis by MedDRA SMQ criteria

Adverse Event Type Criteria Met (a)	Number (%) of Subjects		
	MET+alogliptin 12.5 mg N=876	MET+alogliptin 25 mg N=877	MET+glipizide N=869
TEAEs			
A or (B and C)	0	2 (0.2%)	1 (0.1%)
A	0	0	1 (0.1%)
B and C	0	2 (0.2%)	0
SAE			
A or (B and C)	0	0	1 (0.1%)
A	0	0	1 (0.1%)
B and C	0	0	0
TEAEs Leading to Discontinuation			
A or (B and C)	0	1 (0.1%)	1 (0.1%)
A	0	0	1 (0.1%)
B and C	0	1 (0.1%)	0

Source: Table 1.1.

(a) 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 summaries of SAEs and TEAEs that led to discontinuation if at least 1 of the events was serious or led to discontinuation, respectively.

Source: Safety Update Table 2.b

In summary, there was a slight imbalance in the number of pancreatitis cases in alogliptin + metformin subjects in study MET-302 and ongoing 305. A total of two alogliptin + metformin subjects were discontinued due to this event, although no events were serious. No subjects in MET-008 or OPI-004 reported a narrow-scope term within the acute pancreatitis SMQ or had laboratory values or signs and symptoms that met the SMQ criteria.

Consistent with my previous alogliptin recommendation, if approved, I recommend labeling contain an acute pancreatitis warning consistent with that for other DPP-4 inhibitors, as pancreatitis events have been observed in subjects taking alogliptin. 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: The percentage of subjects with Infections and Infestations AEs in completed phase 3 studies is shown in Table 26. In alogliptin + metformin subjects, it ranged from 21.9 – 38.6%. The incidence of AEs in this SOC was greatest in study OPI-004; this may be due to its longer duration (52- vs. 26-weeks).

Table 26. Infections and Infestations AEs (Completed phase 3 studies)

Study and Treatment Group	Infections and Infestations AEs (n, %)
MET-302	
Placebo (n=106)	20 (18.9)
A25 QD (n=112)	20 (17.9)
A12.5 BID (n=110)	18 (16.4)
M500 BID (n=109)	21 (19.3)
M1000 BID (n=111)	18 (16.2)
A12.5+M500 BID (n=106)	26 (24.5)
A12.5+M1000 BID (n=114)	25 (21.9)
MET-008	
A12.5+M QD (n=213)	68 (31.9)
A25+M QD (n=207)	53 (25.6)
Placebo+Met QD (n=104)	28 (26.9)
OPI-004	
A25+M+P30 (n=404)	156 (38.6)
M+P45 (n=399)	130 (32.6)

Source: SCS Tables 2.gg, 2.hh, and 2.ii

The most common events in completed phase 3 studies were upper respiratory tract infection, nasopharyngitis, sinusitis, bronchitis, influenza, and urinary tract infection. One alogliptin + metformin subject (302/5252-001 in group A12.5+M1000BID) experienced an AE (gallbladder empyema) which resulted in study drug discontinuation. Eight alogliptin + metformin subjects in completed phase 3 trials experienced SAEs within the Infections and Infestations SOC, as follows:

- 302/5252-001 (A12.5+M1000BID): Gallbladder empyema
- 008/319-8006 (A12.5+M): Appendicitis
- 008/447-8038 (A25+M): Urinary tract infection
- 008/502-8008 (A25+M): Postoperative wound infection
- 004/0627-4539 (A25+M+P30): Lobar pneumonia
- 004/1152-4507 (A25+M+P30): Appendicitis
- 004/1243-4502 (A25+M+P30): Pneumonia primary atypical
- 004/1244-4503 (A25+M+P30): Osteomyelitis

Infections and infestations SAEs reported by ≥ 2 subjects in ongoing study 305 are shown in Table 27. The percentage of subjects experiencing an SAE in this SOC was less for the alogliptin + metformin groups when compared to the glipizide + metformin group. In addition, only one alogliptin + metformin subject was discontinued to an infection AE (viral hepatitis).

Table 27. Study 305: Infections and infestations SAEs reported by ≥ 2 subjects total

SOC Preferred Term	Number (%) of Subjects			
	MET+A12.5 (N=873)	MET+A25 (N=877)	MET+Glipizide (N=869)	Total (N=2621)
Infections and infestations	9 (1.0)	9 (1.0)	14 (1.6)	32 (1.2)
Cellulitis	2 (0.2)	1 (0.1)	2 (0.2)	5 (0.2)
Gastroenteritis	2 (0.2)	2 (0.2)	0	4 (0.2)
Dengue fever	1 (0.1)	0	2 (0.2)	3 (0.1)
Hepatitis viral	1 (0.1)	0	2 (0.2)	3 (0.1)
Pneumonia	1 (0.1)	1 (0.1)	1 (0.1)	3 (0.1)
Urinary tract infection	1 (0.1)	0	1 (0.1)	2 (0.1)
Urosepsis	0	1 (0.1)	1 (0.1)	2 (0.1)

Source: Interim CSR 305 Table 12.h

These infection findings are consistent with other DPP4 inhibitors and are not an approvability issue.

Hypo- and Hyperglycemia: Hypoglycemia was classified as follows in phase 3 studies:

- Mild to Moderate:
 - o MET-302:
 - Symptomatic and plasma glucose <70 mg/dl
 - Asymptomatic and blood glucose <70 mg/dl
 - o MET-008, OPI-004, and 305:
 - Symptomatic and blood glucose <60 mg/dl
 - Symptomatic or asymptomatic and blood glucose <50 mg/dl
- Severe:
 - o MET-302: Any episode that required assistance associated with a documented blood glucose <70 mg/dl
 - o MET-008, OPI-004, and 305: Any episode that required assistance associated with a documented blood glucose <60 mg/dl

The incidence of hypoglycemia in completed and ongoing phase 3 studies was low (see Table 28). The majority of events were mild to moderate severity. The applicant's proposal to include a hypoglycemia warning in the Highlights text is acceptable.

Table 28. Hypoglycemic events (Completed and ongoing phase 3 studies)

Study and Treatment Group	Mild to Moderate				Severe	
	Symptomatic		Symptomatic or Asymptomatic			
	Events	N (%)	Events	N (%)	Events	N (%)
MET-302						
Placebo (n=106)	0	0	1	1 (0.9)	0	0
A25 QD (n=112)	0	0	7	2 (1.8)	0	0
A12.5 BID (n=110)	6	4 (3.6)	8	4 (3.6)	0	0
M500 BID (n=109)	0	0	4	2 (1.8)	0	0
M1000 BID (n=111)	8	5 (4.5)	12	2 (1.8)	0	0
A12.5+M500 BID (n=106)	2	1 (0.9)	8	1 (0.9)	0	0
A12.5+M1000 BID (n=114)	1	1 (0.9)	5	2 (1.8)	0	0
MET-008						
A12.5+M QD (n=213)	2	1 (0.5)	1	1 (0.5)	0	0
A25+M QD (n=207)	0	0	0	0	0	0
Placebo+Met QD (n=104)	1	1 (1.0)	0	0	0	0
OPI-004						
A25+M+P30 (n=404)	20	8 (2.0)	11	7 (1.7)	2	2 (0.5)
M+P45 (n=399)	3	2 (0.5)	2	2 (0.5)	0	0
305						
A12.5+M (n=873)		14 (1.6)		0		1 (0.1)
A25+M (n=877)		9 (1.0)		0		0
Glipizide+M (n=869)		172 (19.8)		2 (0.2)		4 (0.5)

Source: SCS Tables 3.z, 3.aa, and 3.bb and Interim CSR 305 Table 12.u

Hyperglycemic rescue criteria were as follows for completed phase 3 studies MET-302, MET-008, and OPI-004:

- Prior to the week 4 visit: A single fasting plasma glucose ≥ 275 mg/dL as determined by the central laboratory and confirmed by a second sample drawn within 7 days after the first sample and analyzed by the central laboratory.
- From the week 4 visit but prior to the week 8 visit: A single fasting plasma glucose ≥ 250 mg/dL as determined by the central laboratory and confirmed by a second sample drawn within 7 days after the first sample and analyzed by the central laboratory.
- From the week 8 visit but prior to the week 12 visit: A single fasting plasma glucose ≥ 225 mg/dL as determined by the central laboratory and confirmed by a second sample drawn within 7 days after the first sample and analyzed by the central laboratory.

- From the week 12 visit through the End of Treatment visit: HbA1c $\geq 8.5\%$ and $\leq 0.5\%$ reduction in HbA1c as compared with the baseline HbA1c confirmed by a second sample drawn within 7 days after the first sample and analyzed by the central laboratory
- Also OPI-004: Any time point during the study. HbA1c raised to $>10\%$ as determined by the central laboratory

Hyperglycemic rescue criteria are as follows in ongoing study 305: Subjects demonstrating persistent hyperglycemia, defined as FPG ≥ 250 mg/dL, confirmed by a repeated FPG test within seven days, after at least two weeks of treatment but prior to Week 20, underwent a dose titration (increase of glipizide or matching placebo from 5 mg up to 20 mg in at least 4-week intervals). Following this dose titration up to Week 20, no further up-titration was allowed and a subject who continued to experience hyperglycemia was rescued per the criteria indicated below.

- From the Week 20 Visit through prior to the Week 26 Visit: HbA1c $\geq 8.5\%$, and confirmed by a second sample drawn within 7 days after the first sample and analyzed by the central laboratory.
- From the Week 26 Visit through prior to the Week 52 Visit: HbA1c $\geq 8.0\%$ AND $\leq 0.5\%$ reduction in HbA1c as compared with the Baseline HbA1c, confirmed by a second sample drawn within 7 days after the first sample and analyzed by the central laboratory.
- From the Week 52 Visit through the End-of-Treatment Visit: HbA1c $\geq 7.5\%$ AND $\leq 0.5\%$ reduction in HbA1c as compared with the Baseline HbA1c, confirmed by a second sample drawn within 7 days after the first sample and analyzed by the central laboratory.

The percentage of subjects who required hyperglycemic rescue in phase 3 studies is shown in Table 29. The percentage in alogliptin + metformin groups ranged from 2.6-12.3%. As expected, the percentage of alogliptin + metformin subjects rescued in placebo-controlled trials MET-302 and MET-008 was less than that of placebo subjects. The percentage of alogliptin + metformin subjects rescued in comparator-controlled trials was also less than comparator (i.e. glipizide or pioglitazone 45 mg) subjects.

Table 29. Subjects (n, %) who required hyperglycemic rescue (Completed phase 3 studies)

Study and Treatment Group	Subjects (n,%) who Required Hyperglycemic Rescue
MET-302	
Placebo (n=106)	41 (38.7)
A25 QD (n=112)	22 (19.6)
A12.5 BID (n=110)	19 (17.3)
M500 BID (n=109)	25 (22.9)

M1000 BID (n=111)	12 (10.8)
A12.5+M500 BID (n=106)	13 (12.3)
A12.5+M1000 BID (n=114)	3 (2.6)
MET-008	
A12.5+M QD (n=213)	19 (9.0)
A25+M QD (n=207)	17 (8.2)
Placebo+Met QD (n=104)	25 (24.0)
OPI-004	
A25+M+P30 (n=404)	44 (10.9)
M+P45 (n=399)	86 (21.7)
305	
A12.5+M (n=873)	101 (11.6)
A25+M (n=877)	79 (9.1)
Glipizide+M (n=869)	103 (12.0)

Source: Summary of Clinical Efficacy Table 3.a, 3.b, and 3.c and Interim CSR 305 Table 11.q

Lactic Acidosis: No cases of lactic acidosis were identified in the SCS, Four-Month Safety Update, or Interim CSR 305.

Decrease in Vitamin B12 Levels and Anemia: Although B12 was not routinely drawn in phase 3 studies, no cases of B12 deficiency were identified in the SCS, Four-Month Safety Update, or Interim CSR 305. Please refer to section 7.4.2 Laboratory Findings for a discussion of hematologic parameters.

7.3.5 Submission Specific Primary Safety Concerns

Alogliptin/metformin FDC Data: This review of hepatic safety information focuses on data that was not previously reviewed under the first alogliptin and alogliptin/pioglitazone FDC CRs. Specifically, I discuss data from ongoing study 305, completed uncontrolled study OLE-012, and relevant postmarketing reports. (Study MET-302 was previously reviewed in the applicant's integrated analysis response to our October 2011 global hepatic safety information request.)

In ongoing study 305, there were no deaths due to liver abnormalities. Table 30 summarizes the number and percentage of subjects with key markedly abnormal hepatic events and events which led to study drug discontinuation. The incidence of discontinuation was generally lower than that of markedly abnormal key hepatic values. The percentage of subjects who discontinued study drug was similar between treatment groups. The percentage of alogliptin subjects with markedly abnormal key hepatic values was lower or equal to the percentage of glipizide subjects.

A12.5+M subject 305/5304-024 had an SAE of ALT increased. This was a 41 year old male with a history of T2DM and renal calculi who began study drug on October 25, 2009 when baseline ALT was 18 U/L. On January 27, 2010, ALT was 135 U/L. Study drug was continued and the subject recovered. On February 13, 2010, ALT was 208 U/L (>5xULN). He was on concomitant rabeprazole and domperidone. The subject was asymptomatic but he was treated for the ALT elevation with ursodiol and pantoprazole. Abdomen and pelvis ultrasound was normal. On February 17, he discontinued study drug. On February 20, he was withdrawn due to liver safety withdrawal criteria. He was hepatitis C negative. The event resolved on March 5.

One A12.5+M and one glipizide+M subject each had ALT >3xULN and total bilirubin >2 mg/dl. However, the A12.5+M subject 305/5304-055 had a history of elevated ALT prior to starting study drug and a concomitant diagnosis of viral hepatitis.

Table 30. 305: Subjects (n, %) with key markedly abnormal hepatic events and events which lead to study drug discontinuation

	A12.5+M N=873	A25+M N=877	Glipizide+M N=869
Key hepatic TEAEs leading to drug discontinuation			
ALT increased	2 (0.2)	1 (0.1)	1 (0.1)
Hepatic enzyme increased	1 (0.1)	1 (0.1)	1 (0.1)
Transaminases increased	1 (0.1)	0	0
Key markedly abnormal hepatic values			
ALT >3xULN	22 (2.5)	11 (1.3)	24 (2.8)
ALT >5xULN	6 (0.7)	2 (0.2)	8 (0.9)
ALT >8xULN	3 (0.3)	1 (0.1)	5 (0.6)
ALT >3xULN & Tbili >2 mg/dl	1 (0.1)	0	1 (0.1)

Source: Interim CSR 305 Table 12.o and 12.p

In completed, uncontrolled, open-label study OLE-012, two events occurred which met the biochemical definition of Hy's law (see Table 31). Both subjects had alternate etiologies for the laboratory abnormalities. These cases were previously submitted (November 7, 2011) and reviewed under the alogliptin CR. No additional events occurred between that data cut-off (October 25, 2011) and the completion of the study in December 2011.

Table 31. OLE-012: Potential biochemical Hy's law events

Subject number	Treatment	Preferred Term	Outcome	Etiology	Serious	Previously Submitted
961-2501	Alogliptin 25 mg	Hepatic enzyme increased ALT increased AST increased	Resolved	Transient and recurrent elevations throughout the study period. Fatty liver.	No	Yes
961-3006	Alogliptin 25 mg	ALT increased AST increased	Resolved	Chemical toxicity and/or ACE inhibitor. Enzyme elevations were transient.	No	Yes

Source: SCS Table 3.a

As requested, the applicant submitted postmarketing liver safety events to both the alogliptin/metformin FDC IND and NDA. See section 2.6 Other Relevant Background Information for a list of postmarketing liver safety cases submitted. Submitted cases were reviewed and determined to either have potential alternate etiologies or not to be serious with the exception of case TCI2012A02494. This was a 91 year old Japanese female with a relevant history of T2DM, CHF, pulmonary stenosis, pleural effusion, aspiration pneumonia, and early dementia who began alogliptin on April 10, 2012. On April 19, ALT was 1266 IU/L, AST 723 IU/L, and total bilirubin 1.0 mg/dl. Alogliptin was discontinued. She died (b) (6) due to "aggravation of aspiration pneumonia and cardiac failure". This case was consulted to OSE's hepatologist Leonard Seeff who concluded that the liver injury was more likely the result of CHF and associated hypotension than drug-induced liver injury.

Alogliptin Second Resubmission Data: 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, on July 26, 2012, the applicant submitted the second alogliptin CR, which contained safety data from 20 controlled phase 2 and 3 studies and the Fourth Japanese PSUR. On August 16, 2012, the applicant submitted this information to alogliptin/metformin FDC NDA 203-414. It constituted a Major Amendment and resulted in a revision of the PDUFA goal date to December 22, 2012.

In controlled phase 2 and 3 studies which contain 9857 subjects exposed to alogliptin, the incidence of transaminase elevation with alogliptin 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, the

current clinical database supports approval of alogliptin. (See my review of the second alogliptin resubmission for full details.) As co-administration with metformin is not expected to alter the liver safety of alogliptin and the alogliptin + metformin data reviewed above did not reveal a signal for hepatotoxicity, I recommend approval of the alogliptin/metformin FDC.

I recommend the applicant include hepatic enzyme elevations in the labeling section 6.2 Postmarketing Experience and section 5 Warnings and Precautions. Hepatotoxicity should be monitored as an adverse event (AE) of special interest in the controlled CV study 402, the PSURs, and by an enhanced pharmacovigilance PMR.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

As the common adverse events in studies MET-008 and OPI-004 were previously reviewed, I focused on the common adverse events in studies MET-302 and 305. The AEs experienced by $\geq 3\%$ of subjects in any treatment group in these studies is shown in Table 32 and Table 33. The percentage of alogliptin + metformin subjects with any AE in studies MET-302 and 305 ranged from 63.2-64.0% to 70.1-72.2%, respectively. These values were less than the placebo group (71.7%) or similar to glipizide comparator (71.1%), respectively. The most common AEs ($\geq 5\%$) in the combination treatment groups were creatinine clearance decreased, diarrhea, dyslipidemia, dyspepsia, headache, hyperglycemia, hypertension, nasopharyngitis, nausea, and upper respiratory tract infection.

Table 32. Study MET-302: AEs experienced by ≥3% of subjects in any treatment group

SOC Preferred Term	Number (%) of Subjects						
	Placebo (N=106)	A12.5 BID (N=110)	A 25 QD (N=112)	M500 BID (N=109)	M1000 BID (N=111)	A12.5+ M500 BID (N=106)	A12.5+ M1000 BID (N=114)
Subjects with Any AE	76 (71.7)	67 (60.9)	61 (54.5)	75 (68.8)	69 (62.2)	67 (63.2)	73 (64.0)
Metabolism and nutrition disorders							
Hyperglycemia	29 (27.4)	13 (11.8)	19 (17.0)	19 (17.4)	9 (8.1)	8 (7.5)	1 (0.9)
Dyslipidemia	6 (5.7)	2 (1.8)	1 (0.9)	7 (6.4)	6 (5.4)	6 (5.7)	2 (1.8)
Hypertriglyceridemia	3 (2.8)	0	2 (1.8)	2 (1.8)	6 (5.4)	5 (4.7)	1 (0.9)
Hypercholesterolemia	1 (0.9)	3 (2.7)	3 (2.7)	1 (0.9)	4 (3.6)	0	1 (0.9)
Hyperkalemia	0	2 (1.8)	1 (0.9)	0	4 (3.6)	1 (0.9)	0
Infections and infestations							
Upper respiratory tract infection	3 (2.8)	3 (2.7)	3 (2.7)	4 (3.7)	3 (2.7)	8 (7.5)	2 (1.8)
Nasopharyngitis	2 (1.9)	1 (0.9)	6 (5.4)	2 (1.8)	3 (2.7)	2 (1.9)	2 (1.8)
Urinary tract infection	1 (0.9)	1 (0.9)	3 (2.7)	1 (0.9)	4 (3.6)	1 (0.9)	3 (2.6)
Sinusitis	2 (1.9)	2 (1.8)	2 (1.8)	2 (1.8)	0	1 (0.9)	4 (3.5)
Influenza	2 (1.9)	2 (1.8)	0	1 (0.9)	1 (0.9)	4 (3.8)	2 (1.8)
Gastrointestinal disorders							
Diarrhea	3 (2.8)	3 (2.7)	1 (0.9)	4 (3.7)	10 (9.0)	6 (5.7)	8 (7.0)
Nausea	1 (0.9)	3 (2.7)	0	4 (3.7)	6 (5.4)	3 (2.8)	6 (5.3)
Dyspepsia	3 (2.8)	1 (0.9)	0	0	2 (1.8)	0	8 (7.0)
Constipation	3 (2.8)	4 (3.6)	0	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.9)
Gastritis	0	2 (1.8)	1 (0.9)	2 (1.8)	5 (4.5)	0	1 (0.9)
Vomiting	1 (0.9)	0	0	0	4 (3.6)	2 (1.9)	1 (0.9)
Investigations							
Creatinine renal clearance decreased	3 (2.8)	4 (3.6)	1 (0.9)	0	6 (5.4)	5 (4.7)	9 (7.9)
Glycosylated hemoglobin increased	4 (3.8)	2 (1.8)	1 (0.9)	2 (1.8)	1 (0.9)	1 (0.9)	2 (1.8)
Nervous system disorders							
Headache	3 (2.8)	5 (4.5)	5 (4.5)	7 (6.4)	4 (3.6)	7 (6.6)	6 (5.3)
Musculoskeletal and connective tissue disorders							
Back pain	1 (0.9)	1 (0.9)	0	6 (5.5)	1 (0.9)	4 (3.8)	0
Pain in extremity	1 (0.9)	1 (0.9)	2 (1.8)	1 (0.9)	4 (3.6)	2 (1.9)	0
General disorders and administration site conditions							
Asthenia	4 (3.8)	0	2 (1.8)	2 (1.8)	2 (1.8)	3 (2.8)	2 (1.8)
Pyrexia	0	2 (1.8)	1 (0.9)	1 (0.9)	5 (4.5)	1 (0.9)	1 (0.9)
Renal and urinary disorders							
Dysuria	0	0	1 (0.9)	0	4 (3.6)	0	1 (0.9)
Vascular disorders							
Hypertension	4 (3.8)	2 (1.8)	3 (2.7)	4 (3.7)	1 (0.9)	4 (3.8)	8 (7.0)

Source: MET-302 Table 15.3.1.2.1.

Note: Includes data collected on or after the date of first dose of double-blind study medication and within 14 days after the date of last dose of double-blind study medication (or on or prior to the date of hyperglycemic rescue, if applicable).

Source: SCS Table 2.d

Table 33. Study 305: AEs by preferred term occurring in 3% of subjects in any treatment group

SOC Preferred Term	Number (%) of Subjects			
	MET+A12.5 (N=873)	MET+A25 (N=877)	MET+Glipizide (N=869)	Total (N=2621)
Subjects with at least 1 TEAE	630 (72.2)	615 (70.1)	623 (71.7)	1868 (71.3)
Blood and lymphatic system disorders	37 (4.2)	51 (5.8)	40 (4.6)	128 (4.9)
Anaemia	13 (1.5)	28 (3.2)	22 (2.5)	63 (2.4)
Gastrointestinal disorders	182 (20.8)	175 (20.0)	170 (19.6)	527 (20.1)
Diarrhoea	49 (5.6)	46 (5.2)	51 (5.9)	146 (5.6)
Nausea	25 (2.9)	26 (3.0)	19 (2.2)	70 (2.7)
Infections and infestations	308 (35.3)	290 (33.1)	262 (30.1)	860 (32.8)
Upper respiratory tract infection	65 (7.4)	73 (8.3)	56 (6.4)	194 (7.4)
Nasopharyngitis	66 (7.6)	50 (5.7)	45 (5.2)	161 (6.1)
Influenza	30 (3.4)	21 (2.4)	31 (3.6)	82 (3.1)
Bronchitis	25 (2.9)	26 (3.0)	29 (3.3)	80 (3.1)
Urinary tract infection	28 (3.2)	25 (2.9)	23 (2.6)	76 (2.9)
Investigations	109 (12.5)	116 (13.2)	99 (11.4)	324 (12.4)
Creatinine renal clearance decreased	22 (2.5)	31 (3.5)	29 (3.3)	82 (3.1)
Metabolism and nutrition disorders	83 (9.5)	80 (9.1)	160 (18.4)	323 (12.3)
Hypoglycaemia	11 (1.3)	5 (0.6)	72 (8.3)	88 (3.4)
Musculoskeletal and connective tissue disorders	149 (17.1)	156 (17.8)	151 (17.4)	456 (17.4)
Back pain	38 (4.4)	35 (4.0)	36 (4.1)	109 (4.2)
Arthralgia	26 (3.0)	28 (3.2)	28 (3.2)	82 (3.1)
Nervous system disorders	106 (12.1)	122 (13.9)	125 (14.4)	353 (13.5)
Headache	40 (4.6)	49 (5.6)	36 (4.1)	125 (4.8)
Dizziness	16 (1.8)	18 (2.1)	21 (2.4)	55 (2.1)
Respiratory, thoracic and mediastinal disorders	80 (9.2)	72 (8.2)	60 (6.9)	212 (8.1)
Cough	27 (3.1)	19 (2.2)	21 (2.4)	67 (2.6)
Vascular disorders	41 (4.7)	56 (6.4)	60 (6.9)	157 (6.0)
Hypertension	29 (3.3)	38 (4.3)	46 (5.3)	113 (4.3)

Source: Table 15.3.1.2.1.

Note: Includes only data collected after the first dose of double-blind study medication and within 14 days after the last dose of double-blind study medication.

Source: Interim CSR 305 Table 12.d

7.4.2 Laboratory Findings

Overview of Laboratory Testing in Development Program: In completed, controlled, phase 3 trials, laboratory samples for hematology and chemistry were collected at every visit. Urinalysis tests were collected at protocol-specified visits. The normal ranges and markedly abnormal criteria for laboratory tests are shown in Table 34; they are acceptable. The sponsor did not thoroughly evaluate lipid levels, as they were only measured in study MET-302. However, I am reassured about the CV safety of alogliptin

because the upper bound of the 95% CI for the risk ratios comparing the incidence of MACE with alogliptin to that of placebo in study 402 was <1.8.

Table 34. 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)	32.0 – 72.0		>3 xULN
BUN (mg/dl)	5.0 – 20.0		>3 xULN
Basophils (%)	0.0 – 3.0		
Bicarbonate (meq/l)	21.0 – 33.0		
Calcium (mg/dl)	8.5 – 10.5	<0.8 xLLN	>1.2 xULN
Chloride (meq/l)	95.0 – 110.0		
Creatinine (mg/dl)	0.7 – 1.4		>1.5 x baseline; >1.5 x baseline & >ULN
Eosinophils (%)	0.0 – 7.0		
Gamma GT (mu/ml)	5.0 – 29.0		>3 xULN
Hematocrit/PCV (%)	M: 37.0 – 51.0 F: 33.0 – 47.0	<0.8 x baseline	
Hemoglobin (g/dl)	M: 12.5-17.0 F: 11.0-15.5	<Baseline – 3 g/dl	
Lactic dehydrogenase (mu/ml)	10.0 – 100.0		>3 xULN
Lymphocytes (%)	12-46		
Microalbumin/Cr ratio	0.0 – 20.0		
MCH (pg)	27.0-34.0		
MCV (fl)	M: 78.0 – 100.0 F: 82.0 – 102.0		
Monocytes (%)	0.0 – 11.0		
Neutrophils (%)	46.0 – 72.0		
Phosphorus (mg/dl)	2.5 – 4.5		
Platelet count (k/cu mm)	125.0 – 375.0	<50 x10 ³ /mm ³	>600 x10 ³ /mm ³
Potassium (meq/l)	3.5 – 5.0	<3 meq/l	>5.8 meq/l
Red blood cells (10 ⁶ /cu mm)	M: 4.0 – 5.6 F: 3.7 – 5.2	<0.8 x baseline	
SGOT (AST) (mu/ml)	8.0 – 22.0		> 3, 5, 8, or 10x ULN; >3 xULN & T bili >2 mg/dl
SGPT (ALT) (mu/ml)	5.0 – 25.0		> 3, 5, 8, or 10x ULN; >3 xULN & T bili >2 mg/dl
Sodium (meq/l)	133.0 – 145.0	<130	>150
Total bilirubin (mg/dl)	0.1 – 1.1		>2 mg/dl
Total protein (g/dl)	6.0 – 8.0	<0.8 xLLN	>1.2 xULN
Uric acid (mg/dl)	M: 4.0 – 8.0 F: 2.0 – 6.0		>10.5 >8.5

Urinary microalb/Cr (mcg/mg)	0.0 – 20.0		
Urinary pH	5.0 – 8.0		
Urinary specific gravity	1.002 – 1.035		
White blood cells (k/cu mm)	3.7 – 11.0	<2 x10 ³ /mm ³	>20 x 10 ³ /mm ³

Selection of Studies and Analyses for Drug-Controlled Comparisons of Laboratory Values: As the laboratory data from studies MET-008 and OPI-004 were previously reviewed as part of the alogliptin NDA and first CR, my review of the laboratory findings focused on phase 3 study MET-302. I analyzed measures of central tendency, outliers or shifts from normal to abnormal, and dropouts for laboratory abnormalities (excluding hypo- and hyperglycemia) for hematology, chemistry, and urinalysis data.

Analyses Focused on Measures of Central Tendency: MET-302 had the following entrance criteria:

- Hemoglobin >12 g/dl for men and >10 g/dl for women
- ALT ≤3x ULN
- Creatinine <1.5 mg/dl for men and <1.4 mg/dl for women

The mean change from baseline to endpoint for hematology, chemistry, and urinalysis parameters in MET-302 is shown in Table 35. Changes were generally small and similar between treatment groups, except for amylase and lipase values which were more variable. However, the number of subjects evaluated for these parameters in each treatment group was small (n=24 – 36), because amylase and/or lipase were only measured in subjects who had persistent nausea and/or vomiting for ≥3 days with or without abdominal pain. (See also Pancreatitis in section 7.3.4.)

Table 35. MET-302: Mean (SD) change from baseline to endpoint for hematology, chemistry, and urinalysis parameters

Laboratory	Placebo N=106	A25 QD N=112	A12.5 BID N=110	M500 BID N=109	M1000 BID N=111	A12.5+M500 BID N=106	A12.5+M1000 BID N=114
WBC (x10 ³ /mm ³)	-0.03 (1.3)	0.29 (1.6)	0.35 (1.5)	0.29 (1.7)	0.50 (1.5)	0.42 (1.3)	0.54 (1.6)
Neutrophils (%)	0.36 (10.5)	2.64 (14.7)	2.17 (9.8)	0.67 (11.9)	1.05 (10.9)	2.84 (9.5)	2.99 (13.7)
Lymphocytes (%)	-0.26 (9.1)	-2.15 (11.7)	-2.14 (7.4)	-0.80 (8.7)	-1.36 (9.0)	-2.42 (8.6)	-2.15 (9.4)
Monocytes (%)	-0.09 (2.5)	-0.27 (3.3)	0.07 (2.7)	-0.12 (3.5)	0.01 (2.4)	-0.20 (2.3)	-0.44 (4.4)
RBC (x10 ⁶ /mm ³)	-0.03 (0.2)	0.01 (0.3)	-0.03 (0.3)	-0.08 (0.3)	-0.08 (0.3)	-0.08 (0.4)	-0.13 (0.3)
Hematocrit (%)	-0.14 (2.0)	0.32 (2.8)	-0.19 (2.2)	-0.65 (2.6)	-0.44 (3.1)	-0.65 (3.2)	-0.86 (2.6)
Hemoglobin (g/dl)	-0.15 (0.6)	0.02 (1.0)	-0.19 (0.7)	-0.38 (0.9)	-0.33 (1.0)	-0.40 (1.0)	-0.53 (0.8)
Platelets (x10 ⁹ /mm ³)	-0.5 (28.0)	-2.8 (37.3)	-2.0 (29.8)	10.6 (35.4)	12.9 (34.8)	2.8 (37.2)	5.3 (34.8)
Albumin (g/dl)	-0.03 (0.2)	-0.02 (0.3)	-0.04 (0.2)	0.01 (0.3)	0.08 (0.3)	0.01 (0.3)	0.02 (0.3)
BUN (mg/dl)	-0.8 (3.1)	1.1 (4.0)	-0.2 (4.0)	0.1 (3.6)	0.3 (3.8)	-0.3 (4.1)	0.8 (3.7)
Creatinine (mg/dl)	0.00 (0.1)	0.02 (0.1)	0.03 (0.1)	0.01 (0.1)	0.00 (0.1)	0.01 (0.1)	0.00 (0.1)
ALT (U/L)	-1.8 (9.0)	-2.0 (9.8)	-1.0 (7.9)	-0.8 (7.5)	-0.7 (9.7)	-1.4 (11.2)	-3.2 (12.7)
AST (U/L)	-1.8 (6.0)	-1.2 (6.2)	-0.3 (6.1)	-1.3 (5.9)	0.1 (6.1)	-1.0 (8.6)	-3.2 (12.6)
Total Bilirubin (mg/dl)	-0.2 (0.2)	-0.04 (0.2)	-0.7 (0.2)	-0.5 (0.2)	-0.01 (0.2)	-0.07 (0.2)	-0.08 (0.1)
GGT (U/L)	-1.0 (11.2)	-0.1 (17.0)	2.2 (13.7)	0.7 (11.9)	-5.8 (17.0)	-3.0 (14.3)	-4.0 (11.2)
Alk Phos (U/L)	-0.3 (10.6)	-1.4 (10.9)	-1.1 (8.7)	-2.5 (13.5)	-7.3 (12.6)	-6.3 (9.2)	-8.2 (10.2)
Lactic dehydrogenase (U/L)	-0.3 (13.3)	2.3 (12.6)	-0.7 (10.5)	-2.6 (11.0)	-5.0 (12.0)	-2.4 (12.2)	-3.7 (18.4)
Amylase (U/L)	-3.1 (17.3)	0.5 (12.5)	1.9 (46.4)	1.3 (9.4)	3.1 (17.7)	3.8 (9.7)	9.6 (12.2)
Bicarbonate (mEq/L)	-0.2 (2.8)	-0.7 (2.6)	0.0 (2.5)	0.0 (2.7)	0.2 (2.6)	0.7 (3.2)	0.2 (2.7)
Calcium (mg/dl)	-0.02 (0.4)	-0.01 (0.4)	-0.04 (0.4)	-0.02 (0.4)	0.11 (0.4)	-0.03 (0.4)	0.01 (0.5)
Chloride (mEq/L)	0.0 (2.4)	0.8 (2.7)	0.5 (2.4)	0.0 (3.1)	0.2 (2.8)	0.8 (2.8)	0.4 (2.6)
Lipase (U/L)	-3.6 (34.8)	-1.8 (22.3)	16.4 (80.7)	1.0 (7.1)	-1.6 (27.2)	5.7 (14.8)	8.8 (19.3)
Magnesium (mEq/L)	-0.03 (0.1)	0.01 (0.1)	0.01 (0.1)	-0.02 (0.1)	-0.06 (0.2)	-0.01 (0.1)	-0.05 (0.1)
Phosphorus (mg/dl)	0.01 (0.4)	-0.05 (0.5)	0.05 (0.4)	0.09 (0.5)	0.12 (0.5)	-0.03 (0.6)	0.12 (0.6)
Potassium (mEq/L)	0.01 (0.4)	0.06 (0.4)	0.04 (0.4)	0.01 (0.4)	0.02 (0.3)	0.02 (0.4)	0.05 (0.5)
Sodium (mEq/L)	-0.4 (2.0)	-0.1 (2.5)	0.4 (2.7)	0.3 (2.6)	0.6 (2.5)	0.9 (2.5)	0.6 (2.3)
Total protein (g/dl)	-0.04 (0.4)	0.00 (0.4)	-0.03 (0.3)	0.00 (0.4)	0.04 (0.4)	0.00 (0.4)	0.01 (0.4)
Uric acid (mg/dl)	-0.34 (0.7)	0.17 (1.0)	0.09 (1.1)	0.23 (1.1)	0.45 (0.9)	0.38 (1.1)	0.61 (1.2)

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Urobilinogen (mg/dl)	-0.03 (0.1)	-0.03 (0.2)	0.02 (0.2)	-0.05 (0.3)	-0.02 (0.2)	0.04 (0.2)	0.02 (0.2)
pH	-0.05 (0.5)	-0.03 (0.5)	-0.02 (0.6)	-0.10 (0.4)	-0.07 (0.5)	0.01 (0.5)	-0.05 (0.5)
Specific gravity	0.0001	-0.0009	-0.0012	-0.00001	-0.0010	-0.0016	-0.0010

Source: SCS Table 3.a, 3.g, 3.n, 3.t, and 3.cc

Outliers or Shifts from Normal to Abnormal: The percentage of subjects with abnormal laboratory parameters is shown in Table 36 by treatment group. Relatively few subjects met the markedly abnormal criteria. However, notable points regarding this data are as follows:

- Nine subjects had markedly abnormal high creatinine values ($>1.5\times$ baseline). The percentage of subjects who met this criterion was similar between treatment groups: 1 (0.9%) A25 QD, 2 (1.9%) A12.5 BID, 2 (1.9%) M500 BID, 1 (0.9%) M1000, 1 (1.0%) A12.5+M500 BID, and 2 (1.8%) A12.5+M1000 BID.
- More subjects experienced a $>25\%$ decrease in eGFR from baseline during treatment using the MDRD formula when compared the C-G formula. The incidence of this decrease in all treatment groups was greater than the incidence of the decrease in the placebo.
- Relatively few subjects experienced a $>50\%$ decrease in eGFR from baseline during treatment (MDRD $>$ C-G). Of the five subjects who experienced this decrease (MDRD formula), all had hypertension and were on concomitant hypertensive medications.
- The percentage of subjects with ALT $>3\times$ ULN was highest in the M1000 BID and A12.5+M1000 BID groups (2.8% and 3.6%, respectively).
- No alogliptin subject has ALT or AST $>5\times$ ULN.
- No subject met Hy's law.

Table 36. MET-302: Subjects (n, %) with abnormal hematology or chemistry parameters

	Placebo N=106	A25 QD N=112	A12.5 BID N=110	M500 BID N=109	M1000 BID N=111	A12.5+M500 BID N=106	A12.5+M1000 BID N=114
Parameter (criterion)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hematocrit low ($<0.8\times$ Baseline)	0	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.9)	1 (1.0)	0
Hemoglobin low ($<$ Baseline-3 g/dL)	0	1 (0.9)	1 (0.9)	0	1 (0.9)	1 (1.0)	0
Platelet count low ($<50\times 10^3/\mu\text{L}$)	0	0	0	0	0	0	1 (0.9)
Red blood cells count low ($<0.8\times$ Baseline)	0	3 (2.7)	0	1 (0.9)	1 (0.9)	1 (1.0)	0
White blood cells count high ($>20\times 10^3/\mu\text{L}$)	0	0	0	0	0	1 (1.0)	0

Serum creatinine							
>ULN with >0.3 mg/dL increase from Baseline	0	0	1 (0.9)	0	1 (0.9)	1 (1.0)	0
≥2×Baseline value	0	0	1 (0.9)	0	0	1 (1.0)	0
>2.0 mg/dL	0	0	0	0	0	0	0
eGFR							
>25% decrease from Baseline (MDRD)	5 (4.8)	12 (10.8)	9 (8.5)	7 (6.6)	9 (8.3)	13 (12.6)	10 (8.9)
>50% decrease from Baseline (MDRD)	0	1 (0.9)	1 (0.9)	0	1 (0.9)	1 (1.0)	1 (0.9)
>25% decrease from Baseline (C-G)	3 (2.9)	7 (6.3)	6 (5.7)	5 (4.7)	9 (8.3)	9 (8.7)	10 (8.9)
>50% decrease from Baseline (C-G)	0	0	1 (0.9)	0	0	1 (1.0)	0
ALT high (>3×ULN)	1 (1.0)	2 (1.8)	1 (0.9)	1 (0.9)	3 (2.8)	2 (1.9)	4 (3.6)
ALT high (>5×ULN)	0	0	0	0	1 (0.9)	0	0
AST high (>3×ULN)	1 (1.0)	1 (0.9)	0	1 (0.9)	1 (0.9)	2 (1.9)	2 (1.8)
AST high (>5×ULN)	0	0	0	0	1 (0.9)	0	0
GGT high (>3×ULN)	2 (1.9)	10 (9.0)	5 (4.7)	6 (5.7)	9 (8.3)	7 (6.8)	5 (4.5)
Total bilirubin high (>2.0 mg/dL)	1 (1.0)	0	0	1 (0.9)	0	0	0
Lipase high (>3×ULN)	0	0	2 (6.9)	0	0	0	1 (2.6)
Potassium low (<3.0 mEq/L)	1 (1.0)	0	0	0	0	0	0
Potassium high (>5.8 mEq/L)	2 (1.9)	0	2 (1.9)	1 (0.9)	0	1 (1.0)	1 (0.9)
Sodium low (<130 mEq/L)	0	0	1 (0.9)	0	0	0	2 (1.8)
Sodium high (>150 mEq/L)	1 (1.0)	0	0	0	0	1 (1.0)	0
Uric acid high (>10.5 mg/dL [men] or >8.5 mg/dL [women])	0	6 (5.4)	2 (1.9)	4 (3.8)	4 (3.7)	2 (1.9)	1 (0.9)

Source: SCS Tables 3.d, 3.j, 3.q, and 3.w

Dropouts for Laboratory Abnormalities: No alogliptin + metformin subjects discontinued study medication due hematology or urinalysis abnormalities in study MET-302.

A list of subjects who discontinued study medication in MET-302 due to renal function-associated AEs is shown Table 37. Numerically more A12.5+M1000 BID subjects were discontinued; the most common reason being creatinine clearance decreased. However, as described in section 5.3, protocol contained renal safety withdrawal criteria. The proposed labeling contraindicates the alogliptin/metformin FDC in subjects with renal impairment and recommends monitoring renal function before and during therapy; this is acceptable.

Table 37. MET-302: Subjects with renal function-associated AEs that led to study drug discontinuation

Subject No.	Age/Gender	Preferred Term
Placebo		
302/5004-010	50/Woman	Renal failure
A12.5 BID		
302/5078-006	61/Woman	Renal impairment
302/5139-014	67/Woman	Renal impairment
302/5247-001	52/Man	Creatinine renal clearance decreased
A25 QD		
302/5252-020	57/Woman	Creatinine renal clearance decreased
302/5255-001	47/Woman	Renal impairment
302/5261-007	63/Man	Renal impairment
M500 BID		
302/5129-009	46/Woman	Renal failure
M1000 BID		
302/5243-002	53/Woman	Glomerular filtration rate decreased
A12.5+M500 BID		
302/5124-011	67/Woman	Renal impairment
302/5182-004	56/Woman	Renal impairment
302/5252-012	45/Man	Creatinine renal clearance decreased
A12.5+M1000 BID		
302/5041-001	78/Man	Creatinine renal clearance decreased
302/5095-002	58/Woman	Creatinine renal clearance decreased
302/5118-001	55/Woman	Blood creatinine decreased
302/5254-021	58/Man	Creatinine renal clearance decreased
302/5285-006	40/Woman	Creatinine renal clearance decreased

Source: SCS Table 3.m

The following subjects were discontinued due to liver function test or lipase abnormalities:

- A12.5+M1000 BID subject 302/5252-001 was discontinued due to an SAE of cholecystitis on day 36. The event resolved on day 49.
- A12.5+M1000 BID subject 302/5039-009 was discontinued on day 29 due to abnormal liver function test. ALT was 23 and 30 U/L at baseline and day 29, respectively (normal 5 – 25 U/L). AST was 17 and 23 U/L on the same days (normal 8- 22 U/L). Bilirubin was normal.
- A12.5+M500 BID subject 302/5070-010 was discontinued on day 113 due to lipase increase, although this subject did not meet MedDRA SMQ criteria for acute pancreatitis. (See also section 7.3.4.)

Summary: As the laboratory data from studies MET-008 and OPI-004 were previously reviewed as part of the alogliptin NDA and first CR, my review of the laboratory findings focused on phase 3 study MET-302. No clinically significant laboratory abnormalities which would preclude approval were identified. For a discussion of hepatotoxicity cases, see section 7.3.5 Submission Specific Primary Safety Concerns.

7.4.3 Vital Signs

In phase 3 studies, subjects were required to have the following entry blood pressure:

- MET-302 and 305: <150/90 mm Hg
- OPI-004: <160/100 mm Hg
- MET-008: <180/110 mm Hg

When the change from baseline in blood pressure and heart rate were reviewed, no meaningful differences were observed (see Table 38 and Table 39). Of the 2244 subjects exposed to alogliptin + metformin, the following five subjects had SAEs related to blood pressure or heart rate. No subjects discontinued study medication due to these events.

- MET-302: Subject 5042-008 (A12.5+M1000 BID) experienced severe hypotension on day 10 that resolved on day 16. The investigator attributed it to lisinopril dose adjustment.
- MET-008:
 - o Subject 520/8010 (A12.5+M) died due to hypertensive heart disease. See section 7.3.1 Deaths.
 - o Subject 263-8006 (A12.5+M) had bradycardia on day 68 that resolved on day 72.
- 305:
 - o Subject 5082-016 (A25+M) had hypertensive crisis and hypertension.
 - o Subject 5513-006 (A25+M) had hypertension.

In summary, the use of alogliptin with metformin does not appear to be associated with a clinically meaningful change in vital signs. In addition, the CV safety of alogliptin was previously demonstrated by the interim analysis of CV study 402 in the first alogliptin CR.

Table 38. Mean change from baseline to endpoint for vital signs (Completed phase 3 studies)

Vital Sign	MET-302							MET-008			OPI-004*	
	PLB	A25QD	A12.5BID	M500BID	M1000BID	A12.5+ M500BID	A12.5+ M1000BID	PLB+M	A12.5+M	A25+M	A25+M +P30	M+P45
N	106	112	110	109	111	106	114	104	213	207	404	399
SBP (mmHg)												
Baseline	127.6	127.2	125.5	125.4	127.7	126.0	126.3	128.6	127.0	127.3	128.8	131.1
Δ from baseline	0.5	1.5	0.7	0.2	-2.5	1.3	0.0	-0.1	2.0	2.2	1.6	1.8
DBP (mmHg)												
Baseline	79.1	77.0	78.2	77.2	78.0	77.0	76.9	78.9	77.8	78.1	79.2	80.4
Δ from baseline	-0.1	1.0	-0.1	-0.5	-0.2	0.5	1.2	-2.4	0.6	1.8	0.0	-0.5
Pulse (bpm)												
Baseline	73.6	73.0	74.0	74.4	75.5	72.6	74.6	75.1	73.8	74.5	74.5	75.1
Δ from baseline	-0.1	1.7	1.5	0.1	1.0	1.0	1.4	0.5	0.5	0.6	1.0	0.4

*For OPI-004, week 52 change from baseline is shown.

Source: SCS Table 4.a, 4.b, and 4.c

Table 39. Study 305: Mean change from baseline to week 52 for vital signs

Variable	Treatment					
	MET+A12.5 (N=873)		MET+A25 (N=877)		MET+Glipizide (N=869)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Systolic blood pressure (mmHg)						
Baseline	873	127.7 (12.33)	877	127.2 (12.07)	869	127.4 (12.40)
Change from Baseline	653	0.5 (12.79)	672	0.8 (12.88)	618	1.8 (12.75)
Diastolic blood pressure (mmHg)						
Baseline	873	78.1 (7.77)	877	77.8 (7.76)	869	77.6 (7.78)
Change from Baseline	653	0.1 (8.12)	672	0.2 (8.32)	618	0.8 (8.76)
Pulse (bpm)						
Baseline	873	74.5 (9.07)	877	74.3 (9.37)	869	74.9 (9.24)
Change from Baseline	653	-0.1 (8.67)	672	0.5 (9.14)	618	0.5 (9.55)

Source: Interim CSR 305 Table 12.s

7.4.4 Electrocardiograms (ECGs)

The approval of metformin in 1995 predated the 2005 and 2008 guidances on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential. The CV safety of metformin has been demonstrated by the subsequent seventeen years' clinical experience.

As described in my review of the first alogliptin CR, 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 QTc and QTcF using the time-averaged baseline was <10 msec for both alogliptin doses on both days. In addition, the CV safety of alogliptin was previously demonstrated by the interim analysis of CV study 402.

As the ECG data from studies MET-008 and OPI-004 were previously analyzed in my alogliptin NDA and first CR reviews, I focused on data from completed study MET-302 and ongoing study 305.

In MET-302, there were no clinically meaningful differences between treatment groups in ECG results. Three subjects shifted from normal to abnormal but not clinically significant at Baseline to abnormal and clinically significant at Week 12 or 26 (two A12.5+M500 BID subjects and 1 A12.5 BID subject). Two additional subjects shifted after hyperglycemic rescue. All but A12.5+M500 BID subject 5211-002's clinically significant shift were transient and resolved.

Subject 5211-002 (study MET-302, A12.5+M500 BID) was a 76 year old female who had an abnormal, clinically significant ECG at weeks 16 and 20. Baseline and week 12 ECGs were abnormal, not clinically significant. Reported AEs for this patient included sinus tachycardia, renal impairment, organic delusional disorder, and dementia. Concurrent medical conditions included T2DM, stable angina pectoris, atherosclerotic cardiosclerosis, heart failure, coronary heart disease, hypertensive cardiomyopathy, autoimmune thyroiditis, nontoxic goiter, dyslipidemia, obesity, chronic ischemia of the cerebrum, arterial hypertension, aortic sclerosis, and dyscirculatoric encephalopathy. The subject voluntarily withdrew from the study.

In ongoing study 305, there were no clinically meaningful differences in overall ECG results. Nine subjects (2 A12.5+M, 2 A25+M, and 5 Glipizide+M) had ECG results shift from normal at Baseline to abnormal and clinically significant at Week 52.

In summary, alogliptin + metformin does not appear to resulting a clinically significant change in mean ECG parameters, the incidence of abnormal ECGs, ECG-related SAEs, or discontinuations.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

No immunogenicity studies of alogliptin + metformin were completed. Alogliptin is a small molecule and, therefore, not expected to be immunogenic. In section, 7.3.4

Significant Adverse Events, I discuss hypersensitivity AEs.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

MET-302 evaluated the safety of A12.5+M500 BID and A12.5+M1000 BID for 26 weeks. MET-008 evaluated the safety of A12.5+M and A25+M for 26 weeks. The rate of SAEs, AEs leading to discontinuation, and AEs for these groups are discussed in sections 7.3.2, 7.3.3, and 7.4.1. The overall percentage of subjects with events in these groups are shown in Table 40.

Although more A12.5+M1000 BID subjects were discontinued due AEs than A12.5+M500 BID subjects in study MET-302 (9.6% vs. 4.7%, respectively), the percentage of subjects with SAEs and AEs were similar between treatment groups. As discussed in section 7.3.3, discontinuations in the A12.5+M1000 BID group occurred mostly in the Investigations SOC (n=6, 5.3%) and Gastrointestinal SOC (n=3, 2.6%). Within these SOC, events were single events except for creatinine renal clearance decreased (n=4, 3.5%). Metformin is associated with dose-dependent gastrointestinal side effects.

In summary, a consistent trend in adverse events by increasing alogliptin or metformin dose was not observed.

Table 40. SAEs, AEs leading to discontinuation, and AEs in studies MET-302 and MET-008 by alogliptin + metformin dose

Adverse Event	MET-302		MET-008	
	A12.5+M500 BID (n=106)	A12.5+M1000 BID (n=114)	A12.5+M (n=213)	A25+M (n=207)
SAEs	2 (1.9)	2 (1.8)	6 (2.8)	8 (3.9)
AEs leading to discontinuation	5 (4.7)	11 (9.6)	7 (3.3)	4 (1.9)
AEs	67 (63.2)	73 (64.0)	134 (62.9)	118 (57.0)

Source: Table 13, Table 15, and CSR MET-008 Table 12.b

7.5.2 Time Dependency for Adverse Events

MET-302 and MET-008 evaluated the safety of alogliptin + metformin at 26 weeks. OPI-004 and ongoing study 305 evaluated the safety of alogliptin + metformin at 52 weeks. However, since OPI-004 evaluated the safety of alogliptin 25 mg + metformin + pioglitazone 30 mg, I will focus on the other three studies. (See Table 41.)

The percentage of subjects with SAEs was slightly higher in 52-week, ongoing study 305, although the percentage of subjects with AEs leading to discontinuation and AEs were more similar between groups. However, the frequency of events cannot be directly compared between studies due to differences in the enrolled populations and study conduct.

Table 41. SAEs, AEs, leading to discontinuation, and AEs by time of endpoint

	Week 26				Week 52	
	MET-302		MET-008		305	
	A12.5+M500 BID (n=106)	A12.5+M1000 BID (n=114)	A12.5+M (n=213)	A25+M (n=207)	A12.5+M (n=873)	A25+M (n=877)
SAEs	2 (1.9)	2 (1.8)	6 (2.8)	8 (3.9)	51 (5.8)	57 (6.5)
AEs leading to discontinuation	5 (4.7)	11 (9.6)	7 (3.3)	4 (1.9)	52 (6.0)	62 (7.1)
AEs	67 (63.2)	73 (64.0)	134 (62.9)	118 (57.0)	630 (72.2)	615 (70.1)

Source: Table 13, Table 14, Table 15, Table 18, Table 33, and CSR MET-008 Table 12.b

7.5.3 Drug-Demographic Interactions

The safety of alogliptin + metformin in special groups was not investigated in the clinical program, because there is no drug interaction between alogliptin and metformin. The safety profile of the FDC is expected to be similar to that of the individual components, as follows:

- Metformin is contraindicated in patients with renal dysfunction (e.g. serum creatinine ≥ 1.5 mg/dl in males, ≥ 1.4 mg/dl in females, or abnormal creatinine clearance).
- Metformin should be avoided in patients with hepatic insufficiency because of the risk of lactic acidosis.
- Patients should be cautioned against excessive alcohol intake when taking metformin, since alcohol potentiates its effects on lactate metabolism.
- Metformin should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.
- The small LS mean change from baseline at week 52 in study 303 suggests that alogliptin may not be very efficacious in adults 65 to 90 years over the long-term, although poor study design complicated the primary efficacy assessment. See also my review of the first alogliptin CR.

See also my review of the alogliptin NDA and metformin prescribing information.

7.5.4 Drug-Disease Interactions

Although the June 26, 2009 alogliptin CR letter stated that an increased mean exposure to alogliptin (AUC) by ~70% was observed in subjects with mild RI compared to subjects with normal renal function, this deficiency was addressed in the first alogliptin CR. The applicant's proposed alogliptin dose adjustment for RI is acceptable. See my review of the first alogliptin CR as well as section 7.5.3.

7.5.5 Drug-Drug Interactions

No drug-interaction studies were conducted with the alogliptin/metformin FDC.

Under the alogliptin NDA, 13 drug- and drug-drug interaction studies were conducted to determine the effects of alogliptin on other drugs and the effect of other drugs on alogliptin. No clinically meaningful interactions were observed. In study 005, no changes in exposure to alogliptin and no clinically meaningful changes in exposure to metformin were observed when alogliptin and metformin were coadministered in a randomized, open-label, three-sequence, three-period crossover study in healthy male and female subjects.

See also Zhihong Li's clinical pharmacology review and the metformin prescribing information.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

As described in my original alogliptin review, alogliptin poses minimal carcinogenic risk to humans based on high exposure multiples at the NOAEL (32x) for rat thyroid C-cell tumors, very high exposure multiples ($\geq 288x$) at doses that caused increased combined thyroid C-cell adenomas and carcinomas in male rats, and absence of any other drug-related tumors in rats ($> 400x$ female MRHD) or mice (60x MRHD).

Although long-acting GLP-1 analogues (e.g. exenatide and liraglutide) increase thyroid C-cell adenomas in rats, 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 three other DPP4 inhibitors (e.g. sitagliptin, vildagliptin, and saxagliptin).

As described in metformin prescribing information, long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both $\sim 4x$ the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

7.6.2 Human Reproduction and Pregnancy Data

Alogliptin: As described in David Carlson's original preclinical review, alogliptin was not teratogenic at doses greater than 200-fold 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 200-fold higher than expected human exposure. The major notable finding from reproductive toxicity studies was a slightly increased percentage of sperm abnormalities in males (NOAEL $\approx 67x$ MRHD). The male findings were consistent with sporadic male reproductive toxicity seen in other non-clinical toxicity studies at high alogliptin doses. However, rat sperm abnormalities did not affect fertility.

Fetal findings were limited to decreased body weight and minor skeletal variations (incomplete ossification of sternebrae, skull bones, and hyoid) at maternally toxic doses. There were no effects at doses that didn't cause maternal toxicity, which provided approximately 100- to 200-fold exposure margins at the NOAELs compared to expected human exposure.

Rat PK studies demonstrated placental transfer of alogliptin in rats and the presence of alogliptin in the milk of lactating rats.

Metformin: Metformin is pregnancy category B. There are no adequate and well-controlled studies of pregnant women with metformin. It was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and size times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin. Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma.

Alogliptin + metformin: A rat embryofetal development study was conducted with the concomitant administration of alogliptin and metformin. No drug-related fetal abnormalities considered relevant to human subjects were identified in the study. See David Carlson's alogliptin CR preclinical review.

No studies were conducted to assess the effect of the alogliptin/metformin FDC on pregnancy and lactation. Pregnant or lactating women were excluded from clinical studies, although the four pregnancies occurred in completed phase 3 studies (see Table 42).

Table 42. Summary of pregnancies in alogliptin clinical program

Study/ Site-Subject Age(yr)/Race	Treatment (duration)	Birth Control Method	Outcome
302/5017-019 37/Asian	A12.5+M500 BID (57 days)	Birth control pills	Outcome is unknown; as of the date of this report, the baby has not yet been born.
302/5138-008 40/Hispanic	M500 BID (86 days)	Barrier method	Outcome is unknown; as of the date of this report, the baby has not yet been born.
302/5252-003 30 Asian	M1000 BID (27 days)	Not known	Subject had uncomplicated vaginal delivery and gave birth to a healthy baby girl weighing 3.75kg. Both mother and baby were reported to be doing well.
OPI-004/1044- 4505 36/White	Not randomized (0 days)	Barrier method	(b) (6) the subject underwent an elective dilation and curettage with no reported complications.

Source: SCS Table 5.a

In the applicant-proposed labeling, alogliptin/metformin FDC is pregnancy category B. The text states that both alogliptin and metformin are secreted in the milk of lactating rats. I generally agree with the proposed pregnancy and nursing mothers label.

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant requests that pediatric studies in subjects 0-9 years be waived because studies are impossible or highly impractical due to the small number of these T2DM subjects. I agree with this request.

The applicant submitted revised pediatric deferral plans on January 20, August 16, and November 7, 2012 for T2DM subjects aged 10-17 years. It includes the following two studies:

- SYR-322_104: A phase 1, single-dose, PK/PD study in children with T2DM, with a matched (gender, race and creatinine clearance) control group in healthy adults, entitled *A Comparative, Randomized, Open-Label, Multi-Center, 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 dose selection is appropriate.
 - Protocol submission: Amendments 7 and 8 were submitted to IND 69,707 on December 15, 2011 and March 22, 2012, respectively.
 - Study completion: September 30, 2013,
 - Report submission: March 31, 2014
 - *Internal Comment: Clinical pharmacology agrees with the proposed sample sizes and doses.*
- SYR-322_309: A Phase 3 study entitled, *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*. This trial is designed as a multicenter, randomized, double-blind, placebo-controlled study in pediatrics 10 to 17 years of age with T2DM evaluating the efficacy and safety of alogliptin (b) (4) compared to placebo. (b) (4)

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

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)

- *Internal Comment: Comments may be conveyed on protocol 309 after it is submitted.*

On August 22, 2012, PeRC agreed with the proposed waiver in T2DM subjects 0-9 years and deferral in T2DM subjects 10-17 years.

(b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Alogliptin is minimally dialyzable. After three hours of hemodialysis in alogliptin study 006, approximately 7.24% of the drug was removed. Hence, hemodialysis is unlikely to be beneficial in an overdose. It is not known if alogliptin is dialyzable by peritoneal dialysis.

As described in the metformin prescribing information, overdose has occurred including ingestion of >50 grams. Hypoglycemia was reported in ~10% of cases, but no casual association with metformin hydrochloride has been established. Lactic acidosis has been reported in ~32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 ml/min and good hemodynamic conditions. Therefore, hemodialysis may be useful for the removal of accumulated drug from patients in whom metformin overdosage is suspected.

No AEs related to overdose were reported during the alogliptin/metformin FDC clinical development program. In the event of an overdose, removal of the unabsorbed material from the gastrointestinal tract should be considered. Clinical monitoring and supportive therapy should be initiated. The applicant-proposed labeling is consistent with this information.

Metformin and DPP-4 inhibitors are not associated with drug abuse or withdrawal and rebound. Hence, no clinical studies were conducted to evaluate these issues. Data from the clinical program also do not suggest alogliptin/metformin FDC would be associated with drug abuse or withdrawal and rebound.

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarket Experience

In the Four-Month Safety Update, the applicant submitted the third Japanese alogliptin PSUR (April 16, 2011 to October, 2011). Alogliptin was approved for use in Japan on April 16, 2010. The cumulative patient exposure in the third PSUR since approval was 117,359 patient-years. This data was analyzed in my first alogliptin CR review.

See also section 7.3.5 Submission Specific Primary Safety Concerns.

9 Appendices

9.1 Literature Review/References

Not applicable.

9.2 Labeling Recommendations

On March 20, 2012, the applicant submitted revised labeling which included safety data from ongoing study 305. As I have reviewed this data and the agency has previously included safety data from ongoing studies (e.g. bladder cancer data in the pioglitazone label), I agree with its inclusion in section 6 Adverse Reactions. The applicant appropriate labels the safety data as “interim”, although it should also specify that it was a “52-week” interim analysis.

See also the following sections:

- In labeling section 14 Clinical Studies, the applicant proposes, (b) (4)

(b) (4)
the applicant should be asked again to remove this language

(b) (4)

On April 17, 2012, OPDP determined that the proposed trade name (b) (4) was unacceptable (b) (4)

(b) (4) On July 19, 2012, DMEPA approved proposed trade name, Kazano.

9.3 Advisory Committee Meeting

Not applicable.

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

/s/

VALERIE S PRATT
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

Documents reviewed:

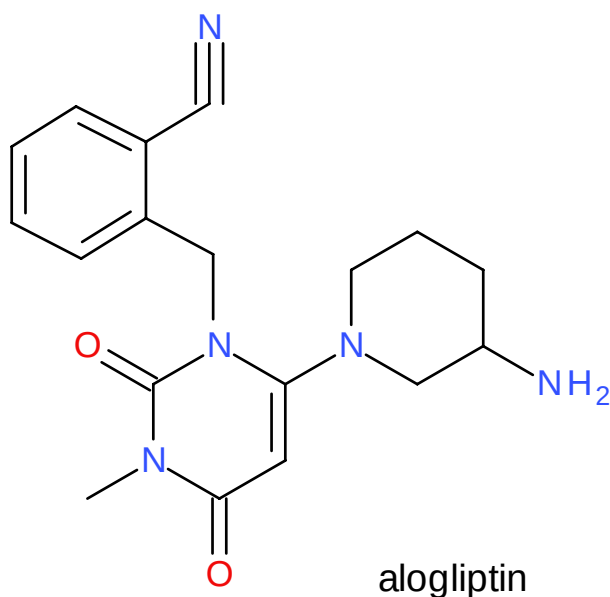
- 1) Consultation request dated 15 October 2012 from Dr. Pratt via Mr. Rich Whitehead and Ms. Margarita Tossa, with requested response date 9 November, OSE tracking #2012-2411.
 - 2) Takeda summary dated 4 October 2012, provided clinical details on cases showing either ALT >10xULN or {ALT/AST >3xULN & 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:



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 not 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 hepatocellular 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. Alogliptin 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

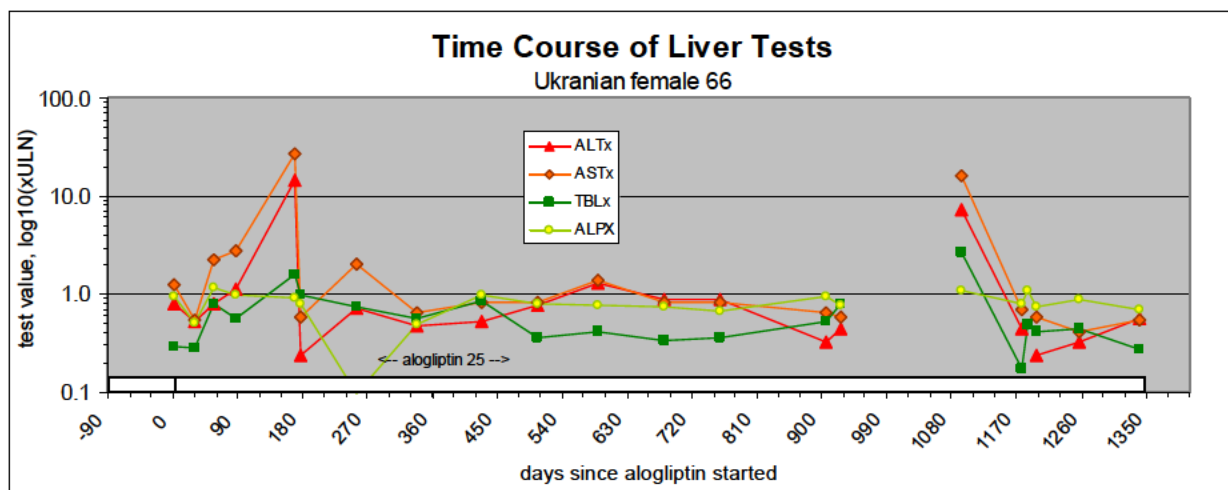
This 49 year old male with hypoacusis and an umbilical hernia began treatment with alogliptin on July 31, 2007. The ALT and AST values preceding treatment and at baseline were mildly abnormal but returned to normal between days 15 and 68. On day 64, he was diagnosed serologically with acute hepatitis 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.



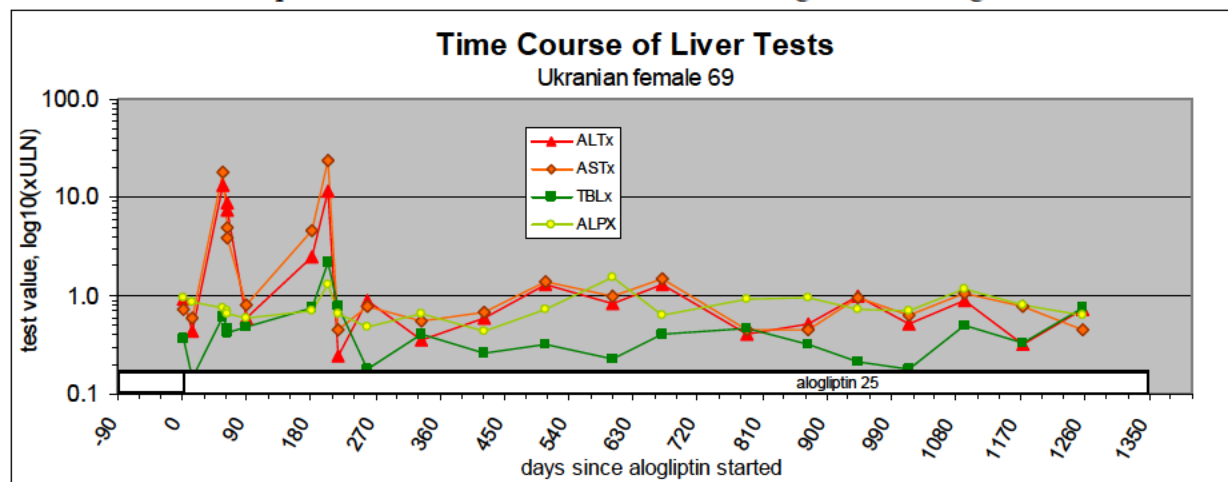
Comment (JRS): Inspection of the data and graphic display shows that this woman tolerated alogliptin very well, but had periodic abnormalities AST > ALT with no cholestasis. She had known heart disease and congestive failure, and the enzyme elevations corresponded to episodes of congestive failure (with 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.



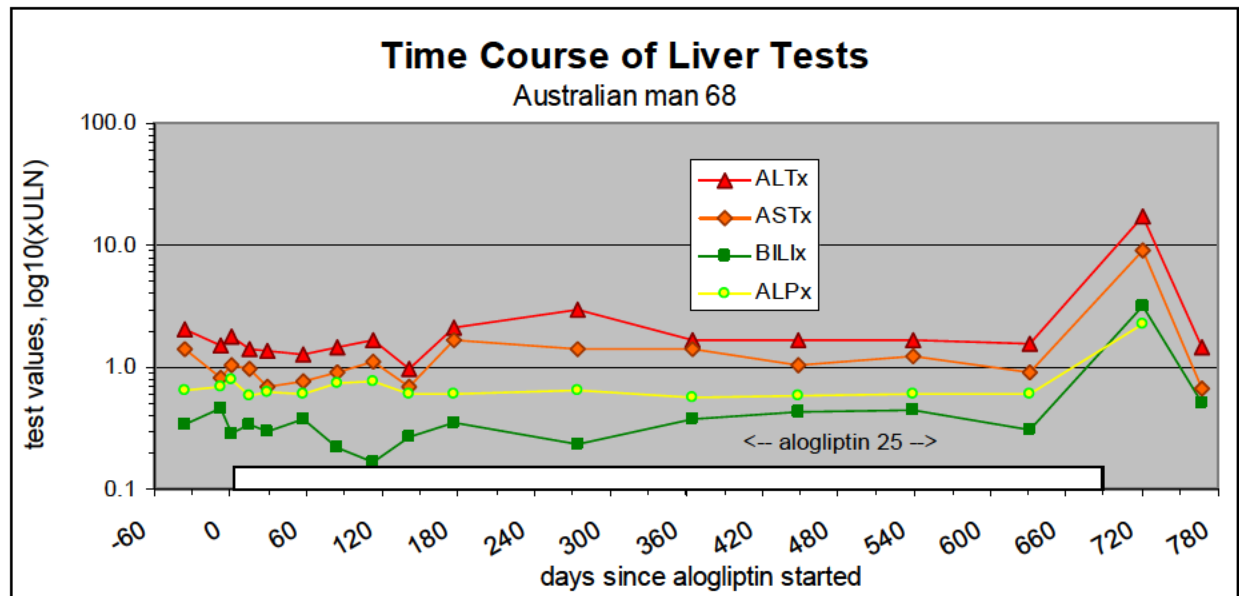
Comment (JRS): The two rather sharp increases in AST and ALT in January and May 2008, were attributed to preceding alcohol and insecticide exposure, but not convincingly. Alogliptin administration continued, and did not appear causative. The pattern of AST > ALT is seen in recurrent alcoholic hepatitis 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, esomeprazole, 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 (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.

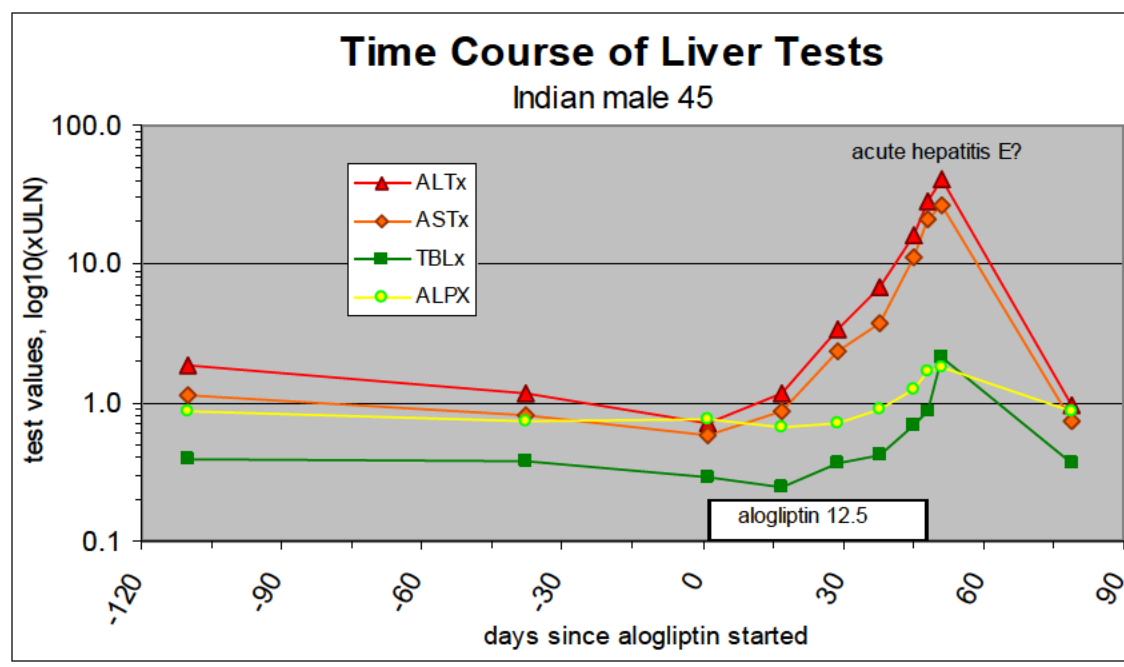


Comment (JRS): The slight but persistent ALT elevations were never investigated or explained, but the patient tolerated alogliptin well for two years. At that point a common duct stone was confirmed, then removed, with resolution. The aminotransferases elevations were relatively greater than the rise in alkaline phosphatase, so there 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 aminotransferases continued 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.



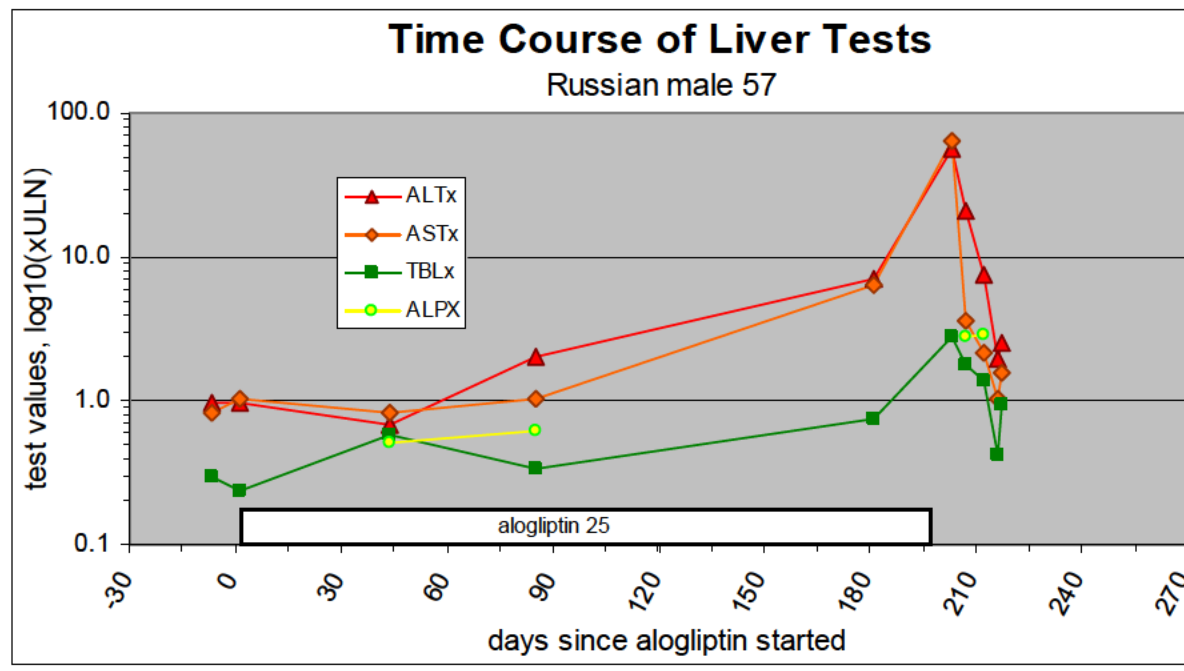
Comment (JRS): This subject showed aminotransferase activity rises about four weeks after starting alogliptin, with sharp subsequent increases that led to stopping the drug three weeks later. The investigator found acute-phase IgM antibodies against acute viral hepatitis E, which subsided within four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

Comment (LBS): Very nice case. The diagnosis could easily have been delayed 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 ALT 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, VERRING 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 drugs – 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 ursodeoxycholic 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 any 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

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

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

/s/

JOHN R SENIOR

11/10/2012

Major contribution by Dr. Leonard Seeff

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203-414

Applicant: Takeda

Stamp Date: 11-22-11

Drug Name:

Alogliptin/metformin FDC

NDA/BLA Type: Standard

505(b)(2)

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.	x			
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?	x			505(b)(2): Glucophage and Nesina
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			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:	x			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	x			QT study 019 evaluated alogliptin.
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			We can refer to alogliptin's liver and hypersensitivity data, since the NDA is cross-referenced.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested)	x			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (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			The company wants to fulfill this requirement by using the proposed pediatric study for the alogliptin NDA.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Presubmission Regulatory Activities:

- April 2, 2009: IND 101,628 submitted.
- December 3, 2009 & March 9, 2010: Comments were conveyed on protocol MET-302.
- April 5, 2011: Written responses provided for type C meeting package.
- August 11, 2011 & September 21, 2011: Email interactions regarding data submitted in the NDA.
- November 2, 2011: Agency recommended the proposed annotated label show the source of the data.
- November 2 and 17, 2011: Comments conveyed on the proposed 120-day Safety Update.

Application: 505(b)(2) with cross-references to Glucophage (metformin HCl) NDA 20-357 and Nesina (alogliptin) NDA 22-271.

Internal Comment: Alogliptin NDA 22-271 is still under review with a PDUFA date of April 25, 2012.

Proposed Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)

Proposed Doses: Alogliptin/metformin FDC 12.5/500 or 12.5/1000 mg twice daily (BID)

Internal Comment: [REDACTED] (b) (4)

[REDACTED] *Metformin is contraindicated in males and females with serum creatinine ≥ 1.5 mg/dl and ≥ 1.4 mg/dl, respectively. See the comment to the sponsor below.*

Clinical Studies:

- Phase 1
 - MET-101: Bioequivalence study
 - MET-102: Food-effect study
 - 322-005: Drug-interaction study with alogliptin and metformin
 - 322-101: Pharmacokinetic (PK) study that assessed daily versus BID dosing
- Phase 3
 - MET-302: *A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of alogliptin plus metformin, alogliptin alone, or metformin alone in subjects with T2DM*
 - 322-008: *A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of SYR-322 when used in combination with metformin in subjects with T2DM (Reviewed under NDA 22-271)*
 - 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*

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

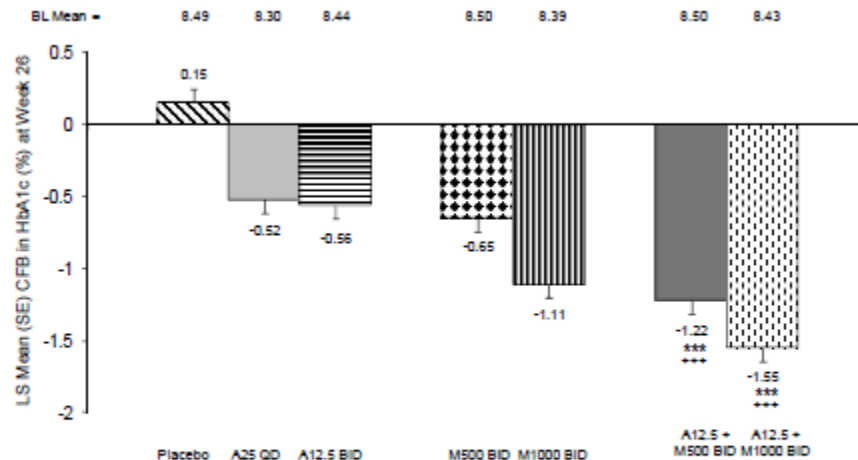
inadequate control on a combination of metformin and 30 mg pioglitazone HCl therapy (Reviewed under the Compete Response [CR] to NDA 22-271)

Table 1. NDA 203-414: Phase 3 clinical studies

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication				
SYR-322MET-302 Synopsis 219-14 countries 16Nov09-30Jun11	Phase 3, multicenter, randomized, double-blind, placebo-controlled Efficacy (HbA1c) and safety	784 subjects with T2DM 374 (47.7%) Men, 410 (52.3%) Women 561 (71.6%) W, 143 (18.2%) A, 37 (4.7%) B, 41 (5.2%) AI or AN, 1 (0.1%) NH or OPI, 1 (0.1%) M 53.5 (22-80) years	26 weeks	Placebo (106/74) A12.5 BID (110/71) A25 QD (112/89) M500 BID (109/94) M1000 BID (111/95) A12.5+M500 BID (106/92) A12.5+M1000 BID (114/94) Total (768/609) (d)
SYR-322-MET-008 Synopsis 115-15 countries 10Mar06-12Jun07	Phase 3, randomized, double-blinded, placebo-controlled, 3-treatment arm design Efficacy (HbA1c) and safety	527 subjects with T2DM being treated with MET alone 265 (50.3%) Men, 262 (49.7%) Women 408 (77.4%) W, 49 (9.3%) O, 42 (8.0%) A, 24 (4.6%) B, 3 (0.6%) AI or AN, 1 (0.2%) NH or OPI 54.7 (22-80) years	26 weeks	MET+ALO 12.5 mg (213/176) MET+ALO 25 mg (207/165) MET+PBO (104/72) Total (524/413)
01-06-TL-322OPI-004 Synopsis 235-17 countries 30Jan07-05Jun09	Phase 3, randomized, multicenter, double-blinded, 2-treatment arm Efficacy (HbA1c) and safety	803 subjects with T2DM and inadequate glycemic control on MET (≥ 1500 mg or MTD) and PIO 30 mg 389 (48.4%) Women, 414 (51.6%) Men 498 (62.0%) W, 157 (19.6%) A, 77 (9.6%) B, 67 (8.3%) O, 2 (0.2%) NH or OPI, 2 (0.2%) AI or AN 55.1 (25-80) years	52 weeks	MET+ALO 25+PIO 30 mg (404/283) MET+PIO 45 mg (399/243) Total (803/526)

Source: Synopses of individual studies

New Efficacy Data:



Source: [MET-302 Tables 15.2.1.1.1, 15.2.1.3.1, 15.2.1.4.1](#)

Note: Subjects who discontinued from double-blind study medication were evaluated using the last post-Baseline value collected within 7 days after the date of last dose unless previously rescued for hyperglycemia, in which case the last value collected on or prior to the date of rescue was used (Analysis 1a as specified in the statistical analysis plan [SAP]).

***P<0.001 versus corresponding alogliptin dose. +++P<0.001 versus corresponding metformin dose.

Figure 1. MET-302: Change from baseline in HbA1c (%) at week 26 (FAS)

Source: Clinical overview Figure 4.a

Safety Data: Total alogliptin exposure is similar to that of the CR (twelve controlled phase 2/3 studies with a total exposure of 5232 subjects). In the SYR-322MET program, 1044 T2DM subjects received at least one dose of alogliptin with metformin in phase 3 studies. The median treatment exposure was 26 weeks in studies MET-302 and 322-008 and 52 weeks in OPI-004.

PREA: The applicant requests a waiver in T2DM subjects 0-9 years and a deferral in subjects 10-17 years (inclusive).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

The following two pediatric studies are planned:

- SYR-322_104: This PK/PD study is discussed in my alogliptin CR review.
 - Study start date: November 11, 2009.
 - Study completion date: October 2012.
 - Report submission date: April 2013.
- SYR-322_309: This phase 3, (b) (4) study is discussed in my alogliptin CR review.
 - Protocol submission: December 2013.
 - Study start date: April 2014.
 - Study completion date: June 2018.
 - Report submission date: July 2019.

We need to take this application to PeRC. Based on the recent requirements for other DPP-4/metformin FDC pediatric development programs, I suspect a pediatric study of alogliptin and metformin will be required. We recently asked the sponsor, under alogliptin NDA 22-271, to submit a revised pediatric plan to evaluate the safety and efficacy of alogliptin as monotherapy and in combination with metformin. This should satisfy the pediatric requirement for both NDAs.

Worldwide Marketing: Alogliptin/metformin FDC is not currently marketed.

I recommend the following at this time:

- OSI consult for study MET-302
- PeRC: Schedule date and ask sponsor to submit the revised protocol to this NDA
- Two comments be sent to the sponsor

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.

Comments for the sponsor:

- Under NDA 22-271, you are seeking approval of alogliptin 25 mg daily for the treatment of type 2 diabetes in subjects with normal renal function. However, this application and the proposed doses are still under review. (b)
(4)

- We refer to your November 7, December 2, and December 7, 2011 liver-related submissions to the alogliptin and alogliptin/pioglitazone fixed-dose combination NDAs. For administrative reasons, submit these documents (and any future liver-related submissions) to the alogliptin/metformin FDC NDA, as well.

Reviewing Medical Officer

Date

Clinical Team Leader

Date

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
01/10/2012

HYLTON V JOFFE
01/10/2012