

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: NDA 203414/0

Drug Name: Alogliptin + Metformin fixed dose combination tablets
(Kazano™)

Indication(s): Treatment of Type 2 diabetes

Applicant: Takeda

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Biometrics Division: Division of Biometrics 2

Statistical Reviewer: Janice Derr, Ph.D.

Concurring Reviewers: J. Todd Sahlroot, Team Leader and Deputy Division Director

Medical Division: Division of Metabolism and Endocrinology Products

Clinical Team: Valerie Pratt, M.D., Medical Reviewer
Carim Kalis, M.D., Medical Team Leader
Mary H. Parks, M.D., Division Director

Project Manager: Mehreen Hai

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1. EXECUTIVE SUMMARY

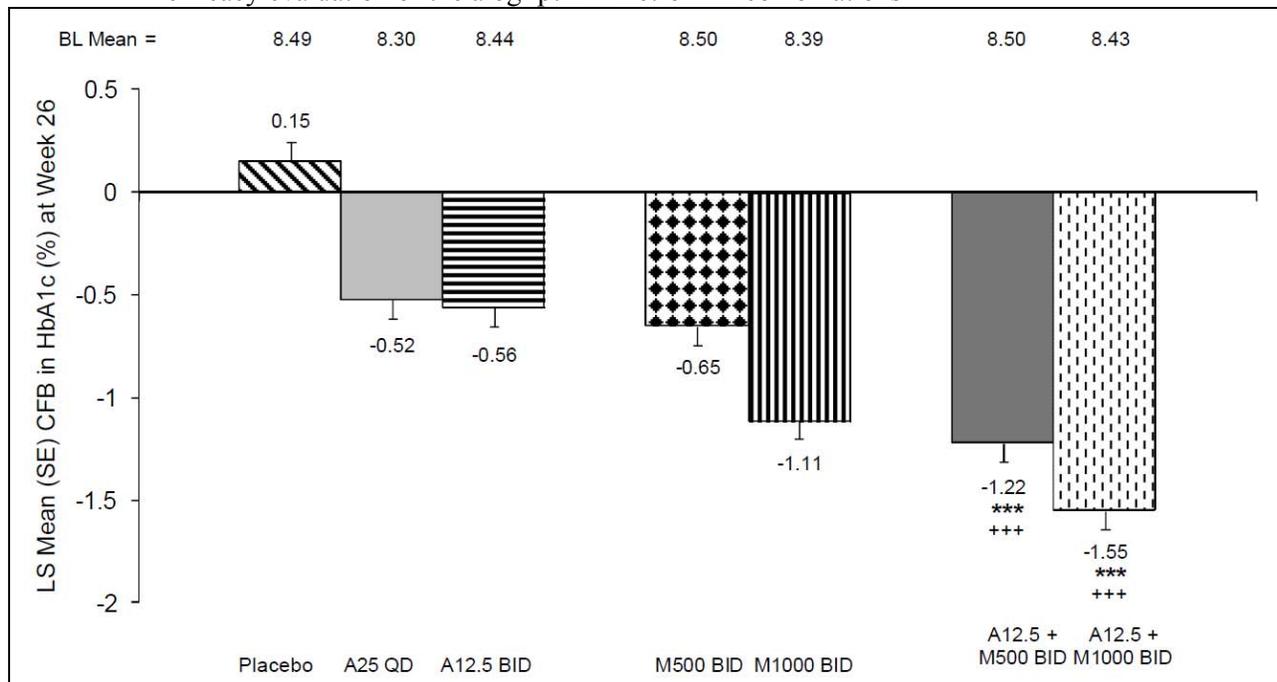
1.1 Conclusions and Recommendations

Efficacy Conclusions: This statistical review focused on the combination Study MET-302, which was designed to evaluate two dosage combinations of alogliptin co-administered with metformin, compared to the single components of the combinations. Study 302 was conducted in 784 patients with type 2 diabetes, randomly allocated across seven treatment arms. Patients were inadequately controlled on diet and exercise alone, with HbA1c between 7.5 and 10.0%. The primary endpoint was HbA1c, expressed as a change from baseline after the 26-week double-blind treatment period.

Results from Study 302 support the superior efficacy of alogliptin co-administered with metformin compared to either alogliptin alone or metformin alone (Figure 1). Two dosage strengths were studied: (1) alogliptin 12.5 mg + metformin 500 mg bid; and (2) alogliptin 12.5 mg + metformin 1000 mg bid. The placebo-adjusted HbA1c response was consistent with a dose-response relationship between the two combinations, -1.4 and -1.7 respectively. The results support the regulatory requirement for combination products, as described in 21 CFR 300.50 (B).

The placebo-adjusted effects of the alogliptin monotherapy arms (-0.6) were fairly similar to the estimates from other Phase 3 studies (-0.6 from monotherapy Study 010 and -0.5 from add-on Study 008). The placebo-adjusted effects of metformin appeared to be reasonably related to its dose.

Figure 1 Study 302; Primary efficacy endpoint (HbA1c change from baseline at week 26); primary efficacy evaluation of the alogliptin + metformin combinations



Note: Analyses are based on the FAS analysis set with LOCF imputation for dropouts and rescues

Source: Study 301 clinical report, Figure 11.i

The results for fasting plasma glucose (FPG) supported the superior efficacy of the alogliptin + metformin combinations. Mean body weight at week 26 stayed within $\pm 2\%$ of baseline body weight in the combination and component treatment arms. The effect of the alogliptin + metformin combinations was also fairly neutral in terms of changes from baseline in cholesterol (total, HDL and LDL) and triglycerides.

In Study 302, the placebo arm had the largest percentage of subjects who discontinued and/or who met the criteria for inadequate glycemic control, or “rescue” (57%). The two arms with metformin 1000 mg bid had the smallest percentages of discontinued/rescued subjects (19% in the combination arm and 24% in the monotherapy arm). The majority of rescues, 100 out of 140, took place at week 12 and beyond. This supports a concern expressed by the review division at the protocol stage that the change from FPG-based rescue criteria up until week 12 to HbA1c-based criteria at week 12 and beyond would result in a large number of rescues.

Each combination appeared to have a fairly similar relationship to its components for males and females, Caucasians and Asians, Hispanic/Latinos and non-Hispanic/Latinos, subjects in the US and subjects outside the US, and subjects with baseline HbA1c ≤ 8.5 and subjects with baseline HbA1c > 8.5 . Study 302 did not have enough subjects in the 65 years and older age group for an assessment of the age subgroup.

Study 302 also included two treatment arms that were designed to compare the 25 mg total daily dose of alogliptin, delivered either as 25 mg qd or as 12.5 mg bid. These two arms had a nearly identical mean HbA1c response at week 26 of -0.6. The 95% CI of the difference between the two arms was (-0.3, 0.3). This CI does not exceed a non-inferiority margin of 0.3 that I obtained post-hoc by calculating half of the placebo-adjusted effect of the alogliptin 25 mg qd arm. This finding provides post-hoc support to extending the conclusions about safety and efficacy from clinical studies of the 25 mg qd dose to the 12.5 mg bid dose used in the combination product. The 12.5 mg bid dosing schedule is used in the combination product because of the metformin dosing schedule.

Recommendations for Part 14 of the label for the combination product are included in Part 5.3 of this review.

1.2 Brief Overview of Clinical Studies

This review is an evaluation of the Phase 3 study MET-302. Study 302 was designed to evaluate alogliptin co-administered with metformin by comparing it to each component on its own, in subjects who were inadequately treated with diet and exercise (HbA1c between 7.5 and 10.0%). Subjects were randomly assigned to one of 7 treatment groups: (1) placebo; (2) metformin 500 mg bid; (3) metformin 1000 mg bid; (4) alogliptin 12.5 mg bid; (5) alogliptin 25 mg qd; (6) alogliptin 12.5 mg bid + metformin 500 mg bid; (7) alogliptin 12.5 mg bid + metformin 1000 mg bid. The primary endpoint was determined after 26 weeks of double-blind treatment.

Two other Phase 3 studies, reviewed in earlier NDA submissions, also support the efficacy of alogliptin + metformin: Study 322-008, reviewed under NDA 022271 (alogliptin) was an add-on study for subjects who had inadequate glycemic control on metformin alone; and Study OPI-004, reviewed under NDA 022426 (alogliptin + pioglitazone), was conducted in subjects who had inadequate glycemic control on metformin and 30 mg of pioglitazone therapy. These studies are not reviewed further in this review.

1.3 Statistical Issues and Findings

An issue that arose during the review of Study 302 was the identification (by the applicant) of 13 subjects who enrolled at two or more sites under separate ID numbers, and eight subjects who enrolled in both Study 302 and Study SYR-322_305 concurrently. The applicant evaluated each set of multiple enrollments, and determined the status of the data from each ID with respect to the analysis databases of Study 302. Dr. Valerie Pratt, the clinical reviewer for this NDA, reviewed this information and concurred with the applicant's determinations. As a sensitivity analysis, I analyzed the primary HbA1c endpoint after excluding all of the data from the seven study sites that had multiple enrollments. The results were not substantially different from the primary results obtained with these sites included.

2. INTRODUCTION

2.1 Overview

Kazano™ is a fixed dose combination (FDC) tablet that contains alogliptin and metformin. The alogliptin + metformin combination is intended for twice daily (bid) dosing at the following tablet strengths: (1) alogliptin 12.5 mg + metformin 500 mg; and (2) alogliptin 12.5 mg + metformin 1000 mg. The proposed indication is “Kazano is a dipeptidyl-peptidase-4 (DPP-4) inhibitor and a biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.”

This statistical review fits in with the reviews from the Office of Clinical Pharmacology (Dr. Zhihong Li) and the clinical review division (Dr. Pratt), in addressing the following key review issues:

Comparing the twice daily dosing schedule of the FDC tablet to the once daily dosing schedule of alogliptin: The alogliptin clinical development program evaluated two doses of alogliptin, 12.5 mg and 25 mg, that were administered once daily (qd). The 25 mg daily dose is the recommended therapeutic clinical dose. Because metformin is administered bid, the alogliptin + metformin FDC tablet was developed for bid dosing. The applicant conducted a pharmacokinetic study (322-101) to evaluate the bioequivalence of the daily and twice daily dosing schedules. Dr. Li is reviewing Study 322-101. In addition, the Phase 3 study MET-302 included a daily dosing arm and a twice daily dosing arm (25 mg total daily dose in each arm). The statistical comparison of these two arms in Study MET-302 is included in this review. The establishment of bioequivalence from Study 322-101 and additional support for “clinical similarity” (no criteria were pre-specified) from Study MET-302 provide a key link to the

already existing information about safety and efficacy from the Phase 3 clinical studies, because these studies used the qd dosing schedule.

Comparing the FDC tablet to co-administered alogliptin + metformin tablets: The Phase 1 study MET-101 evaluated the bioequivalence of the FDC tablets to the co-administered tablets. Dr. Li is reviewing Study MET-101. The establishment of bioequivalence is a key link to the already existing information about safety and efficacy from the Phase 3 clinical studies, because these studies used the co-administered tablets of alogliptin and metformin.

Evaluating the contribution of each component to the clinical efficacy of the alogliptin + metformin combination: The proposed indication refers to use “as an adjunct to diet and exercise.” In the context of this indication, the combination of alogliptin + metformin must address the regulatory requirements for evaluating a combination product¹. The Phase 3 Study MET-302 was designed to compare alogliptin co-administered with metformin to each component on its own. The patient population consisted of patients who were inadequately treated with diet and exercise, but had not been treated with other antidiabetic products. This review is a statistical evaluation of Study MET-302.

Evaluating the efficacy of alogliptin with metformin as background medication: Additional information about the efficacy of alogliptin co-administered with metformin comes from the Phase 3 studies 322-008 and OPI-004. These studies were both conducted in patients who had metformin as their background medication (prior to randomization). These studies were reviewed under other NDA submissions (see part 2.1.2 of this review).

2.1.1 Class and Indication

Alogliptin (Nesina™) is a selective inhibitor of the enzymatic activity of dipeptidyl peptidase (IV) (DPP-4) and is referred to as a DPP-4 inhibitor. The metabolic effect of DPP-4 inhibitors is to limit postprandial glucose excursions by augmenting glucose-stimulated insulin secretion. The alogliptin NDA (022271) and the FDC combination of alogliptin with pioglitazone (NDA 022426) are both currently under review by the Agency, at the time of this statistical review.

Metformin (Glophage™) is a commercially available biguanide that is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Metformin was originally approved for use in the U.S. in 1995, under NDA 020357.

2.1.2 Specific Studies Reviewed

In this review, I evaluate the Phase 3 study MET-302. A brief description is as follows:

¹ See 21 CFR 300.50 (B) Combination Drugs: (a) Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.

Study MET-302 was designed to evaluate alogliptin co-administered with metformin by comparing it to each component on its own, in subjects who were inadequately treated with diet and exercise. Subjects were randomly assigned to one of 7 treatment groups: (1) placebo; (2) metformin 500 mg bid; (3) metformin 1000 mg bid; (4) alogliptin 12.5 mg bid; (5) alogliptin 25 mg qd; (6) alogliptin 12.5 mg bid + metformin 500 mg bid; (7) alogliptin 12.5 mg bid + metformin 1000 mg bid. The primary HbA1c endpoint was determined after 26 weeks of double-blind treatment.

The other two Phase 3 studies that are included in this submission were reviewed under other NDA submissions, and I will not review them further in this review:

Study 322-008 was submitted under NDA 022271 (alogliptin). Study 322-008 was an add-on study for subjects who had inadequate glycemic control on metformin alone. Subjects were randomly assigned to one of three treatment groups: metformin with placebo, metformin with alogliptin 12.5 mg qd, or metformin with alogliptin 25 mg qd. The primary endpoint was determined after 26 weeks of double-blind treatment.

Study OPI-004 was submitted under NDA 022426 (alogliptin + pioglitazone). Study OPI-004 was conducted in subjects who had inadequate glycemic control on metformin and 30 mg of pioglitazone therapy. Subjects were randomly assigned to one of two treatment groups: (1) the addition of alogliptin 25 mg to the metformin and pioglitazone background therapy, or (2) up-titration of the pioglitazone dose from 30 mg to 45 mg. Study 004 was evaluated as a non-inferiority comparison between the two arms. The primary endpoint was determined after 52 weeks of double-blind treatment.

2.1.3 Major Statistical Issues

An issue that arose during the review of Study 302 was the identification (by the applicant) of 13 subjects who enrolled at two or more sites under separate ID numbers, and eight subjects who enrolled in both Study 302 and Study SYR-322_305 concurrently. The applicant evaluated each set of multiple enrollments, and determined the status of the data from each ID with respect to the analyses databases of Study 302. Dr. Pratt reviewed this information and concurred with the applicant's determinations. As a sensitivity analysis, I analyzed the primary HbA1c endpoint after excluding all of the data from the seven study sites that had multiple enrollments. The results were not substantially different from the primary results obtained with these sites included.

2.2 Data Sources

Submissions and data that I reviewed for the complete response resubmission of NDA [REDACTED] are summarized below:

(b) (4)

Data sources for NDS 203414/0

Number	Date	Description
0001	11/22/2011	NDA 203414/0 Alogliptin + Metformin original submission
\cdesub1\evsprod\NDA_203414		

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Subjects with multiple enrollments: In the clinical report for Study 302, the applicant identified 13 subjects who enrolled at two or more sites under separate ID numbers, and eight subjects who enrolled in both Study 302 and Study SYR-322_305 concurrently.² I will refer to this situation as “multiple enrollments.” The multiple enrollments were identified by the contract research organization responsible for data management, (b) (4) by comparing the demographic data of all enrolled subjects. (b) (4) conducted a follow-up evaluation and concluded that the subjects with multiple IDs had actually enrolled more than once, in violation of the study protocol. Some subjects had been concurrently enrolled and randomized to different study arms. As an illustration, the time course of HbA1c levels from one subject who enrolled at three sites under three different IDs is shown in Table 1.

The applicant evaluated each set of multiple enrollments, and determined the status of the data from each ID with regard to the analysis databases of Study 302. Dr. Pratt reviewed this information and concurred with the applicant’s determinations (see Appendix A, Table 16 and Table 17). As a sensitivity analysis, I analyzed the primary HbA1c endpoint after excluding all of the data from the seven study sites that had multiple enrollments. A summary of the study sites and a description of the involvement of the Office of Scientific Investigations is included in Part 3.2.1 of this review. The results of the sensitivity analysis are included in Part 3.2.4 of this review.

As a result of finding replicate enrollments in Study 302, the Division expressed concern about the possibility that there may be replicate enrollments in the ongoing cardiovascular outcomes study, Study SYR322_402. Based on the rationale that it is particularly important in Study 402 to establish the actual exposure to alogliptin and comparator drugs for each subject, and to attribute all cardiovascular outcomes comprehensively to each subject, the Division requested that the applicant monitor the database of cardiovascular trial SYR-322_402 for multiple enrollments, both within the study and across other alogliptin studies (see the information requested dated May 16, 2012). The applicant agreed, and the Division concurred with their monitoring plan.

² This finding was reported in Part 10.2 of the clinical report of Study 302 and described further in Appendix 16.2.4.5. See Appendix A of this review for a summary of this information. Study SYR-322_305 was ongoing at the time of the submission of NDA 203414/0. These findings represent multiple enrollments from 20 separate subjects (one subject enrolled in two sites in Study 302 and also enrolled in Study 305).

Table 1 Study 302; HbA1c records from one subject who enrolled at three sites in Florida under three different ID numbers

ID	5078010		5149024		5301038	
Site	5078		5149		5301	
Location	Opa Locka, FL		Hialeah, FL		Boca Raton, FL	
Assigned	Alogliptin 12.5 mg + Metformin 500 mg		Metformin 500 mg		Screen failure	
Date	Visit Type	HbA1c	Visit Type	HbA1c	Visit Type	HbA1c
4/22/10			Screening	9.2		
5/25/10	Screening	9.1				
5/27/10			Stabilization	9.0		
6/4/10			Baseline	9.1		
6/18/10	Unscheduled	8.7				
6/28/10	Baseline	8.8				
7/6/10			Week 4	8.8		
7/26/10	Week 4	8.7				
7/30/10			Week 8	8.7		
8/23/10	Week 8	8.6				
8/24/10			Week 12	8.6		
9/9/10			unscheduled	8.5		
9/21/10	Week 12	8.9				
9/24/10			Week 16	8.9		
9/30/10	Unscheduled	8.7				
10/18/10	Week 16	8.5				
10/21/10					Screening	8.4
10/28/10			Week 20	8.4		
11/9/10	Week 20	8.3				
12/27/10			Week 26/EOT	8.6		
12/28/10	Week 26/EOT	8.6				

Note: The applicant determined that “due to simultaneous enrollment at two sites, the clinical data may be contaminated and the efficacy and safety profiles for each distinct subject ID will be difficult to establish; therefore, subjects 50810 and 5149024 will be excluded from the FAS, the PPS, and the safety set. Subject 5301038 was a screen failure and would not have been included in any of these analysis sets.” For a summary of the determinations for all of the subjects with multiple enrollments, see Appendix A of this review.

Source: Analysis by this reviewer, from the applicant’s database D EFFLAB

3.2 Evaluation of Efficacy

3.2.1. Study design and endpoints

Design: Study MET-302 was an international, multi-center, randomized, double-blind and placebo-controlled study. The study was planned to enroll at least 735 subjects (105 per arm) with type 2 diabetes who were inadequately controlled on diet and exercise alone for at least 2 months prior to screening and who had an HbA1c concentration between 7.5% and 10.0%. The study included a screening period of at most 2 weeks, a placebo run-in / stabilization period of 4 weeks, a double-blind treatment period of 26 weeks and a follow-up period of 2 weeks after the end of study or early termination visit.

At the conclusion of the placebo run-in / stabilization period, 784 subjects were randomly assigned with equal allocation to the following 7 treatment arms:

- Alogliptin placebo bid + metformin placebo bid (n=109)
- Alogliptin placebo bid + metformin 500 mg bid (n=114)
- Alogliptin placebo bid + metformin 1000 mg bid (n=111)
- Alogliptin 12.5 mg bid + metformin placebo bid (n=113)
- Alogliptin 25 mg qd + metformin placebo bid (n=112)
- Alogliptin 12.5 mg bid + metformin 500 mg bid (n=111)
- Alogliptin 12.5 mg bid + metformin 1000 mg bid (n=114)

Randomization: The allocation was 1:1 across all 7 treatment arms. There were no stratification variables.

Study sites: Study 302 was conducted in 14 countries. For purposes of analysis, the countries were subdivided into four regions of the world (Table 2). The study was conducted from November 16, 2009 (first subject enrolled) to June 23, 2011 (data for primary endpoint collected from the last subject).

Seven sites in the U.S. had subjects with multiple enrollments, either at different sites as part of Study 302, or as part of Study SYR-322_305 (see Part 3.1 of this review for additional information). Four of the sites where most of the multiple enrollments took place were in the Miami, FL area, in close proximity to each other (Table 3). The Office of Scientific Investigations (OSI) inspected Site 5301 in Boca Raton, FL, as part of their review of this NDA. The original reason for selecting Site 5301 for inspection did not relate to the issue of multiple enrollments. However, Dr. Janice Pohlman, the OSI reviewer for this NDA, extended the inspection of Site 5301 to include this issue (see the review by Dr. Pohlman).

Table 2 Study 302; Number of study sites and randomized subjects by country and region of the world

Region	Country	No. of sites	No. of subjects randomized
North America	U.S.	85	258
Latin America	Mexico	21	155
	Puerto Rico	9	27
Asia	India	16	120
Europe and Rest of World	Czech Republic	3	6
	Hungary	7	21
	Israel	5	12
	Lithuania	4	13
	Poland	8	16
	Romania	5	23
	Russia	11	52
	Slovakia	8	27
	South Africa	4	4
	Ukraine	12	50
Totals		198	784

Source: Analysis by this reviewer

Table 3 Study 302; Study sites with subjects who enrolled more than once under different ID numbers

Site ID: Location	Number screened	Number randomized	Number with enrollments at other sites within Study 302 and/or Study 305
5301: Boca Raton, FL	50	27	13
5078: Opa Locka, FL	35	10	9
5149: Hialeah, FL	46	11	8
5105: Cutler Bay, FL	7	3	1
5114: Salt Lake City, UT	12	3	1
5275: Salt Lake City, UT	7	2	1
5121: Houston, TX	1	3	1
Totals	158	59	(multiple enrollments from 20 separate subjects)

Source: Study 302 clinical report, Appendix 16.2.4.5, and Appendix A of this review

Criteria for withdrawing from the study: At the start of Study 302 (the first subject was enrolled on November 16, 2009), the protocol specified that subjects who withdrew early from the study would be classified in one of the following categories:

1. Lack of efficacy
2. Adverse event
3. Major protocol violation
4. Lost to follow-up
5. Voluntary withdrawal
6. Study termination
7. Pregnancy
8. Investigator discretion
9. Other

The “lack of efficacy” category referred to subjects who met criteria for inadequate glucose control, because these subjects were withdrawn from the study. However, with the implementation of Protocol Amendment 1 (June 8, 2010), the “lack of efficacy” category was omitted, because the management of subjects who met criteria for inadequate glucose control changed. Subjects who met the criteria for inadequate glucose control were rescued and allowed to continue on double-blind study treatment with the rescue medication until completion of the treatment period. The rescue medication was treatment with a sulfonylurea drug unless otherwise indicated, at the investigator’s discretion.

This change took place as a result of a recommendation from the Division. In an advice letter dated 12/3/09, the Division made the following request: “The protocol states that subjects who are rescued will complete an early termination visit. Please consider not discontinuing these subjects from the study, but rather following them until completion of the treatment period to allow for a more complete assessment of safety.” The applicant agreed with this recommendation and implemented Protocol Amendment 1.

Criteria for hyperglycemic rescue:

After more than 1 week of treatment (> 7 days) but prior to the Week 4 visit: A single fasting plasma glucose ≥ 275 mg/dL (≥ 15.27 mmol/L) 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 (≥ 13.88 mmol/L) 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 (≥ 12.49 mmol/L) 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.

As part of the discussion about hyperglycemic rescue, the Division also expressed concern that the criteria for rescue from week 12 on would lead to a large proportion of rescues after week 12. Week 12 is the week when the rescue criteria change from being based on fasting plasma glucose (FPG) to being based on HbA1c. The Division recommended that the criteria for rescue be based on FPG throughout the entire primary endpoint period (the first six months of the study), after which the criteria would be switched to being based on HbA1c (see the advice letters dated December 3, 2009 and February 11, 2010). However, the applicant disagreed and continued to implement the criteria for rescue as originally described in the protocol. In this review I summarize the proportion of rescues prior to week 12 and from week 12 on to the study endpoint.

Statistical power and the size of the study: The applicant calculated the number of subjects to be randomized in the study, 105 per treatment arm, on the basis of the following assumptions and estimates: (1) a treatment effect of 0.55 between a combination and each of its components; (2) a standard deviation of 1.0; (3) a two-sided α of 0.025 for each comparison between a combination and each of its components; (4) 90% power. The applicant noted further that 105 subjects per treatment arm also provided 90% power to detect a treatment effect of 0.45 between any two pairs of arms with an unadjusted two-sided α of 0.05, assuming a standard deviation of 1.0.

Efficacy endpoints: The primary efficacy endpoint was the change from baseline in HbA1c at week 26. Secondary endpoints were listed as HbA1c (change from baseline) at weeks 4, 8, 12, 16 and 20; and fasting plasma glucose at weeks 1, 2, 4, 8, 12, 16, 20 and 26. The protocol also listed several exploratory endpoints, most of which were evaluated at more than one time period. The protocol did not provide a plan for controlling Type I error in the secondary endpoints.

3.2.2. Subject disposition, and demographic and baseline categories

Disposition: Two aspects of disposition in Study 302 are related and I will consider them together. The protocol changed while the study was underway with respect to the disposition of subjects who met the criteria for inadequate glycemic control (also referred to as “rescue.”) The majority of subjects who met the criteria for rescue did so after Protocol Amendment 1 was implemented (Figure 2). For this reason, the percentage of rescued subjects who completed the double-blind period of Study 302 was greater than the percentage of rescued subjects who were discontinued due to lack of efficacy (Figure 2 and Table 4). A small number of subjects were rescued, continued in the study, and then later discontinued due to other reasons. The applicant

characterized subjects with respect to both completing study medication and completing study visits. I found that the percentages in both classifications were fairly similar across the study arms. For this reason, I chose to discuss disposition with respect to the completion of study medication.

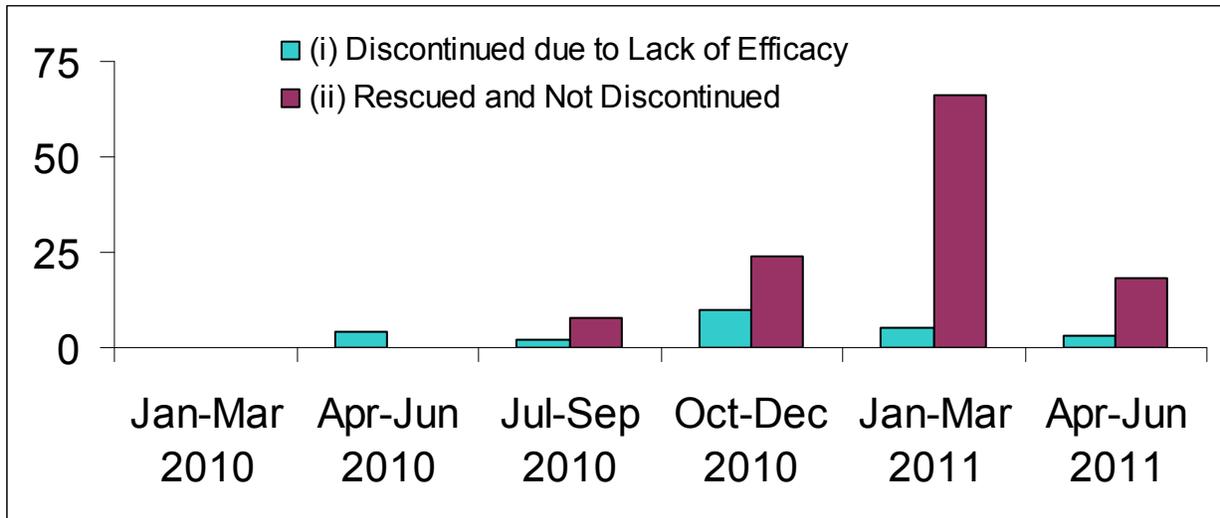
The placebo arm had the largest percentage of subjects who discontinued and/or were rescued (57%; Table 4). The two arms with the metformin 1000 mg bid dose had the smallest percentage of subjects who discontinued and/or were rescued (19% in the alogliptin 12.5 mg + metformin 1000 mg bid arm and 24% in the metformin 1000 mg bid arm). Of note is the difference in the percentage of discontinuations and/or rescues between the alogliptin 25 mg qd arm (36%) and the alogliptin 12.5 mg bid arm (48%), a difference which is largely due to a larger percentage of subjects in the alogliptin 12.5 mg bid arm who discontinued (37%) compared to the percentage in the alogliptin 25 mg qd arm (21%; Table 4). I don't know why this would be the case.

The majority of subjects who met the criteria for inadequate glycemic control did so at week 12 or beyond (100 out of 140), which is when the criteria changed from being based on FPG to being based on HbA1c (Table 5). This supports the concern expressed by the review division at the protocol stage that the HbA1c-based criteria at week 12 would result in a large number of rescues.

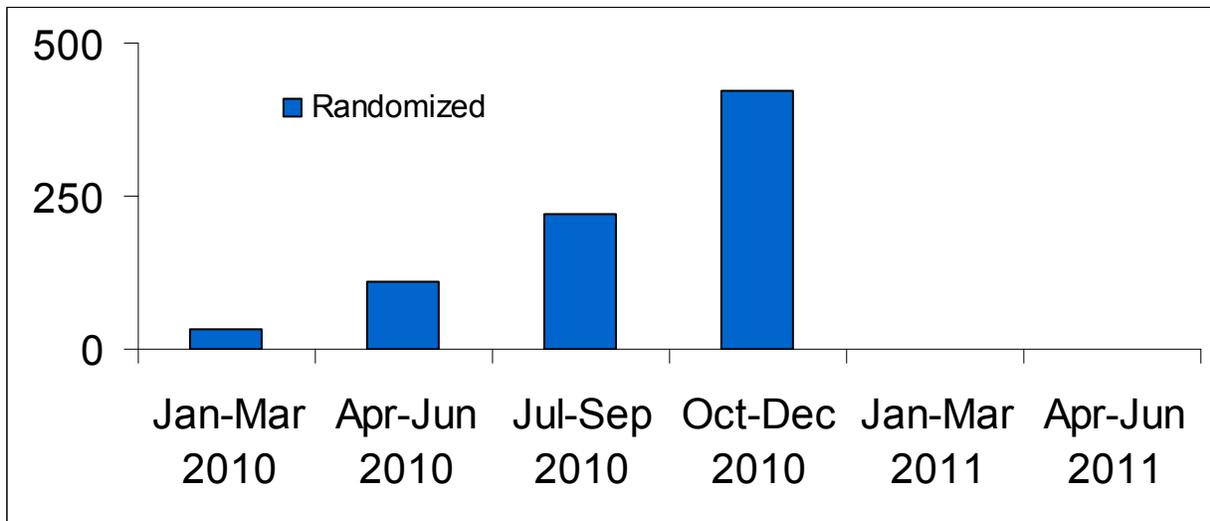
The summary statistics for baseline demographic and subject characteristics are included in Table 6.

Figure 2 Study 302; Number of patients randomized and number of patients who met the criteria for inadequate glucose control, by 3-month period

A. Number of patients who met criteria for inadequate glycemic control and were: (i) discontinued from the study, with “Lack of Efficacy” as the reason for discontinuation, or (ii) rescued and not discontinued from the study, following the implementation of Protocol Amendment 1 (June 8, 2010)



B. Number of subjects randomized



Notes: One subject was enrolled in December 2009 and was included in the tally for Jan-Mar 2010. Although Protocol Amendment 1 was dated June 8, 2010, some subjects were discontinued from the study due to lack of efficacy through April 2011. The first subject to be rescued under Protocol Amendment 1 was recorded in August 2010 and the last rescued subject was recorded in June 2011.

Source: Analysis by this reviewer

Table 4 Study 302; Disposition and rescue status

Arm	Completion status (%) ¹		Met criteria for rescue ² (%)
Placebo N ³ =109	Completed study medication	74 (67.9%)	
	Rescue criteria not met	47	
	Rescue criteria met	27	27
	Discontinued study medication	35 (32.1%)	
	Rescue criteria met (LOE) ¹	9	9
	Voluntary withdrawal	13	2
	Adverse event	4	2
	Lost to follow-up	4	
	Other ⁴	5	1
			<hr/> 41 (37.6%)
Alogliptin 25 mg qd N=112	Completed study medication	89 (79.5%)	
	Rescue criteria not met	72	
	Rescue criteria met	17	17
	Discontinued study medication	23 (20.5%)	
	Rescue criteria met (LOE)	3	3
	Voluntary withdrawal	8	
	Adverse event	4	
	Lost to follow-up	8	2
	Other	0	
		<hr/> 22 (19.6%)	
Alogliptin 12.5 mg bid N=113	Completed study medication	71 (62.8%)	
	Rescue criteria not met	59	
	Rescue criteria met	12	12
	Discontinued study medication	42 (37.2%)	
	Rescue criteria met (LOE)	6	6
	Voluntary withdrawal	16	
	Adverse event	7	
	Lost to follow-up	7	2
	Other	6	
		<hr/> 20 (17.8%)	
Metformin 500 mg bid N=114	Completed study medication	94 (82.5%)	
	Rescue criteria not met	68	
	Rescue criteria met	26	26
	Discontinued study medication	20 (17.5%)	
	Rescue criteria met (LOE)	2	2
	Voluntary withdrawal	10	
	Adverse event	3	
	Lost to follow-up	2	
	Other	9	
		<hr/> 28 (24.6%)	

Continued on the next page

Arm	Completion status (%) ¹		Rescue status ² (%)
Metformin 1000 mg bid N ³ =111	Completed study medication	95 (85.6%)	12 (10.8%)
	Rescue criteria not met	84	
	Rescue criteria met	11	
	Discontinued study medication	16 (14.4%)	
	Rescue criteria met (LOE)	1	
	Voluntary withdrawal	6	
	Adverse event	2	
	Lost to follow-up	5	
	Other ⁴	2	
Alogliptin 12.5 mg + Metformin 500 mg bid N=111	Completed study medication	92 (82.9%)	14 (12.6%)
	Rescue criteria not met	80	
	Rescue criteria met	12	
	Discontinued study medication	19 (17.1%)	
	Rescue criteria met (LOE)	2	
	Voluntary withdrawal	8	
	Adverse event	5	
	Lost to follow-up	2	
	Other	2	
Alogliptin 12.5 mg + Metformin 1000 mg bid N=114	Completed study medication	94 (82.5%)	3 (2.6%)
	Rescue criteria not met	92	
	Rescue criteria met	2	
	Discontinued study medication	20 (17.5%)	
	Rescue criteria met (LOE)	1	
	Voluntary withdrawal	5	
	Adverse event	11	
	Lost to follow-up	2	
	Other	1	
All study arms combined N=784	Completed study medication	609 (77.7%)	140 (17.9%)
	Rescue criteria not met	502	
	Rescue criteria met	107	
	Discontinued study medication	175 (22.3%)	
	Rescue criteria met (LOE)	24	
	Voluntary withdrawal	66	
	Adverse event	36	
	Lost to follow-up	30	
	Other	19	
<i>Notes (on next page)</i>			

Notes:

¹ Percentages are based on the number of randomized subjects

² At the start of the study, subjects who met the criteria for “inadequate glucose control” (also known as “rescue”) were discontinued from the study with the reason code “Lack of Efficacy (LOE).” After the implementation of Protocol Amendment 1, subjects who met the criteria for inadequate glucose control were rescued and continued in the study. Some of the rescued subjects then discontinued later, due to other reasons (not LOE).

³ The number (N) of randomized subjects

⁴ The “Other” category in this table is a combination of “major protocol deviation,” “study termination,” “pregnancy,” “PI discretion” and “other.”

Sources: Study 302 clinical report, Figure 10.1, Table 10.1, and additional analysis by this reviewer

Table 5 Study 302; Number of subjects rescued prior to week 12 (FPG-based criteria) and from week 12 on (HbA1c-based criteria)

Arm	Rescued prior to Week 12 ¹	Rescued at Week 12 or later	Total number rescued
Placebo	16	25	41
Alogliptin 25 mg qd	6	16	22
Alogliptin 12.5 mg bid	4	16	20
Metformin 500 mg bid	9	19	28
Metformin 1000 mg bid	1	11	12
Alogliptin 12.5 mg + Metformin 500 mg bid	4	10	14
Alogliptin 12.5 mg + Metformin 1000 mg bid	0	3	3
Totals	40 (28.6%)	100 (71.4%)	140

Notes:

¹ Rescue (meeting the criteria for inadequate control of hyperglycemia) prior to Day 78, with respect to the analysis window for week 12. Prior to week 12, the criteria are based on FPG. At week 12 and beyond, the criteria are based on HbA1c.

Source: Analysis by this reviewer

Table 6 Study 302; Baseline and demographic characteristics

	Placebo N=109	Treatment Arm						Total N=784
		A25 qd N=112	A12.5 bid N=113	M500 bid N=114	M1000 bid N=111	A12.5 + M500 bid N=111	A12.5 + M1000 bid N=114	
Age (yr)								
Mean ± 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	53.5 ± 10.3
< 65	100 (91.7%)	103 (92.0%)	96 (85.0%)	95 (83.3%)	94 (84.7%)	91 (82.0%)	96 (84.2%)	675 (86.1%)
≥ 65	9 (8.3%)	9 (8.0%)	17 (15.0%)	19 (16.7%)	17 (15.3%)	20 (18.0%)	18 (15.8%)	109 (13.9%)
Sex								
Male	55 (50.5%)	48 (42.9%)	63 (55.8%)	47 (41.2%)	51 (45.9%)	48 (43.2%)	62 (54.4%)	374 (47.4%)
Female	54 (49.5%)	64 (57.1%)	50 (44.2%)	67 (58.8%)	60 (54.1%)	63 (56.8%)	52 (45.6%)	410 (52.3%)
Race								
White	76 (69.7%)	84 (75.0%)	83 (73.5%)	85 (74.6%)	79 (71.2%)	76 (68.5%)	78 (68.4%)	561 (71.6%)
Asian	20 (18.3%)	17 (15.2%)	21 (18.6%)	19 (16.7%)	20 (18.0%)	20 (18.0%)	26 (22.8%)	142 (18.2%)
American Indian /Alaskan Native	5 (4.6%)	8 (7.1%)	5 (4.4%)	3 (2.6%)	6 (5.4%)	9 (8.1%)	5 (4.4%)	41 (5.2%)
Black	8 (7.3%)	3 (2.7%)	3 (2.7%)	6 (5.3%)	6 (5.4%)	6 (5.4%)	5 (4.4%)	37 (4.7%)
Native Hawaiian / Pacific Islander	0	0	1 (0.9%)	0	0	0	0	1 (0.1%)
Multiracial	0	0	0	0 (0.9%)	0	0	0	1 (0.9%)
Ethnicity								
Hispanic / Latino	45 (41.3%)	43 (38.4%)	43 (38.1%)	45 (39.5%)	42 (37.8%)	45 (40.5%)	39 (34.2%)	302 (38.5%)
Not Hispanic / Latino	64 (58.7%)	69 (61.6%)	70 (61.9%)	69 (60.5%)	69 (62.2%)	66 (59.5%)	75 (65.8%)	482 (61.5%)
Geographic Region								
North America	37 (33.9%)	36 (32.1%)	38 (33.6%)	37 (32.5%)	36 (32.4%)	36 (32.4%)	38 (33.3%)	258 (32.9%)
Latin America	25 (22.9%)	27 (24.1%)	25 (22.1%)	26 (22.8%)	26 (23.4%)	27 (24.3%)	26 (22.8%)	182 (23.2%)
Europe/ Rest of World	31 (28.4%)	32 (28.6%)	32 (28.3%)	33 (28.9%)	32 (28.8%)	32 (28.8%)	32 (28.1%)	224 (28.6%)
Asia	16 (14.7%)	17 (15.2%)	18 (15.9%)	18 (15.8%)	17 (15.3%)	16 (14.4%)	18 (15.8%)	120 (15.3%)

	Placebo	Treatment Arm						Total
		A25 qd	A12.5 bid	M500 bid	M1000 bid	A12.5 + M500 bid	A12.5 + M1000 bid	
	N=109	N=112	N=113	N=114	N=111	N=111	N=114	N=784
Baseline 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	8.4 ± 0.8
≤ 8.5	65 (59.6%)	67 (59.8%)	67 (59.3%)	67 (58.8%)	66 (59.5%)	66 (59.6%)	67 (58.8%)	465 (59.3%)
> 8.5	44 (40.4%)	45 (40.2%)	46 (40.7%)	47 (41.2%)	45 (40.5%)	45 (40.5%)	47 (41.2%)	319 (40.7%)
BMI, kg/m²								
Mean ± SD	31.2 ± 5.3	30.8 ± 5.2	30.4 ± 5.2	30.2 ± 4.8	30.5 ± 5.0	30.9 ± 5.4	31.0 ± 5.4	30.7 ± 5.2
Diabetes duration (yr)								
Mean ± SD	4.3 ± 4.8	3.7 ± 4.2	4.0 ± 4.8	3.8 ± 3.9	4.1 ± 4.6	4.1 ± 4.8	4.2 ± 5.0	4.0 ± 4.6

Source: Study 302 clinical report, Table 10.b and Table 10.c

3.2.3. Statistical methodologies

Analysis sets: The full analysis set (FAS) was used for the primary efficacy analysis. The FAS consisted of all randomized subjects who had a baseline assessment and at least one valid post-baseline assessment for the variable being analyzed. The primary method of imputation, incorporated into the FAS, was the last observation carried forward (LOCF), referring to either the time at discontinuation or the time at rescue. The per protocol set (PPS) included all FAS subjects who had no major protocol violations. This means that the PPS set also incorporated LOCF for subjects who were rescued or who were discontinued for reasons that still permitted their inclusion in the PPS.

As part of a sensitivity analysis, the applicant evaluated several versions of the FAS, which varied according to whether and how LOCF was applied, and whether or not data collected post-rescue was included. A summary of the version of the FAS is shown in Table 7. Note that with respect to the primary analysis of covariance model (i.e., the analysis that includes only week 26 and baseline data), Model 1b is one version of a completers population, with no post-rescue data included; and Model 2b is another version of a completers population with post-rescue data included.

Table 7 Study 302; Analysis populations with respect to the treatment of dropouts and rescues

	Subjects who dropped out	Subjects who met rescue criteria	
		Discontinued post- rescue	Rescued and remained in the study
Model 1a (primary)	LOCF	LOCF (post-rescue)	LOCF (post-rescue)
Model 1b	No LOCF	No LOCF	No post-rescue data
Model 2a	LOCF	LOCF	Post-rescue data
Model 2b	No LOCF	No LOCF	Post-rescue data

Note: The applicant referred to the analysis populations by the model numbers shown in this table.

Source: Study 302 clinical report, Table 9 f

Statistical analysis methods for the primary efficacy endpoint: The primary efficacy analysis consisted of two separate sets of comparisons between each bid combination of alogliptin and metformin:

- Set 1: alogliptin 12.5 mg / metformin 500 mg bid combination arm compared to the alogliptin 12.5 mg arm and the metformin 500 mg bid arm
- Set 2: alogliptin 12.5 mg / metformin 1000 mg bid combination arm compared to the alogliptin 12.5 mg arm and the metformin 1000 mg bid arm

Each of these sets of comparisons was evaluated at a 2-sided α of 0.025. Both comparisons between a combination and its constituent doses needed to be statistically significant in order to support the efficacy of the combination.

The primary efficacy analysis model was an analysis of covariance (ANCOVA) model with change from baseline in HbA1c at week 26 as the response variable, treatment and geographic region as fixed effects, and baseline HbA1c as a continuous covariate.

Supportive analyses included an ANCOVA model that added the treatment by geographic interaction and the treatment by baseline HbA1c interaction to the primary model. Other supportive analyses included conducting the primary ANCOVA model applied to the PPS, and conducting the primary ANCOVA model applied to a modified version of the FAS, where post-rescue measurements of HbA1c were included instead of using LOCF at the point of rescue, in subjects who were not discontinued at the point of rescue.

Protection of Type I error: Protection of Type I error in the analysis of the primary endpoint was protected by evaluating each bid combination of alogliptin and metformin at a 2-sided α of 0.025. To meet regulatory requirements, both comparisons between a combination and its component doses need to be statistically significant. For secondary and exploratory analyses, no statistical adjustments were made for multiple comparisons.

Secondary efficacy endpoints: Continuous secondary and exploratory variables were analyzed using the primary model as specified for the analysis of HbA1c, but with the corresponding baseline value used as a covariate (in place of baseline HbA1c). Time to hyperglycemic rescue was analyzed using a Cox proportional hazards regression model with an effect for treatment, a stratification factor for geographic region, and a covariate for baseline HbA1c. The incidence of clinical response endpoints were analyzed using a logistic regression model with effects for treatment and geographic region and a covariate for baseline HbA1c.

Secondary objective: A secondary objective described in the protocol was to compare the alogliptin 12.5 mg bid arm with the alogliptin 25 mg qd arm. A conclusion of “similarity” would support the extension of conclusions about safety and efficacy from clinical studies of the 25 mg qd dosing schedule to the 12.5 mg bid dosing schedule. The 12.5 mg bid dosing schedule is used in the FDC product because of the metformin dosing schedule. However, the criterion for deciding that the two dosing schedules are “similar” was not pre-specified. As a post-hoc

approach, I assumed that the focus was on assessing the non-inferiority of the alogliptin 12.5 mg bid arm to the alogliptin 25 mg qd arm. Because Study 302 had a placebo arm, I estimated an internal non-inferiority margin by calculating half of the placebo-adjusted mean effect of the alogliptin 25 mg qd arm.

3.2.4. Results and Conclusions

Primary efficacy endpoint: Treatment with alogliptin co-administered with metformin resulted in a mean change from baseline in HbA1c at week 26 that was statistically significantly different, in the direction of greater efficacy, than each of its components (Table 8 and Figure 3). Both dose levels, alogliptin 12.5 mg + metformin 500 mg bid and alogliptin 12.5 mg + metformin 1000 mg bid, had an effect on HbA1c that was greater than their respective components. Each active arm in the study design also had a significant effect on HbA1c in comparison with placebo (Table 9). The results from the additional analysis populations that the applicant pre-specified supported the efficacy of the two combinations in comparison with their respective components (Table 10).

I was able to repeat the results from the primary efficacy analysis, although some of the estimates that I obtained were different by ± 0.1 in the % units of HbA1c (Table 10), with additional results reported in Appendix A). I attribute these differences to the discrepancies in the total number of subjects in each arm that the applicant reported and that I obtained by analyzing the applicant's databases (Table 11). I don't know what the source(s) of these discrepancies are. However, I believe that they don't affect the overall study conclusions.

I conducted an additional analysis, excluding the seven study sites that had subjects with multiple enrollments (see Part 3.1 of this review for a description of the multiple enrollments). The results were not substantially different from the primary results with these studies included (Table 10).

I compared the effects of alogliptin and metformin between arms, although I recognize that Study 302 was not powered for these comparisons. In addition, I compared the effects of the alogliptin and metformin monotherapy arms to effects estimated from other studies. Here are my key findings for the primary endpoint, HbA1c change from baseline at week 26:

- The placebo-adjusted effect of the alogliptin + metformin 500 mg bid arm was smaller than the alogliptin + metformin 1000 mg bid arm (-1.4 compared to -1.7, respectively; Table 9). This finding is consistent with a dose-response relationship in metformin between the two combinations.
- The placebo-adjusted effects of the alogliptin monotherapy arms were fairly similar to the estimates from other Phase 3 studies (-0.6 in both the bid and the qd monotherapy arms, compared to -0.6 in monotherapy Study 010 and -0.5 in the add-on to metformin Study 008)³.

³ See Table 11 for the results from the monotherapy arms in Study 302. See the statistical review of NDA 022271/0 submitted 12/21/2007, Table 7 for the results from Study 008 and Study 010.

- The placebo-adjusted effects of the metformin monotherapy arms on HbA1c were somewhat smaller than the results reported in the most recent Glucophage™ label (2008; Table 2). In Study 302, the effects were -0.7 in the metformin 500 mg bid monotherapy arm and -1.2 in the 1000 mg bid monotherapy arm. From the Glucophage label, the results from a study of metformin in patients previously treated with dietary management alone appear to have a greater placebo-adjusted effect after 29 weeks of treatment. We can estimate the placebo-adjusted effect to be -1.8, based on change from baseline results of -1.4 for the Glucophage arm and 0.4 for the placebo arm (baseline HbA1c of 8.4 for the Glucophage arm and 8.2 for the placebo arm). The Glucophage dose is described as “up to 2550 mg/day” and this may be the key difference between the label study and Study 302. The Glucophage dose may have been titrated and optimized for each patient in the label study, whereas in Study 302 the metformin dose was fixed in each arm, with the higher dose arm fixed at 2000 mg/day.
- The placebo-adjusted effects of each combination were fairly similar to the additive combination of the placebo-adjusted effects of each component in the combination (Table 9).

Comparing alogliptin 12.5 mg bid with alogliptin 25 mg qd: The alogliptin component had a nearly identical effect on HbA1c at week 26 when given either as 12.5 mg bid or 25.0 mg qd, -0.6, with a 95% CI of (-0.9, -0.3; Table 9). The post-hoc estimate of the non-inferiority margin was half of this effect, or 0.3. The difference between the alogliptin 12.5 mg bid arm and the alogliptin 25 mg qd arm does not exceed this margin: the mean difference is 0.0 and the 95% CI is (-0.3, 0.3); (Table 9). This finding provides post-hoc support to extending conclusions on safety and efficacy from clinical studies of the 25 mg qd dose to the 12.5 mg bid dose in the combination product.

Fasting plasma glucose: The results for fasting plasma glucose, expressed as a change from baseline at week 26, also supported the superiority of the alogliptin + metformin combinations in comparison with their respective components (Table 12 and Figure 4).

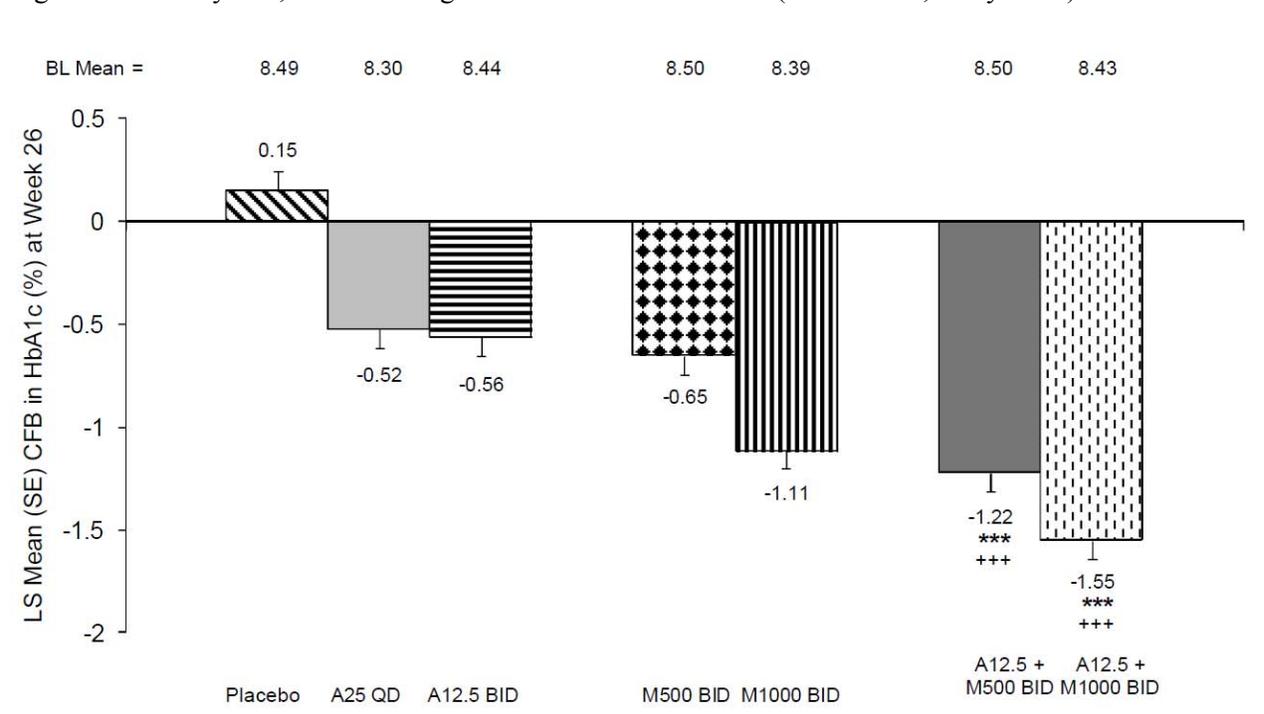
Body weight: Mean body weight at week 26 stayed within $\pm 2\%$ of baseline body weight in the combination and component treatment arms (Table 13). The effect of metformin was in the direction of weight loss (i.e., between week 26 and baseline) in the component and combination arms, and the effect of alogliptin was fairly neutral on weight.

Lipid endpoints: The applicant reported that the effect of alogliptin and metformin on changes from baseline in cholesterol (total, HDL and LDL) and triglycerides was fairly neutral. Some exploratory comparisons between combination and component arms were nominally statistically significant, but small in magnitude. This is apparent in the results for LDL-cholesterol, depicted in Table 14.

Table 8 Study 302; Primary efficacy endpoint (HbA1c change from baseline at week 26); primary efficacy evaluation of the alogliptin + metformin combinations

	Placebo	A25 qd	A12.5 bid	M500 bid	M1000 bid	A12.5 + M500 bid	A12.5 + M1000bid
Randomized, n	109	112	113	114	111	111	114
Baseline HbA1c, n	102	104	104	103	108	102	111
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)
Week 26 Change from baseline (FAS/LOCF; Model 1a)							
LS Mean ± sem	0.2±0.1	-0.5±0.1	-0.6±0.1	-0.7±0.1	-1.1±0.1	-1.2±0.1	-1.6±0.1
Combinations vs. components							
A12.5+M500 vs. components							
LS Mean difference			-0.7	-0.6			
97.5% CI			(-1.0, -0.4)	(-0.7, -0.3)			
p-value			< 0.001	< 0.001			
A12.5+M1000 vs. components							
LS Mean difference			-1.0		-0.4		
97.5% CI			(-1.3, -0.7)		(-0.7, -0.2)		
p-value			< 0.001		< 0.001		

Figure 3 Study 302; HbA1c change from baseline at week 26 (FAS/LOCF; analysis 1a)



Note: All analyses are based on the FAS analysis set with LOCF imputation for dropouts and for rescues (Applicant's analysis 1a)

Sources: Study 301 clinical report, Table 11.h and Figure 11.i

Table 9 Study 302; Primary efficacy endpoint (HbA1c change from baseline at week 26); comparisons among single component arms

	Placebo	A25 qd	A12.5 bid	M500 bid	M1000 bid	A12.5 + M500 bid	A12.5 + M1000bid
Randomized, n	109	112	113	114	111	111	114
Baseline HbA1c, n	102	104	104	103	108	102	111
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)
Week 26 Change from baseline (FAS/LOCF) ¹							
LS Mean ± sem	0.2±0.1	-0.5±0.1	-0.6±0.1	-0.7±0.1	-1.1±0.1	-1.2±0.1	-1.6±0.1
1. Alogliptin 12.5 bid vs. 25 qd							
LS Mean difference			0.0				
95% CI			(-0.3, 0.2)				
p-value			0.759				
2. Combinations vs. placebo							
A12.5+M500 bid vs. placebo							
LS Mean difference						-1.4	
95% CI						(-1.6, -1.1)	
p-value						< 0.001	
A12.5+M1000 bid vs. placebo							
LS Mean difference							-1.7
95% CI							(-2.0, -1.5)
p-value							< 0.001
3. Components vs. placebo							
A12.5 bid vs. placebo							
LS Mean difference			-0.6				
95% CI			(-0.9, -0.3)				
p-value			< 0.001				
A25 qd vs. placebo							
LS Mean difference		-0.6					
95% CI		(-0.9, -0.3)					
p-value		< 0.001					
M500 vs. placebo							
LS Mean difference				-0.7			
95% CI				(-1.0, -0.4)			
p-value				< 0.001			
M1000 vs. placebo							
LS Mean difference					-1.2		
95% CI					(-1.5, -0.9)		
p-value					< 0.001		
4. Combinations vs. (alogliptin component + metformin component) ²							
A12.5+M500 combination vs. (A12.5 component + M500 component)							
LS Mean difference						0.1	
95% CI						(-0.4, 0.5)	
p-value						0.788	
A12.5+M1000 component vs. (A12.5 component + M1000 component)							
LS Mean difference							0.1
95% CI							(-0.3, 0.5)
p-value							0.650

Placebo	A25 qd	A12.5 bid	M500 bid	M1000 bid	A12.5 + M500 bid	A12.5 + M1000bid
<i>Notes:</i>						
¹ All analyses are based on the FAS analysis set with LOCF imputation for dropouts and for rescues (Applicant’s analysis 1a).						
² The comparison between the combinations and the sum of the alogliptin and metformin components was constructed from a linear contrast in the form: [A+M combination] – [A component] – [M component] + [Placebo] = 0. This was derived from the statement [A+M combination] – [Placebo] = {[A component] – [Placebo]} + {[M component] – [Placebo]}. The alogliptin 12.5 mg bid arm was used for the alogliptin component.						
<i>Sources:</i>						
Analysis 1 and 2: From Study 301 clinical report, Table 11.i						
Analysis 3: By this reviewer, using applicant’s database D_Efflab, subsetted for HbA1c, FAS database, and Visit 13 (Week 26/End of Treatment)						

Table 10 Study 302; Primary and sensitivity analyses for the comparison of the two combinations with their respective components

		A12.5 + M500 bid	A12.5 + M1000 bid	A12.5 bid	M500 bid	M1000 bid
A. FAS with LOCF applied to dropouts and rescues (Applicant’s primary analysis 1a)						
1. Applicant’s analysis	n	102	111	104	103	108
Week 26 Mean CFB ± sem		-1.2 ± 0.1	-1.6 ± 0.1	-0.6 ± 0.1	-0.7 ± 0.1	-1.1 ± 0.1
A12.5+M500 vs. components						
LS Mean Difference				-0.7	-0.6	
95% CI				(-0.1, -0.4)	(-0.9, -0.3)	
p-value				< 0.001	< 0.001	
A12.5+M1000 vs. components						
LS Mean Difference				-1.0		-0.4
95% CI				(-1.3, -0.7)		(-0.7, -0.2)
p-value				< 0.001		< 0.001
2. This reviewer’s analysis	n	100	105	94	101	102
Week 26 LS Mean CFB ± sem		-1.3 ± 0.1	-1.7 ± 0.1	-0.6 ± 0.1	-0.7 ± 0.1	-1.2 ± 0.1
A12.5+M500 vs. components						
LS Mean Difference				-0.7	-0.6	
95% CI				(-1.0, -0.4)	(-0.9, -0.2)	
p-value				< 0.001	< 0.001	
A12.5+M1000 vs. components						
LS Mean Difference				-1.0		-0.4
95% CI				(-1.3, -0.7)		(-0.7, -0.1)
p-value				< 0.001		< 0.001

	A12.5 + M500 bid	A12.5 + M1000 bid	A12.5 bid	M500 bid	M1000 bid
3. Omitting 7 study sites that included subjects with multiple enrollments (See Part 3.1 of this review)					
n	95	98	89	94	98
Week 26 LS Mean CFB ± sem	-1.4 ± 0.1	-1.8 ± 0.1	-0.6 ± 0.1	-0.8 ± 0.1	-1.2 ± 0.1
A12.5+M500 vs. components					
LS Mean Difference			-0.7	-0.5	
95% CI			(-1.0, -0.4)	(-0.8, -0.2)	
p-value			< 0.001	< 0.001	
A12.5+M1000 vs. components					
LS Mean Difference			-1.1		-0.5
95% CI			(-1.5, -0.8)		(-0.8, -0.2)
p-value			< 0.001		< 0.001
B. Completers: FAS with no LOCF for dropouts and no data post-rescue (Applicant's Analysis 1b)					
n	78	91	59	66	84
Week 26 LS Mean CFB ± sem	-1.4 ± 0.1	-1.7 ± 0.1	-0.9 ± 0.1	-1.1 ± 0.1	-1.3 ± 0.1
A12.5+M500 vs. components					
LS Mean Difference			-0.5	-0.3	
95% CI			(-0.8, -0.2)	(-0.6, -0.1)	
p-value			< 0.001	0.009	
A12.5+M1000 vs. components					
LS Mean Difference			-0.8		-0.3
95% CI			(-1.1, -0.5)		(-0.6, -0.1)
p-value			< 0.001		0.004
C. FAS with LOCF applied to dropouts, and post-rescue data kept in (Applicant's analysis 2a)					
n	103	111	104	104	109
Week 26 LS Mean CFB ± sem	-1.3 ± 0.1	-1.6 ± 0.1	-0.7 ± 0.1	-0.8 ± 0.1	-1.2 ± 0.1
A12.5+M500 vs. components					
LS Mean Difference			-0.6	-0.4	
95% CI			(-0.9, -0.3)	(-0.7, -0.2)	
p-value			< 0.001	< 0.001	
A12.5+M1000 vs. components					
LS Mean Difference			-0.9		-0.4
95% CI			(-1.2, -0.6)		(-0.6, -0.1)
p-value			< 0.001		0.002
D. FAS with no LOCF applied to dropouts and post-rescue data kept in (Applicant's analysis 2b)					
n	88	92	71	89	95
Week 26 LS Mean CFB ± sem	-1.4 ± 0.1	-1.7 ± 0.1	-0.8 ± 0.1	-0.9 ± 0.1	-1.2 ± 0.1
A12.5+M500 vs. components					
LS Mean Difference			-0.5	-0.4	
95% CI			(-0.8, -0.2)	(-0.7, -0.1)	
p-value			< 0.001	< 0.001	
A12.5+M1000 vs. components					
LS Mean Difference			-0.9		-0.5
95% CI			(-1.2, -0.6)		(-0.7, -0.2)
p-value			< 0.001		< 0.001

	A12.5 + M500 bid	A12.5 + M1000 bid	A12.5 bid	M500 bid	M1000 bid	
E. Per Protocol, with LOCF applied to certain dropouts and certain rescues based on protocol						
Applicant's analysis 1a	n	84	88	70	82	90
Week 26 LSMean CFB ± sem		-1.3 ± 0.1	-1.7 ± 0.1	-0.5 ± 0.1	-0.8 ± 0.1	-1.1 ± 0.1
A12.5+M500 vs. components						
LS Mean Difference				-0.8	-0.5	
95% CI				(-1.1, -0.4)	(-0.9, -0.2)	
p-value				< 0.001	< 0.001	
A12.5+M1000 vs. components						
LS Mean Difference				-1.2		-0.6
95% CI				(-1.5, -0.8)		(-0.9, -0.3)
p-value				< 0.001		< 0.001
<i>Sources:</i>						
A1. Analysis 1a, Table 11 h				B. Analysis 1b. Table 15.2.1.1.2		
A2. Analysis by this reviewer				C. Analysis 2a. Table 15.2.1.1.3		
A3. Analysis by this reviewer				D. Analysis 2b. Table 15.2.1.1.4		
				E. PPS population, analysis 1a: Table 15.2.1.2.1		

Table 11 Study 302; Analysis populations, number of cases in each treatment arm in different analysis sets, from the applicant's clinical report and from my analysis of the applicant's databases

	Placebo	Treatment Arm						Total
		A25 qd	A12.5 bid	M500 bid	M1000 bid	A12.5 + M500 bid	A12.5 + M1000 bid	
1. Number of cases randomized								
Applicant	109	112	113	114	111	111	114	784
My analysis ¹	109	112	113	114	111	111	114	784
2. Number of cases in the FAS								
Applicant	106	112	110	109	111	106	114	768
My analysis ¹	106	112	110	109	111	106	114	768
3. Number of cases reported for HbA1c at baseline, FAS								
Applicant	102	104	104	103	108	102	111	734
My analysis ²	106	112	109	109	111	104	113	764
4. Number of cases reported for HbA1c at week 26, FAS/LOCF								
Applicant	102	104	104	103	108	102	111	734
My analysis ²	92	101	94	101	102	100	105	695
5. Number of cases reported for the PP data set								
Applicant	84	85	70	83	91	85	88	586
My analysis ¹	84	85	70	83	91	85	88	586
<i>Notes:</i>								
¹ I used the applicant's database D_Master for tallies of randomized, FAS and PPS subjects								
² I used the applicant's database D_Efflab, subsetted for HbA1c, FAS database, and Visit. Baseline is Visit 5, and Week 26/End of Treatment is Visit 13								
<i>Source:</i> Study 302 clinical report, Table 11.a and Table 11.h								

Table 12 Study 302; Fasting plasma glucose (mg/dL) change from baseline at week 26 (FAS/LOCF, Model 1a)

	Placebo	A25 qd	A12.5 bid	M500 bid	M1000 bid	A12.5 + M500 bid	A12.5 + M1000bid
Randomized, n	109	112	113	114	111	111	114
Baseline FPG, n	105	112	106	106	110	106	112
Mean (SD)	187 (45)	178 (52)	177 (43)	180 (50)	181 (52)	176 (51)	185 (50)
Week 26 Change from baseline (FAS/LOCF); mg/dl							
LS Mean ± sem	12 ± 5	-6 ± 4	-10 ± 4	-12 ± 4	-32 ± 4	-32 ± 4	-46 ± 4
Combinations vs. components:							
A12.5+M500 vs. components							
LS Mean difference			-22	-20			
97.5% CI			(-35, -10)	(-33, -8)			
p-value			< 0.001	0.002			
A12.5+M1000 vs. components							
LSMean difference			-36	-14			
97.5% CI			(-49, -24)	(-26, -2)			
p-value			< 0.001	0.025			

Figure 4 Study 302; Fasting plasma glucose changes from baseline (mg/dL) at week 26 (FAS/LOCF, Model 1a)

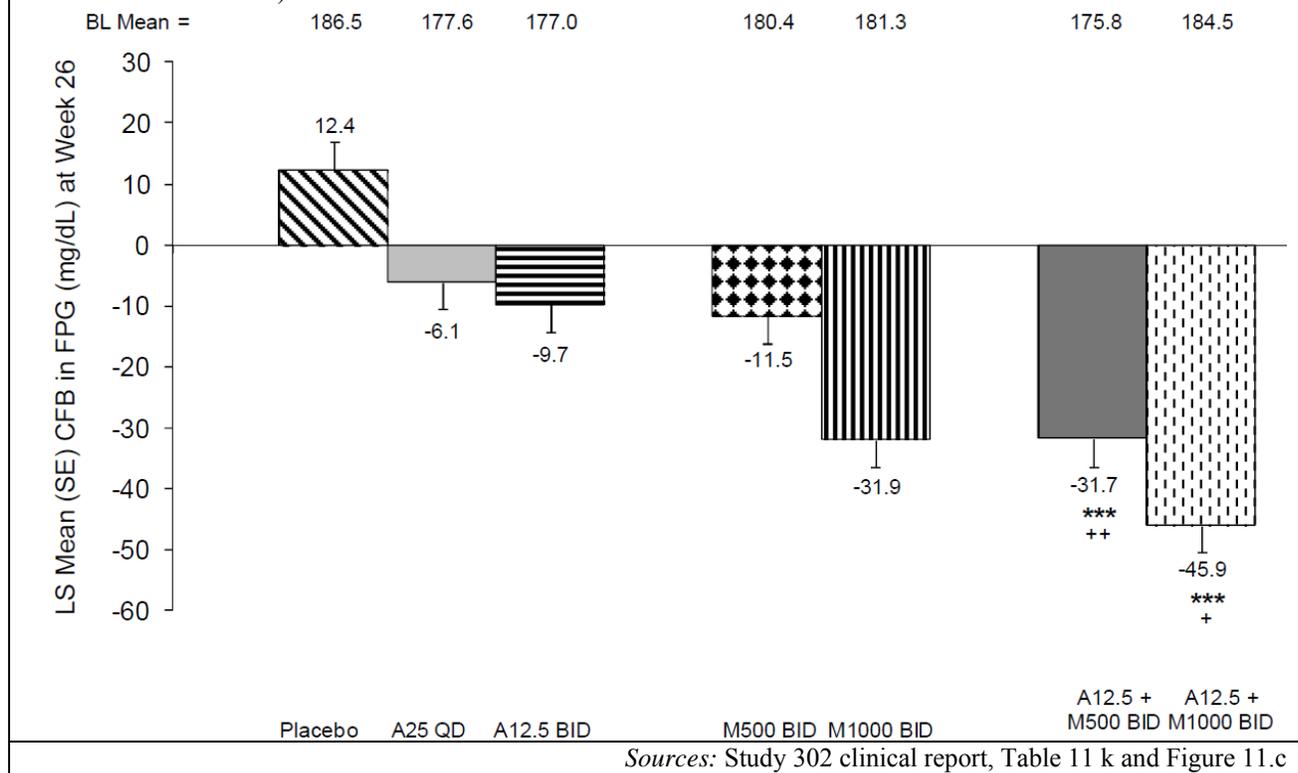


Table 13 Study 302; Body weight (kg) change from baseline at week 26 (FAS/LOCF, Model 1a)

	A12.5 bid	M500 bid	M1000 bid	A12.5 + M500 bid	A12.5 + M1000 bid
Randomized, n	113	114	111	111	114
Baseline weight, n	89	92	101	94	103
Mean (SD)	82.8 (17.5)	81.7 (17.1)	81.8 (17.6)	82.7 (16.5)	86.6 (17.5)
Week 26 Change from baseline (FAS/LOCF); mg/dl					
LS Mean \pm sem	0.0 \pm 0.3	-0.8 \pm 0.3	-1.3 \pm 0.3	-0.6 \pm 0.3	-1.2 \pm 0.3
Combinations vs. components:					
A12.5+M500 vs. components					
LS Mean difference	-0.6	0.2			
97.5% CI	(-1.3, 0.2)	(-0.6, 1.0)			
p-value	0.168	0.555			
A12.5+M1000 vs. components					
LS Mean difference	-1.2		0.1		
97.5% CI	(-1.9, -0.4)		(-0.7, 0.8)		
p-value	0.003		0.840		
<i>Note:</i> Only the results for the five treatment arms involved in the evaluation of the combinations are shown in this table.					
<i>Source:</i> Study 302 clinical report, Table 15.2.9.1.1					

Table 14 Study 302; LDL cholesterol (mg/dL) change from baseline at week 26 (FAS/LOCF, Model 1a)

	A12.5 bid	M500 bid	M1000 bid	A12.5 + M500 bid	A12.5 + M1000 bid
Randomized, n	113	114	111	111	114
Baseline weight, n	96	100	100	100	107
Mean (SD)	113.8 (38.4)	117.4 (35.4)	116.3 (36.1)	115.7 (32.1)	109.5 (30.0)
Week 26 Change from baseline (FAS/LOCF); mg/dl					
LS Mean \pm sem	7.7 \pm 3.2	2.1 \pm 3.1	1.5 \pm 3.1	-3.6 \pm 3.1	-4.9 \pm 3.0
Combinations vs. components:					
A12.5+M500 vs. components					
LS Mean difference	-11.4	-5.7			
97.5% CI	(-20.2, -2.6)	(-14.4, 3.0)			
p-value	0.011	0.197			
A12.5+M1000 vs. components					
LS Mean difference	-12.6		-6.4		
97.5% CI	(-21.2, -4.0)		(-14.9, 2.2)		
p-value	0.004		0.145		
<i>Note:</i> Only the results for the five treatment arms involved in the evaluation of the combinations are shown in this table.					
<i>Source:</i> Study 302 clinical report, Table 15.2.13.1.1					

3.3 Evaluation of Safety

An evaluation of the safety of alogliptin co-administered with metformin is included in the clinical review by Dr. Valerie Pratt.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The effect of subgroups in a combination study is a little difficult to tease out. This is because the seven treatment arms in Study 302 represent the applicant's interest in several assessments:

- the contribution of alogliptin and metformin components to the efficacy of each of two combinations
- the activity of each treatment arm when compared to placebo
- the degree of similarity of the 25 mg daily dose of alogliptin, when delivered as a divided dose twice a day, and as a single dose once a day.

These assessments were obtained from specific comparisons between sets of model-based means obtained from the analysis of covariance model. In a study design with fewer arms, for example, with one active treatment arm and a placebo arm, the interaction of a subgroup such as sex would be assessed by adding the treatment arm by sex interaction term to the analysis of covariance model. A p-value of < 0.1 would typically be used to signal that the placebo-adjusted effect of the active treatment may differ in an important way between males and females. However, in Study 302, this interaction term would be difficult to interpret and its p-value may not be related to subgroup effects of interest.

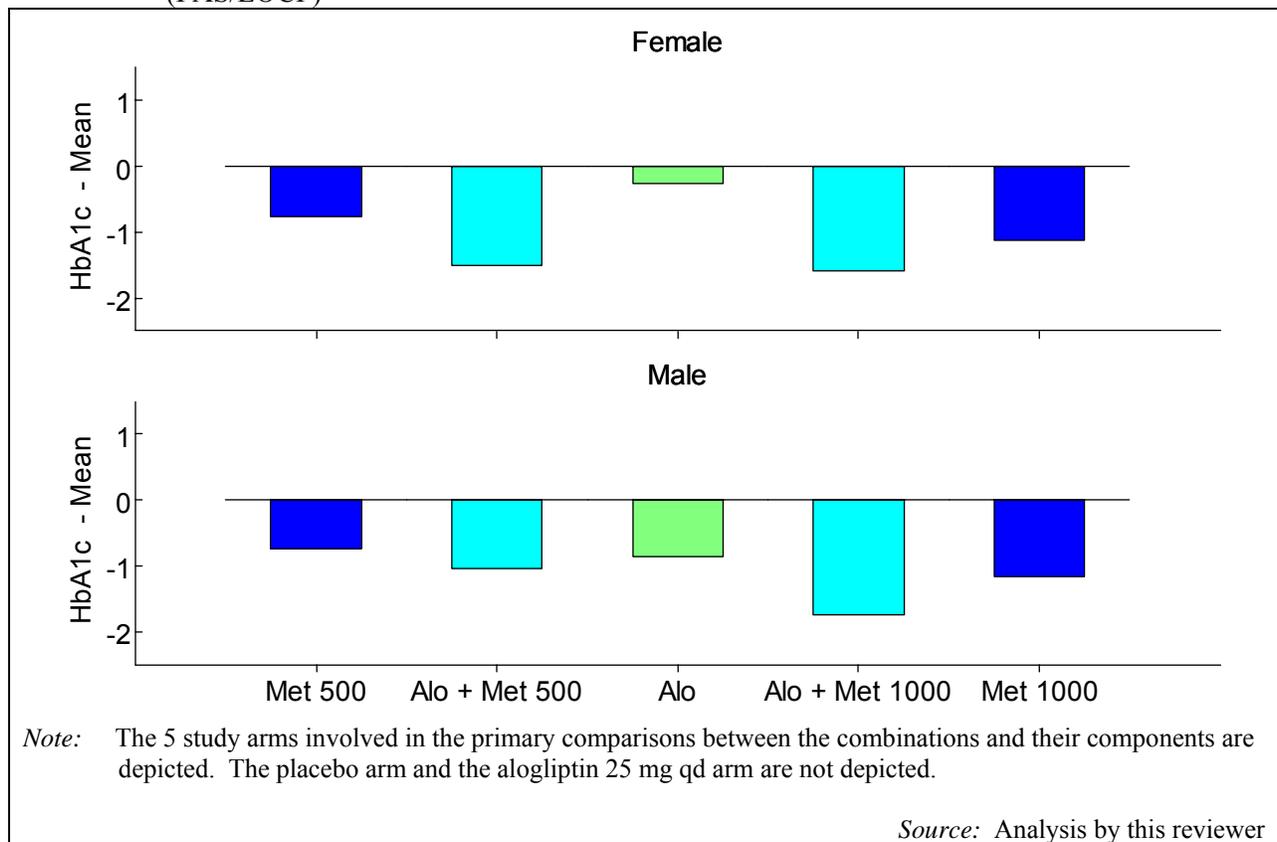
In fact, even after narrowing the focus to the comparisons of the two combinations to their components, it is not clear how to define the contrasts that would signal an important difference between males and females (for example) in the comparisons between a combination and its components. For this reason, I used bar charts of the descriptive means of subgroups, arranged to depict these comparisons visually. These bar charts suggest in general that each combination has a fairly similar relationship to its components for males and females (Figure 5), Caucasians and Asians (Figure 6), Hispanic/Latinos and non-Hispanic/Latinos (Figure 7), subjects in the US and subjects outside the US (Figure 8), and subjects with baseline HbA1c ≤ 8.5 and subjects with baseline HbA1c > 8.5 (Figure 9). Study 302 did not have enough subjects in the 65 years and older age group for an assessment of the age subgroup.

I believe that the other clinical studies that involved alogliptin added to a metformin background (Study 004 and Study 008) provide a clearer interpretation of the effect of subgroups on the

HbA1c endpoint. The statistical review of these studies did not identify interactions with gender, age, race, geographic region, baseline HbA1c or baseline BMI⁴.

4.1 Sex, Race, Age and Geographic Region

Figure 5 Study 302; HbA1c change from baseline at week 26; descriptive means by gender (FAS/LOCF)



⁴ For a statistical review of Study 008, see the review of NDA 022271/0 submission dated 12/21/2007, statistical review dated 9/2/2008. For a statistical review of Study 004, see the review of NDA 022426/0 submission dated 7/23/11, statistical review dated 11/18/2011.

Figure 6 Study 302; HbA1c change from baseline at week 26; descriptive means by race (FAS/LOCF)

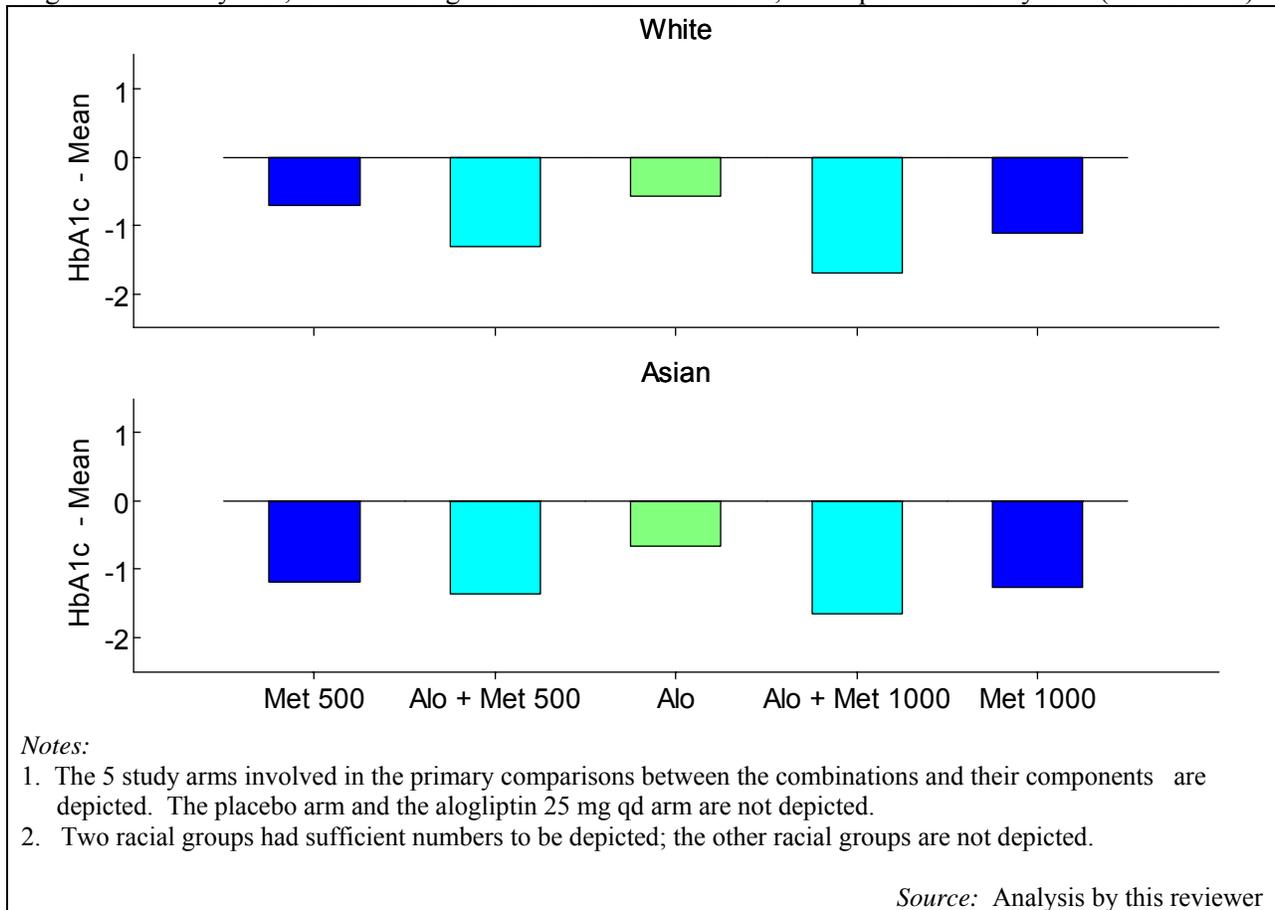


Figure 7 Study 302; HbA1c change from baseline at week 26; descriptive means by ethnicity (FAS/LOCF)

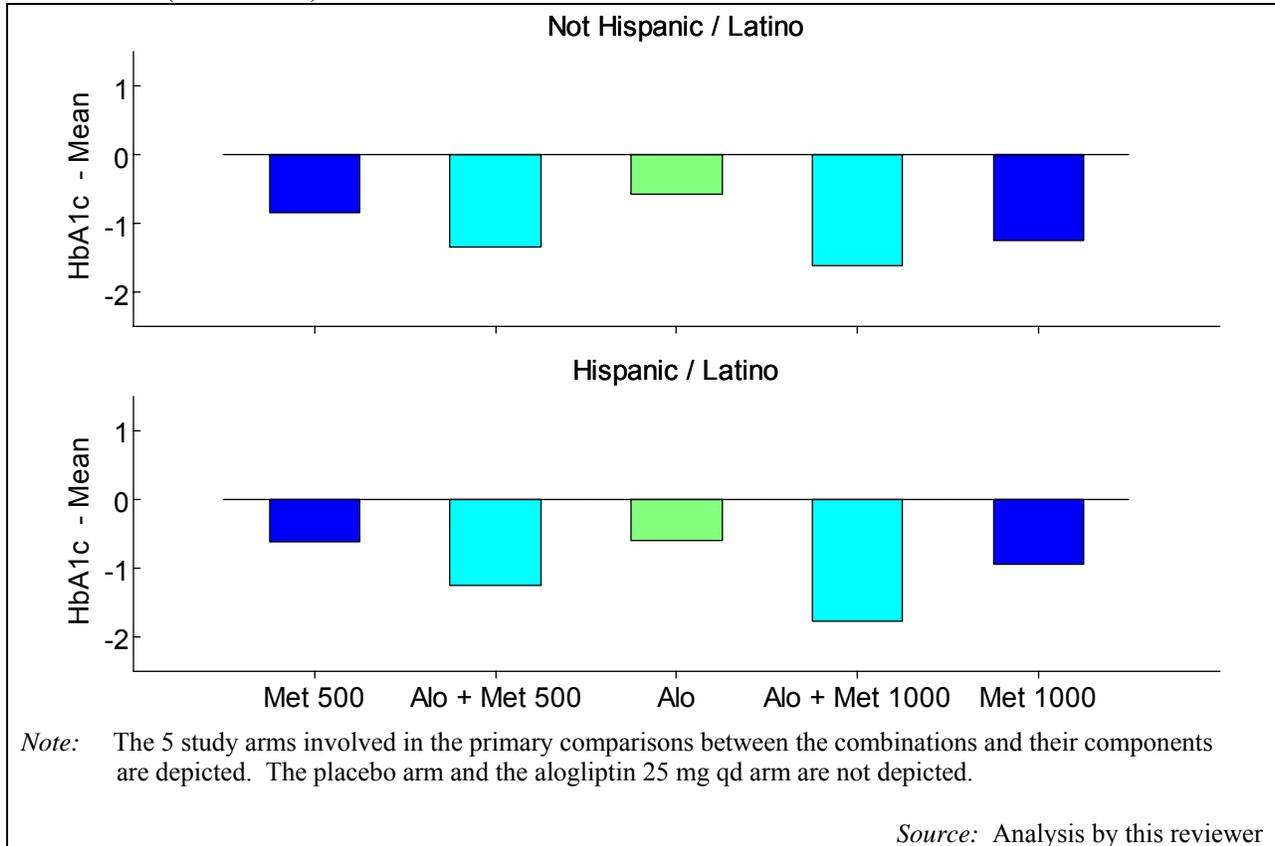
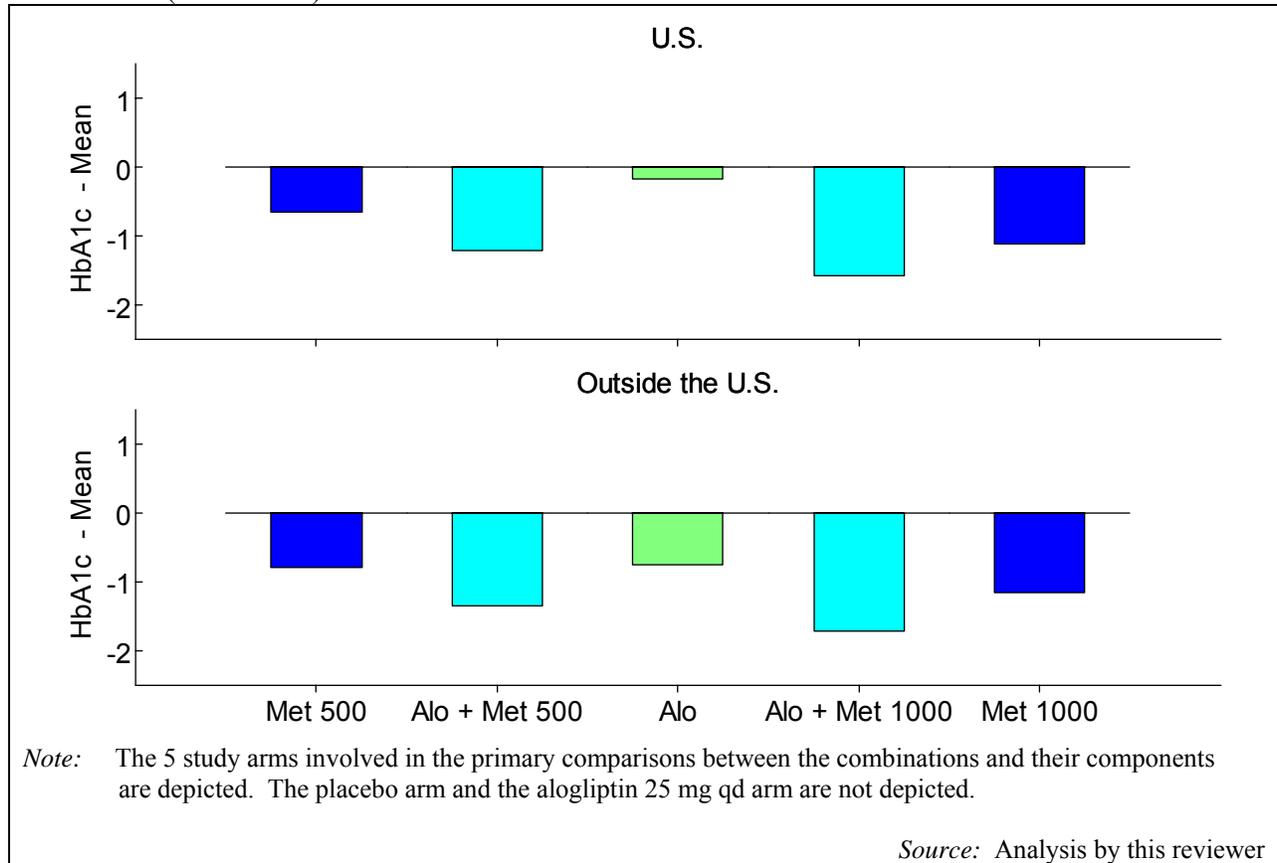
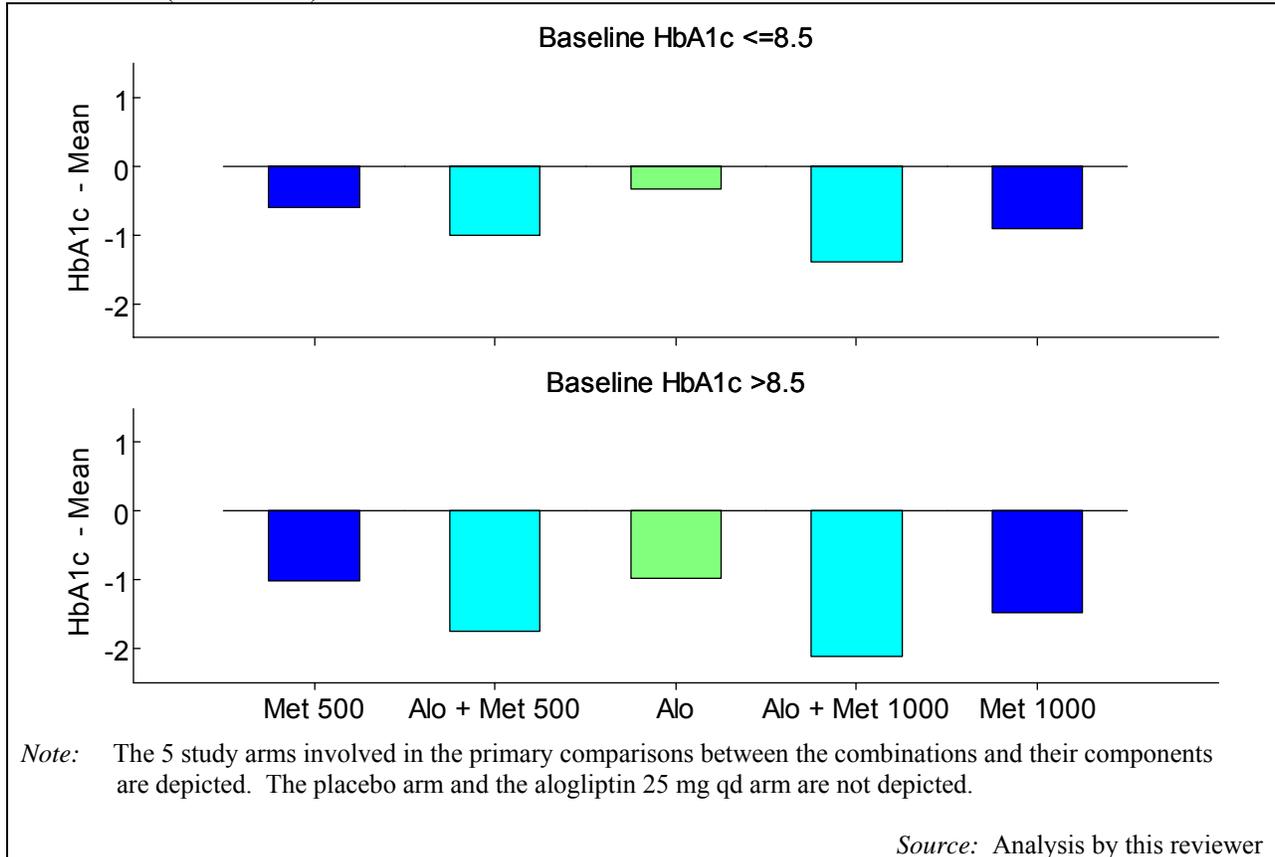


Figure 8 Study 302; HbA1c change from baseline at week 26; descriptive means by geographic region (FAS/LOCF)



4.2 Other Special/Subgroup Populations

Figure 9 Study 302; HbA1c change from baseline at week 26; descriptive means by baseline HbA1c (FAS/LOCF)



5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

An issue that arose during the review of Study 302 was the identification (by the applicant) of 13 subjects who enrolled at two or more sites under separate ID numbers, and eight subjects who enrolled in both Study 302 and Study SYR-322_305 concurrently. The applicant evaluated each set of multiple enrollments, and determined the status of the data from each ID with respect to the analyses databases of Study 302. Dr. Pratt reviewed this information and concurred with the applicant's determinations. As a sensitivity analysis, I analyzed the primary HbA1c endpoint after excluding all of the data from the seven study sites that had multiple enrollments. The results were not substantially different from the primary results obtained with these sites included.

The collective evidence for the efficacy and safety of the combination product, for use in patients with Type 2 diabetes who are inadequately controlled with diet and exercise, is obtained from the combination Study 302. Additional evidence for efficacy and safety of alogliptin co-administered with metformin comes from Study 008, which evaluated alogliptin as an add-on to metformin, and from Study 004, which evaluated alogliptin as an add-on to metformin and pioglitazone in a non-inferiority comparison to an up-titration of pioglitazone.

The evidence that supports the extension of conclusions about efficacy and safety of clinical studies of the 25 mg qd dosing schedule to the 12.5 mg bid dosing schedule that is used in the combination product comes from the comparison between the two dosing schedules in the two monotherapy arms of Study 302.

5.2 Conclusions

Results from the combination Study 302 support the superior efficacy of alogliptin co-administered with metformin compared to either alogliptin alone or metformin alone, at two dosage strengths: (1) alogliptin 12.5 mg + metformin 500 mg bid; and (2) alogliptin 12.5 mg + metformin 1000 mg bid. Patients had type 2 diabetes that was inadequately controlled with diet and exercise alone. The effect of alogliptin in the combinations was fairly similar to the effect of alogliptin as monotherapy. The effect of metformin appeared to be reasonably related to its dose. The placebo-adjusted effects of each combination were fairly similar to the additive combination of the placebo-adjusted effects of each component in the combination.

Results from Study 302 also supported the conclusion that the alogliptin 25 mg total daily dose produced a fairly similar HbA1c response at week 26 when delivered as a 25 mg qd dose and as a 12.5 mg bid dose. This result supports the development of the FDC product, which is delivered as a bid dose because of the metformin dosing schedule.

5.3 Recommendations for Labeling

Recommendations for Part 14 of the alogliptin / metformin FDC label are summarized in Table 15. The tradename KAZANO is used in the proposed label summary.

Table 15 Recommendations for Part 14 of the alogliptin / metformin FDC label

Proposed Label Summary (Version dated 3/18/12)	Statistical Review Comments
<p>14 CLINICAL STUDIES</p> <p>The co-administration of alogliptin and metformin has been studied in patients with type 2 diabetes inadequately controlled on either diet and exercise alone, on metformin alone or metformin in combination with a thiazolidinedione.</p> <p>There have been no clinical efficacy studies conducted with KAZANO; however bioequivalence of KAZANO with co-administered alogliptin and metformin tablets was demonstrated, and efficacy of the combination of alogliptin and metformin has been demonstrated in three Phase 3 efficacy studies.</p> <p>A total of (b) (4) patients with type 2 diabetes were randomized in (b) (4) double-blind, placebo- or active-controlled clinical safety and efficacy studies conducted to evaluate the effects of KAZANO on glycemic control. The racial distribution of patients exposed to study medication was (b) (4) White, (b) (4) Asian, (b) (4) Black, and (b) (4) other racial groups. The ethnic distribution was (b) (4) Hispanic. Patients had an overall mean age of approximately (b) (4) years (range (b) (4) to 80 years). In patients with type 2 diabetes, treatment with KAZANO produced clinically meaningful and statistically significant improvements in A1C versus comparator.</p> <p style="text-align: center;">Alogliptin and Metformin Co-administration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise</p> <p>In a 26-week, double-blind, active-controlled study, a total of 784 patients inadequately controlled on diet and exercise alone (mean baseline A1C=8.4%) were randomized to 1 of 7 treatment groups: placebo; metformin HCl 500 mg or metformin HCl 1000 mg twice daily, alogliptin 12.5 mg twice daily, or alogliptin 25 mg daily; alogliptin 12.5 mg in combination with metformin HCl 500 mg or metformin HCl 1000 mg twice daily. Both co-administration treatment arms (alogliptin 12.5 mg + metformin HCl 500 mg and alogliptin 12.5 mg + metformin HCl 1000 mg) resulted in significant improvements in A1C (Figure 3) and FPG when compared with their respective individual alogliptin and metformin component regimens (b) (4). Co-administration treatment arms demonstrated improvements in 2-hour postprandial glucose (PPG) compared to alogliptin alone or metformin alone (b) (4).</p>	<p>This is a summary of Study 302 which was reviewed in this review.</p> <p>Re-express the results for the percentages of patients requiring hyperglycemic rescue (b) (4)</p>

Proposed Label Summary (Version dated 3/18/12)	Statistical Review Comments
<p>(b) (4)</p>	<p>(b) (4)</p>
<p>Improvements in A1C were not affected by gender, age, race, (b) (4) or baseline BMI. (b) (4)</p>	<p>I recommend (b) (4)</p> <p>See Part 4 of this review.</p>
<p>(b) (4) Lipid effects were neutral.</p>	<p>(b) (4)</p>

Proposed Label Summary (Version dated 3/18/12)

Statistical Review Comments

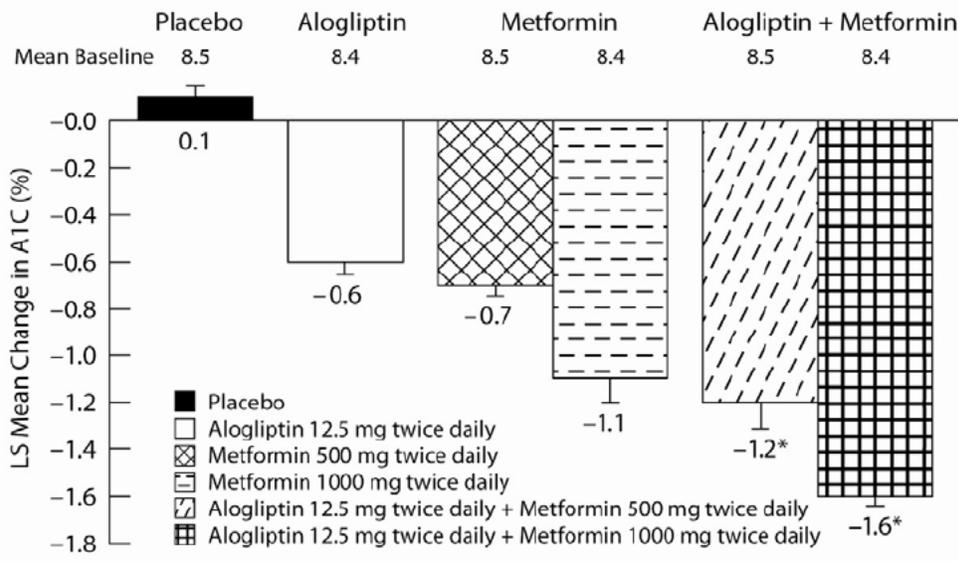
(b) (4)

Statistical review comments:

For each endpoint in Table 7, add three rows: (1) Difference from metformin 500 mg twice daily (adjusted mean with 95% CI); (2) Difference from metformin 1000 mg twice daily (adjusted mean with 95% CI) and (3) Difference from alogliptin (adjusted mean with 95% CI). Include the study results for the two combinations in the appropriate cells of the table. Use a symbol to denote $p < 0.05$ and reference with a footnote “ $p < 0.05$ when compared to corresponding doses of metformin and alogliptin alone.”

(b) (4)

Proposed Label Summary (Version dated 3/18/12) **Statistical Review Comments**



Intent-to-treat population using last observation on study prior to discontinuation of double-blind study medication or sulfonylurea rescue therapy for patients needing rescue.
 *P<0.001 when compared to metformin and alogliptin alone.

Figure 3: Change From Baseline A1C at Week 26 with Alogliptin and Metformin Alone and Alogliptin in Combination with Metformin

Statistical review comment for Figure 3:

Modify the footnote reference to the symbol * (b) (4)

Alogliptin and Metformin Co-administration in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone

In a 26-week double-blind, placebo-controlled study, a total of 527 patients already on metformin (mean baseline A1C=8%) were randomized to receive alogliptin 12.5 mg, alogliptin 25 mg, or placebo once daily. Patients were maintained on a stable dose of metformin HCl (b) (4) during the treatment period. Alogliptin 25 mg in combination with metformin resulted in statistically significant improvements from baseline in A1C and FPG at Week 26, when compared to placebo (b) (4)

This is a summary of Study 008 which was reviewed under NDA 022271/0 (Alogliptin; NESINA™)

The description of Study 008 also occurs in Part 14 of the NESINA™ label and is currently in development for that label.

The revised description should be applied to the description in this label also.

Proposed Label Summary (Version dated 3/18/12)	Statistical Review Comments
<p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(w) (4)</p> <p>Lipid effects were also neutral.</p>	<p>(b) (4)</p>
<p>(b) (4)</p>	<p>(b) (4)</p>
<p>Alogliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin in Combination with Pioglitazone</p> <p>In a 52-week, active-comparator study, a total of 803 patients inadequately controlled (mean baseline A1C=8.2%) on a current regimen of pioglitazone 30 mg and metformin</p>	<p>This is a summary of Study OPI-004 which was reviewed under NDA 022426 (alogliptin + pioglitazone; OSENI™).</p> <p>The description of Study OPI-004 also occurs in Part 14 of the NESINA label and in Part 14 of</p>

Proposed Label Summary (Version dated 3/18/12)	Statistical Review Comments
<p>were randomized to either receive the addition of once daily alogliptin 25 mg or the titration of pioglitazone 30 mg to 45 mg following a 4-week single-blind, placebo run-in period. Patients were maintained on a stable dose of metformin HCl (b) (4)</p>	<p>the OSENI label. This description is currently in development for those labels. The revised description should be applied to the description in this label also.</p>
<p>In combination with pioglitazone and metformin, alogliptin 25 mg was shown to be statistically superior in lowering A1C and FPG compared with the titration of pioglitazone from 30 to 45 mg at Week 52 (b) (4)</p> <p>[Redacted]</p>	
<p>Improvements in A1C were not affected by gender, age, race, (b) (4) or baseline BMI. (b) (4)</p> <p>[Redacted]</p> <p>(b) (4) Lipid effects were neutral.</p>	

Proposed Label Summary (Version dated 3/18/12)	Statistical Review Comments
(b) (4)	

Appendix A: Study 302; Subjects with multiple enrollments

In the clinical report for Study 302, the applicant identified 13 subjects who enrolled at two or more sites (Table 16), and eight subjects who enrolled both in Study 302 and in ongoing Study SYR-322_305 (Table 17). One subject enrolled at two sites in Study 302 and at one site in Study 305 (“Set 4” in both tables). The applicant evaluated each set of multiple enrollments, and made a determination with regard to the status of data from each involved subject. The Division concurred with the applicant’s determinations.

Table 16 Subjects with multiple IDs at different sites within Study MET 302 (Each set represents one subject)

	Subject ID	Site number, Location	Randomized?	Last visit date, No. days on study	Status at the final visit	Applicant’s decision regarding database
Set 1						
A	5078007	Site 5078, Opa Locka FL	Randomized 6/1/10 to Metformin 500 mg	Last visit 12/15/10, 184 days on study	Completed	Excluded from the FAS, the PPS and the safety set.
B	5149014	Site 5149, Hialeah, FL	Randomized 3/18/10 to Metformin 500 mg	Last visit 10/6/10, 191 days on study	Completed	Excluded from the FAS, the PPS and the safety set.
Set 2						
A	5078010	Site 5078, Opa Locka FL	Randomized 6/28/10 to Alogliptin 12.5 mg + Metformin 500 mg	Last visit 1/12/11, 184 days on study	Completed	Excluded from the FAS, the PPS and the safety set.
B	5301038	Site 5301, Boca Raton FL	Screen failure on 11/12/10		Screen failure	Would not be in the databases.
C	5149024	Site 5149, Hialeah, FL	Randomized 6/4/10 to Metformin 500 mg	Last visit 1/11/11, 207 days on study	Completed	Excluded from the FAS, the PPS and the safety set.
Set 3						
A	5149037	Site 5149, Hialeah, FL	Randomized 7/26/10 to Metformin 500 mg	Last visit 1/25/11, 184 days on study	Completed	Excluded from the FAS, the PPS and the safety set.
B	5301024	Site 5301, Boca Raton FL	Run-in failure on 11/10/10		Run-in failure	Would not be in the databases.
Set 4						
A	5301004	Site 5301, Boca Raton, FL	Randomized 10/21/10 to Aloglitpin 12.5 mg	Last visit 10/26/10, 5 days on study	Voluntary withdrawal (not rescued)	Excluded from the FAS, the PPS and the safety set.
B	5149029	Site 5149, Hialeah, FL	Randomized 7/26/10 to Placebo	Last visit 10/18/10, 85 days on study	Voluntary withdrawal (not rescued)	Excluded from the FAS, the PPS and the safety set.

	Subject ID	Site number, Location	Randomized?	Last visit date, No. days on study	Status at the final visit	Applicant's decision regarding database
Set 5						
A	5078019	Site 5078, Opa Locka FL	Randomized 8/27/10 to Placebo	Last visit 4/1/11, 187 days on study.	Completed	Excluded from the FAS, the PPS and the safety set.
B	5301020	Site 5301, Boca Raton, FL	Run-in failure 11/8/10		Run-in failure	Would not be in the databases.
Set 6						
A	5301019	Site 5301, Boca Raton, FL	Screen failure 9/12/10		Screen failure	Would not be in the databases.
B	5078020	Site 5078 Opa Locka FL	Randomized 8/27/10 to Metformin 500 mg	Last visit 4/5/10, 203 days on study	Completed	Included in the FAS and the safety set; excluded from the PPS set.
Set 7						
A	5078021	Site 5078, Opa Locka FL	Screen failure 7/23/10		Screen failure	Would not be in the databases.
B	5301032	Site 5301, Boca Raton, FL	Randomized 10/28/10 to Alogliptin 12.5 mg + Metformin 1000 mg	Last visit 5/1/11, 190 days on study	Completed	Included in the FAS and the safety set; excluded from the PPS set.
Set 8						
A	5149032	Site 5149, Hialeah, FL	Run-in failure 8/4/10		Run-in failure	Would not be in the databases.
B	5078033	Site 5078, Opa Locka FL	Randomized 12/6/10 to Alogliptin 12.5 mg + Metformin 500 mg	Last visit 6/20/11, 180 days on study	Completed	Included in the FAS and the safety set; excluded from the PPS set.
Set 9						
A	5078003	Site 5078, Opa Locka FL	Screen failure 4/16/10		Screen failure	Would not be in the databases.
B	5149013	Site 5149, Hialeah FL	Run-in failure 4/7/10		Run-in failure	Would not be in the databases.
Set 10						
A	5114012	Site 5114, Salt Lake City, UT	Screen failure 9/23/10		Screen failure	Would not be in the databases.

	Subject ID	Site number, Location	Randomized?	Last visit date, No. days on study	Status at the final visit	Applicant's decision regarding database
B	5275007	Site 5275, Salt Lake City, UT	Run-in failure	12/23/10	Run-in failure	Would not be in the databases.
Set 11						
A	5078035	Site 5078, Opa Locka FL	Run-in failure	12/22/10	Run-in failure	Would not be in the databases.
B	5301048	Site 5301, Boca Raton, FL	Run-in failure	12/22/10	Run-in failure	Would not be in the databases.
Set 12						
A	5149046	Site 5149, Hialeah, FL	Screen failure	9/30/10	Screen failure	Would not be in the databases.
B	5301010	Site 5301, Boca Raton, FL	Run-in failure	10/19/10	Run-in failure	Would not be in the databases.
Set 13						
A	5078014	Site 5078 Opa Locka FL	Screen failure	7/21/10	Screen failure	Would not be in the databases.
B	5301008	Site 5301 Boca Raton FL	Randomized	11/1/10 to Metformin 500 mg	Last visit 5/18/11, 187 days on study	Completed Included in the FAS and the safety set; excluded from the PPS set.
<i>Sources:</i> Study 302 clinical report, Appendix 16.2.4.5, Table 1, and additional analysis by this reviewer (using the applicant's databases D DEMOG and D Master)						

Table 17 Subjects with multiple IDs with participation in both Study MET_302 and Study SYR-322_305 (Each set represents one subject)

	Subject ID	Site number, Location ¹	Randomized?	Last visit date, No. days on study	Study 305 subject: status at the final visit	Applicant's decision regarding database
Set 1						
Study 302	5105005	Site 5105, Cutler Bay, FL	Randomized 10/21/10 to Alogliptin 12.5 mg + Metformin 500 mg	Last visit 5/19/11, 202 days on study	Completed	Excluded from the FAS, the PPS and the safety set.
Study 305	5078009	Site 5078	Randomized 1/18/2010,	Ongoing ²		
Set 2						
Study 302	5121009	Site 5121, Houston TX	Randomized 8/10/10 to Alogliptin 12.5 mg + Metformin 1000 mg	Last visit 2/22/11, 197 days on study	Completed	Included in the FAS and the safety set; excluded from the PPS set.
Study 305	5118008	Site 5118	Randomized 12/3/09, completed 6/6/10			
Set 3						
Study 302	5149004	Site 5149, Hialeah FL	Randomized 3/9/10 to Alogliptin 12.5 mg	Last visit 7/8/10, 122 days on study	Rescued, withdrawn, lack of efficacy	Excluded from the FAS, the PPS and the safety set.
Study 305	5007045	Site 5007	Randomized 7/16/10	Completed 9/9/10		
Set 4³						
Study 302	5149029	Site 5149, Hialeah FL	Randomized 7/26/10 to Placebo	Last visit 10/18/10, 85 days on study	Voluntary withdrawal, was not rescued	Excluded from the FAS, the PPS and the safety set.
Study 302	5301004	Site 5301, Boca Raton FL	Randomized 10/21/10 to Alogliptin 12.5 mg	Last visit 10/26/10, 6 days on study	Voluntary withdrawal, was not rescued	Excluded from the FAS, the PPS and the safety set.
Study	5007071	Site 5007	Randomized 9/30/10	Completed 2/3/11		

	Subject ID	Site number, Location ¹	Randomized?	Last visit date, No. days on study	Study 305 subject: status at the final visit	Applicant’s decision regarding database
	305					
	Set 5					
Study 302	5301015	Site 5301, Boca Raton FL	Randomized 10/28/10 to Metformin 500 mg	Last visit 5/10/11, 195 days on study	Completed	Excluded from the FAS, the PPS and the safety set.
Study 305	5007076	Site 5007	Randomized 9/30/10	Completed 3/21/11		
Study 305	5078026	Site 5078	Randomized 9/30/10	Completed 3/21/11		
	Set 6					
Study 302	5301017	Site 5301, Boca Raton FL	Randomized 10/28/10 to Placebo	Last visit 5/13/11, 198 days on study	Completed	Excluded from the FAS, the PPS and the safety set.
Study 305	5078033		Randomized 5/10/10	Ongoing		
	Set 7					
Study 302	5301041	Site 5301, Boca Raton FL	Randomized 12/1/10 to Alogliptin 12.5 mg + Metformin 500 mg	Last visit 1/26/11, 57 days on study	Lost to follow-up, was not rescued	Excluded from the FAS, the PPS and the safety set.
Study 305	5007060	Site 5007	Randomized 8/17/10	Ongoing		
	Set 8					
Study 302	5301050	Site 5301, Boca Raton FL	Randomized 12/9/10 to Alogliptin 12.5 mg	Last visit 6/20/11, 194 days on study	Completed	Excluded from the FAS, the PPS and the safety set.
Study 305	5007077	Site 5007	Randomized 10/1/10	Ongoing		
Notes:						
¹ The location of sites for Study 305 was not available at the time of submission of NDA 203414/0.						
² Subjects in Study 305 who are listed as “ongoing” with reference to July 25, 2011, the date when Appendix 16.2.4.5 was finalized.						
³ The subject in “Set 4” of this table is also represented as “Set 4” in the previous table because of this subject’s enrollment in two study sites in Study 302.						
<i>Sources:</i> Study 302 clinical report, Appendix 16.2.4.5, Table 2, and additional analysis by this reviewer (using the applicant’s databases D_DEMOG and D_Master)						

Appendix B: Study 302; Primary efficacy evaluation, additional results

Table 18 Study 302; Primary efficacy endpoint (HbA1c change from baseline at week 26); primary efficacy evaluation and related evaluations (Model 1a: FAS with LOCF and no post-rescue data)

	Placebo	A25 qd	A12.5 bid	M500 bid	M1000 bid	A12.5 + M500 bid	A12.5 + M1000 bid
Number of cases randomized							
Applicant	109	112	113	114	111	111	114
My analysis ¹	109	112	113	114	111	111	114
Number of cases with HbA1c at baseline, FAS							
Applicant	102	104	104	103	108	102	111
My analysis	106	112	109	109	111	104	113
Number of cases with HbA1c at week 26, FAS/LOCF							
Applicant	102	104	104	103	108	102	111
My analysis	92	101	94	101	102	100	105
Mean HbA1c at baseline (standard deviation)							
Applicant	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)
My analysis	8.5 (0.7)	8.4 (0.9)	8.4 (0.7)	8.5 (0.8)	8.4 (0.7)	8.5 (0.8)	8.4 (0.7)
Week 26 Change from baseline (FAS/LOCF), LS Mean ± SEM							
Applicant	0.2 ± 0.1	-0.5 ± 0.1	-0.6 ± 0.1	-0.7 ± 0.1	-1.1 ± 0.1	-1.2 ± 0.1	-1.6 ± 0.1
My analysis	0.0 ± 0.1	-0.6 ± 0.1	-0.6 ± 0.1	-0.7 ± 0.1	-1.2 ± 0.1	-1.3 ± 0.1	-1.7 ± 0.1
1. Coadministration regimens vs. components							
Applicant							
A. A12.5+M500 bid vs. components							
LS Mean difference			-0.7	-0.6			
(97.5% CI)			(-1.0, -0.4)	(-0.7, -0.3)			
p-value			< 0.001	< 0.001			
My analysis							
LS Mean difference			-0.7	-0.6			
(97.5% CI)			(-1.0, -0.4)	(-0.9, -0.2)			
p-value			p<0.001	p<0.001			
Applicant							
B. A12.5 + M1000 bid vs. components							
(97.5% CI)			-1.0		-0.4		
p-value			(-1.3, -0.7)		(-0.7, -0.2)		
			< 0.001		< 0.001		
My analysis							
LS Mean difference			-1.1		-0.5		
(97.5% CI)			(-1.4, -0.7)		(-0.8, -0.2)		
p-value			p<0.001		p<0.001		
2. Alogliptin bid vs. qd regimens							
Applicant							
A. A12.5 bid vs A25 qd							

	Placebo	A25 qd	A12.5 bid	M500 bid	M1000 bid	A12.5 + M500 bid	A12.5 + M1000 bid
LSMean difference			0.0				
95% CI			(-0.3, 0.2)				
p-value			0.759				
My analysis							
LSMean difference			0.0				
95% CI			(-0.3, 0.3)				
p-value			p=0.886				
B. A12.5 bid vs. placebo							
LS Mean difference				-0.6			
95% CI				(-0.9, -0.3)			
p-value				p<0.001			
C. A 25 qd vs. placebo							
LS Mean difference			-0.6				
95% CI			(-0.9, -0.3)				
p-value			p<0.001				
3. Coadministration regimens vs. placebo							
Applicant							
A. Comparison of A12.5 + M500 bid vs. placebo							
LS Mean difference						-1.4	
95% CI						(-1.6, -1.1)	
p-value						< 0.001	
My analysis							
LS Mean difference						-1.3	
95% CI						(-1.6, -1.0)	
p-value						p<0.001	
Applicant							
B. Comparison of A12.5 + M1000 bid vs. placebo							
LS Mean difference							-1.7
95% CI							(-2.0, -1.5)
p-value							< 0.001
My analysis							
LS Mean difference							-1.7
95% CI							(-2.0, -1.4)
p-value							p<0.001
4. Components compared to placebo (my analysis)							
A. A12.5 bid vs. placebo							
LS Mean difference			-0.6				
95% CI			(-0.9, -0.3)				
p-value			< 0.001				
B. A 25 qd vs. placebo							
LS Mean difference			-0.6				
95% CI			(-0.9, -0.3)				
p-value			< 0.001				
C. M500 vs. placebo							

	Placebo	A25 qd	A12.5 bid	M500 bid	M1000 bid	A12.5 + M500 bid	A12.5 + M1000 bid
LS Mean difference					-0.7		
95% CI					(-1.0, -0.4)		
p-value					< 0.001		
D. M1000 vs. placebo							
LS Mean difference						-1.2	
95% CI						(-1.5, -0.9)	
p-value						< 0.001	
<i>Notes:</i>							
¹ I used the applicant's database D_Efflab, subsetted for HbA1c, FAS database, and Visit. Baseline is Visit 5, and Week 26/End of Treatment is Visit 13							
<i>Sources:</i> Study 302 clinical report, Table 11.h, Table 11.i, and additional analysis by this reviewer.							

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/s/

JANICE A DERR
07/17/2012

JON T SAHLROOT
07/17/2012
concur

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Today's date: 1/4/12

NDA Number: 203414/0

Applicant: Takeda

Stamp Date: 11/22/11

Drug Name: Alogliptin +
Metformin FDC

NDA/BLA Type: standard review

PDUFA goal date: 9/22/12

Filing Meeting: 1/10/12

The purpose of this NDA submission is to provide information in support of alogliptin + metformin fixed dose combination. There is only one Phase 3 study that has not received a statistical review. This is Study MET-301. The other two Phase 3 studies were reviewed, Study 322-008 in the original NDA 022271/0 submission and Study OPI-004 in the submission that was a response to the Division's Complete Response to the original submission. The filing review focuses on Study MET-301.

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Study MET-301
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓ note 1
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	✓
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓

Note 1: No ISE data files were included. The Division agreed with Takeda that this would be okay.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Requests for 74-day letter: No requests

Content Parameter (possible review concerns for 74-day letter)	Study MET-301
Designs utilized are appropriate for the indications requested.	✓
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	N/A
Appropriate references for novel statistical methodology (if present) are included.	N/A
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Summary of the design of Study 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.”

Inclusion criteria: previously treated with diet and exercise; HbA1c between 7.5% and 10.0%

7 treatment groups, randomized 1:1:1:1:1:1:1

- Placebo, n=109
- Metformin 500 mg bid, n=114
- Metformin 1000 mg bid, n=111
- Alogliptin 12.5 mg bid, n=113
- Alogliptin 25 mg qd, n=112
- Alogliptin 12.5 mg bid + metformin 500 mg bid, n=111
- Alogliptin 12.5 mg bid + metformin 1000 mg bid, n=114

Figure 2.a Schematic of Study Design for Study MET-302

	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

Primary endpoint was assessed at week 26 (HbA1c change from baseline)

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/s/

JANICE A DERR
01/04/2012

JON T SAHLROOT
01/04/2012