CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022271Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

NDA /Serial Number:	NDA 022271 (IND 069707)
Drug Name:	Alogliptin tablets
Indication(s):	Type 2 diabetes
Applicant	Takeda
Date(s):	Pediatric Study Protocol Synopsis
	Statistics review: September 21, 2012
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Janice Derr, Ph.D.
Concurring Reviewers:	J. Todd Sahlroot, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Valerie Pratt, M.D., Clinical Reviewer
	Karim Calis, M.D., Medical Team Leader
Project Manager:	Richard Whitehead

Background: A synopsis of Study 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" is included in the IND for alogliptin. The sponsor plans to submit the protocol on November 30, 2013 and to complete the study by January 31, 2019. As part of the complete response to the applicant's July 2011 submission to the alogliptin NDA, dated April 25, 2012, the Division included questions about the proposed design of Study 309. Takeda responded to these questions in a letter dated June 26, 2012. A brief description of the design of Study 309 is included as the end of this memo.

This memo includes statistical recommendations that are based on the study synopsis. I note that the synopsis included only a brief description of the applicant's plan for the analysis of the primary endpoint, and no description of the primary analysis data set. These statistical recommendations may be transmitted to the applicant.

Statistical review comments that may be transmitted to the applicant:

We have the following preliminary statistical review comments, based on the synopsis of Study SYR-322_309:

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[redacted]

(3) Data standards: CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for

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sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

Description of Study SYR-322_309 (this description is for review purposes only and should not be transmitted to the sponsor).

Study 309 is designed to evaluate the efficacy and safety of alogliptin [redacted] (b) (4) Study 309 will enroll pediatric subjects 10 to 17 years of age, inclusive, with T2DM evaluating the efficacy and safety of alogliptin [redacted] (b) (4) (b) (4)

[redacted] (b) (4)

The primary analysis will be conducted (b) (4)

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/s/

JANICE A DERR
09/20/2012

JON T SAHLROOT
09/20/2012

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-271, 22-426
Drug Name:	Nesina (alogliptin), alogliptin + pioglitazone
Indication(s):	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)
Applicant:	Takeda Global Research & Development Center, Inc.
Date(s):	Letter Date: 7/25/11 PDUFA Goal Date: 1/25/12
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Eugenio Andraca-Carrera, Ph.D.
Concurring Reviewers:	Mat Soukup, Ph.D. Aloka Chakravarty, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
Clinical Team:	Medical Officer: Valerie Pratt, M.D. Medical Team Leader: Hylton Joffe, M.D.
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Keywords: type 2 diabetes mellitus, cardiovascular safety, stratified Cox model

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1 Executive Summary

The proposed indication of alogliptin is the treatment of type 2 diabetes mellitus (T2DM). The proposed therapeutic dosage is 25 mg, administered orally once a day. Per the request of the Division of Metabolism and Endocrinology Products this statistical review evaluates the cardiovascular (CV) safety of alogliptin in 12 Phase 2 and Phase 3 randomized clinical trials (Trials OPI-001, OPI-002, OPI-004, 003, INS-011, MET-008, PLC-010, SULF-007, TZD-009, 301, 303 and 402). This review focuses on the pre-marketing evaluation of cardiovascular safety only. A separate statistical review addressing efficacy is being conducted by Dr. Janice Derr.

1.1 Conclusions and Recommendations

The Sponsor assessed the CV safety of alogliptin through a dedicated CV trial alone, and through a pooled, stratified, analysis of 12 randomized, controlled Phase 2 and Phase 3 trials, including the dedicated CV trial, based on a Statistical Analysis Plan (SAP) agreed upon by the FDA on February 23rd, 2010. The Sponsor and the FDA agreed that the CV safety of alogliptin be reviewed in the dedicated CV trial alone, and in all controlled phase 2-3 trials combined, including the dedicated CV trial. Special consideration is given to corroboration of results from both sets of analyses.

The agreed upon population of interest consisted of all subjects randomized in the 12 trials. The primary safety endpoint was major adverse cardiovascular events (MACE), a composite endpoint of cardiovascular death, myocardial infarction (MI) and non-fatal stroke. Events were adjudicated by an independent Cardiovascular Endpoints Committee (CEC) in accordance to FDA Guidance. The comparator group was comprised of all non-alogliptin comparator groups and included metformin, glipizide, sulfonylurea products, insulin, pioglitazone, and placebo.

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The criteria for adequate cardiovascular safety of new antidiabetic products set forth in the FDA Diabetes Guidance (2008)[1] reads:

> *For completed studies, before submission of the new drug application (NDA)/biologics license application (BLA):*
>
> - *Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8.*

The upper-bound of the 95% confidence interval of the hazard ratio of MACE of alogliptin vs. all comparators meets the 1.8 non-inferiority hazard ratio margin. It is therefore our recommendation that alogliptin be considered safe with respect to the risk of major cardiovascular events for the purpose of approval for the treatment of T2DM, within the statistical bounds recommended in the aforementioned Diabetes Guidance.

1.2 Brief Overview of Clinical Studies

In this NDA application, Takeda submitted data for 12 randomized Phase 2 and Phase 3 trials. All trials were conducted in subjects with type 2 diabetes mellitus. Ten of these trials (OPI-001, OPI-002, OPI-004, 003, INS-011, MET-008, PLC-010, SULF-007, TZD-009 and 303) were designed to either determine the benefit of treatment containing alogliptin on glycemic control,

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or to determine the change of glycosylated hemoglobin (HbA1c) from baseline associated with alogliptin. Study 301 was designed to evaluate the effect of alogliptin alone and alogliptin plus pioglitazone versus placebo on postprandial triglycerides. Study 402 is an ongoing trial designed to assess cardiovascular safety of alogliptin vs. placebo, in addition to standard care. A detailed discussion of the design of these trials is provided in Section 3.1.1.

1.3 Statistical Issues and Findings

The primary agreed upon safety endpoint of interest is Major Adverse Cardiovascular Events (MACE), and is comprised of CV death, nonfatal myocardial infarction, and nonfatal stroke.

In the SAP agreed upon by the FDA on February 23rd, 2010, it was determined that the CV safety of alogliptin be evaluated in two analyses: a pooled analysis of 12 Phase 2 and Phase 3 clinical trials for alogliptin, including the dedicated cardiovascular trial Study 402; and in Study 402 alone.

The pooled analysis of 12 Phase 2 and Phase 3 clinical trials, including the dedicated cardiovascular trial Study 402, evaluated the risk of MACE associated with alogliptin compared to all non-alogliptin comparator groups (including metformin, glipizide, other sulfonylurea products, insulin, pioglitazone, and placebo). In this review, the 'pooled analysis' refers to a Cox proportional hazards model stratified by study. Because the pooled analysis is stratified by study, it preserves subjects' randomization to different trials. Secondary analyses were fit to estimate the Mantel-Haenszel incidence rate ratio and the Mantel-Haenszel incidence rate difference. The incidence rate difference was the only method in this analysis to use information from trials with zero events. More details about the statistical methodology used in this review are provided in Section 3.1.3.

The dedicated CV safety trial, Study 402, follows a sequential design with an overall one-sided Type-I error rate of 0.025 to demonstrate the non-inferiority of the hazard ratio of MACE associated with the use of alogliptin vs. placebo with a hazard ratio margin of 1.8. The upper bound of the repeated confidence interval for the hazard ratio is calculated using an O'Brien-Fleming-type spending function designed to preserve an overall one-sided false-rejection rate of 2.5% for ruling out a HR greater than or equal to 1.8.

Table 1 shows results of the pooled analysis for the primary MACE endpoint. The results from the stratified Cox proportional hazards model, the Mantel-Haenszel incidence rate ratio and incidence rate difference are shown with their corresponding 95% confidence intervals. Table 2 shows results of the Cox proportional hazards model for the primary MACE endpoint and the secondary MACE+ endpoint in Study 402. A more complete discussion of the statistical methodology used in this review can be found in Section 3.1.3. A discussion of the results can be found in Section 3.1.6.

Secondary analyses assessed the hazard ratio of individual components of MACE associated with alogliptin. Sensitivity analyses were conducted on the effect of early events on the hazard ratio of MACE in Study 402. Additional subgroup analyses evaluated the hazard ratio of MACE

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associated with the use of alogliptin vs. all comparators in subgroups defined by baseline demographics and CV risk factors. Detailed results are provided in Section 3.1.6 and Section 4.

Table 1. Primary and Secondary Analyses of Pooled Phase 2 and Phase 3 Clinical Trials

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Table 2. Analysis of Primary MACE and Secondary MACE+ in Study 402

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2 Introduction

2.1 Product Description and Regulatory Background

Alogliptin is a highly selective dipeptidyl peptidase-IV (DPP-IV) inhibitor. The proposed indication of alogliptin is the treatment of type 2 diabetes mellitus (T2DM). The proposed dosage is 25 mg, orally, once a day.

Takeda submitted new drug application (NDA) 022271 on December 27, 2007 seeking FDA approval to market Nesina (alogliptin) Tablets for the treatment of type 2 diabetes mellitus. The NDA was amended several times between February 2008 and May 2009. On June 25, 2009, the FDA informed Takeda that the application could not be approved because Takeda did not provide evidence to show that use of alogliptin does not result in an unacceptable increase in cardiovascular (CV) risk, as recommended in the December 2008 Guidance to Industry, entitled *Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, found at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

In the Complete Response Letter to Takeda, the FDA noted that "Specifically, the upper bounds of the 95% confidence intervals for the risk ratios comparing the incidence of major adverse cardiovascular events (MACE) with alogliptin to the incidence of MACE with placebo exceeded the 1.8 criterion recommended to support approvability. To resolve this deficiency, you should conduct a cardiovascular safety trial that satisfies the 1.8 upper bound criterion incorporating appropriate design features as described in the abovementioned guidance."

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

On February 23rd, 2010, Takeda and the FDA held a face-to-face meeting. At the meeting both parties agreed on the Statistical Analysis Plan (SAP) of a dedicated CV safety trial. It was agreed by both parties that the CV safety of alogliptin be reviewed in the dedicated CV trial alone, and in all controlled phase 2-3 trials combined, including the dedicated CV trial.

This review addresses Takeda's resubmission of NDA 022271 on July 13, 2011.

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2.2 Clinical Trial Overview

Takeda conducted analyses to assess the cardiovascular safety of alogliptin by combining data from 12 randomized, controlled, clinical trials including 1 Phase 2, 8 Phase 3, and 3 Phase 3b trials. Table 3 summarizes the design, duration, and sample size of these trials. Eleven of these trials have been completed and their final database has been locked. The twelfth trial, Study 402, is an ongoing dedicated CV safety trial. The dataset provided in the NDA resubmission for Study 402 was locked on April 29, 2011. As agreed upon, Takeda conducted a stratified CV safety analysis of the 12 trials and an analysis of Study 402 alone.

The SAPs for the combined analysis of the 12 trials, and for the design and analysis of Study 402 alone were agreed upon by the FDA on February 23rd, 2010.

The combined, stratified analysis of the 12 clinical trials will be referred to as "the pooled analysis" in the remainder of this review. Note that the pooled analysis is stratified by study and therefore preserves the randomization to each of the 12 trials. A detailed discussion of the methodology used to combine these trials can be found in the Statistical Methodologies section of this review.

2.3 Data Sources

The applicant submitted electronic documents and datasets individually for 12 trials: OPI-001, OPI-002, OPI-004, 003, INS-011, MET-008, PLC-010, SULF-007, TZD-009, 301, 303 and 402. In addition, the applicant submitted pooled datasets for Demography Data (D_DEMOG), Major Adverse Cardiovascular Events (D_MACE) and Subject Summary (D_MASTER). Clinical study reports (CSRs) of each individual trial were reviewed to evaluate trial protocols.

The following file folder available within the CDER Electronic Document Room (EDR) was used in this review:

\\Cdsesub1\evsprod\NDA022271\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes

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Table 3: List of Trials Included in Pooled CV Analysis

Trial ID	Phase	Duration of Treatment	Total Sample Size	Alogliptin Dosage (mg) (N per arm)					Control (N)	Control	Co-treatment			
				6.25	12.5	25	50	100			Ins	Pio	Met	Sulf
OPI-001	3	26 weeks	1554	-	518	519	-	-	517	Pio, Placebo		X	X	
OPI-002	3	26 weeks	655	-	164	328	-	-	163	Pio		X		
OPI-004	3	52 weeks	803	-	-	404	-	-	399	Pio		X	X	
003	2	12 weeks	265	44	44	45	44	45	43	Met, Sulf, or both			X	X
INS-011	3	26 weeks	390	-	131	129	-	-	130	Ins	X		X	
MET-008	3	26 weeks	527	-	213	210	-	-	104	Met			X	
PLC-010	3	26 weeks	329	-	133	131	-	-	65	Placebo				
SULF-007	3	26 weeks	500	-	203	198	-	-	99	Sulf				X
TZD-009	3	26 weeks	493	-	197	199	-	-	97	Pio		X	X	X
301	3b	16 weeks	71	-	-	47	-	-	24	Placebo		X		
303	3b	52 weeks	441	-	-	222	-	-	219	Glipizide				
402	3b	Not fixed	2134	-	-	1058*	-	-	1076	Placebo	X		X	X

*Ins = insulin, Pio = pioglitazone, Met = metformin, Sulf = sulfonylurea
Source: Created by reviewer. Dataset: d_mace.xpt

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3 Statistical Evaluation

This review focuses on the pooled analysis of cardiovascular risk in the 12 trials, and the analysis of cardiovascular risk in Study 402 alone. For a complete statistical evaluation of efficacy results, please refer to the review authored by Dr. Janice Derr.

3.1 Evaluation of Safety

3.1.1 Trial Designs

Twelve trials are included in the pooled analysis: OPI-001, OPI-002, OPI-004, 003, INS-011, MET-008, PLC-010, SULF-007, TZD-009, 301, 303 and 402. A summary of the 12 trials is shown in Table 3.

The 12 studies included in the pooled analysis share similar goals. The goal of Study 402 is to assess cardiovascular safety. The goal of Study 301 was to evaluate the effect of alogliptin alone and alogliptin plus pioglitazone versus placebo on postprandial triglycerides. The main goal of the other 10 studies, besides studies 301 and 402, was either to determine the benefit of treatment containing alogliptin on glycemic control, or to determine the change of glycosylated hemoglobin (HbA1c) from baseline associated with alogliptin. Note that in the original description of the trials alogliptin is also referred to as 'SYR-322' and 'SYR110322'.

All studies, except for Study 402, had similar inclusion criteria: men or women aged 18 to 80, with BMI between 23 and 45 kg/m^2, with a diagnosis of T2DM, who were inadequately controlled under their current regimen. Study 003 enrolled subjects aged 18 to 75 instead of 18 to 80. Study 301 enrolled subjects aged 18 to 70 instead of 18 to 80. Study 303 was limited to elderly subjects aged 65 to 90.

Study 402 was conducted in an enriched population with higher background cardiovascular risk than the other studies. The inclusion criteria for Study 402 read: "Men and women with T2DM who have a diagnosis of ACS (myocardial infarction or unstable angina requiring hospitalization) within 15 to 90 days prior to randomization."

A description of the design of the 12 trials utilized in the pooled analysis of MACE is provided below.

OPI-001 is a Phase 3 study. According to the Sponsor this is an: "International, multicenter, randomized, double-blind, placebo controlled, 12-treatment arm study in subjects with type 2 diabetes who were inadequately controlled on a current regimen of metformin alone. The study was designed to assess the efficacy and safety of alogliptin in combination with pioglitazone as compared with either alogliptin or pioglitazone alone." The primary efficacy endpoint was the change from Baseline (Day 1) in HbA1c at Week 26. The study consisted of a Prescreening Period of up to 2 weeks, an optional 12-week metformin Titration Period, a Screening Period of

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up to 2 weeks, a 4-week Run-in/Stabilization Period, a 26-week Treatment Period followed by an end-of treatment visit (or early termination visit), and a 2-week Follow-up Period. Eligible subjects were allowed to enter an open-label extension study. Metformin was dispensed at the start of the Stabilization Period and as needed at subsequent visits. *The time from a subject's first received study medication to his/her last recorded visit, not including the optional open-label study, is included in the pooled analysis.* At the end of the Stabilization Period 1,554 subjects were randomized in approximately equal numbers (128 to 130 subjects per group) to 1 of the following 12 treatment regimens: placebo, alogliptin 12.5 mg, alogliptin 25 mg, pioglitazone 15 mg, pioglitazone 15 mg plus alogliptin 12.5 mg, pioglitazone 15 mg plus alogliptin 25 mg, pioglitazone 30 mg, pioglitazone 30 mg plus alogliptin 12.5 mg, pioglitazone 30 mg plus alogliptin 25 mg, pioglitazone 45 mg, pioglitazone 45 mg plus alogliptin 12.5 mg, pioglitazone 45 mg plus alogliptin 25 mg. The trial had the following inclusion criteria: men or women aged 18 to 80, with BMI between 23 and 45 kg/m^2, with a diagnosis of T2DM, who were inadequately controlled with metformin alone. The study was conducted between May 2006 and March 2008.

OPI-002 is a Phase 3 study. According to the Sponsor this is an: "International, multicenter, randomized, double-blind, 4-treatment arm study in subjects with type 2 diabetes mellitus who have failed treatment with diet and exercise, designed to assess the efficacy and safety of alogliptin in combination with pioglitazone as compared with either alogliptin or pioglitazone alone." The primary efficacy endpoint was the change from Baseline (Day 1) in HbA1c at Week 26. The study consisted of a Screening Period of up to 2 weeks, a 4-week Run-in/Stabilization Period, a 26 week treatment period, and a 2-week Follow-up Period. Eligible subjects were allowed to enter an open-label extension study. *The time from a subject's first received study medication to his/her last recorded visit, not including the optional open-label study, is included in the pooled analysis.* At the end of the Stabilization Period 655 subjects were randomized as follows: 164 to alogliptin 25 mg alone, 163 to pioglitazone 30 mg alone, 164 to alogliptin 12.5 mg with pioglitazone 30 mg, and 164 to alogliptin 25 mg with pioglitazone 30 mg. The trial had the following inclusion criteria: men or women aged 18 to 80, with BMI between 23 and 45 kg/m^2, with a diagnosis of T2DM, who were inadequately controlled under their current regimen. The study was conducted between November 2006 and February 2008.

OPI-004 is a Phase 3 study titled: "A Multicenter, Randomized, Double-Blind Study to Determine the Efficacy and Safety of the Addition of SYR- 22 25 mg versus Dose Titration from 30 mg to 45 mg of ACTOS® Pioglitazone HCl in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Control on a Combination of Metformin and 30g of Pioglitazone HCl Therapy." The primary endpoint for this study was change from Baseline (Day 1) HbA1c at Week 26 and Week 52. The study consisted of a Screening Period of up to 2 weeks, a 4-week Run-in/Stabilization Period, and a 52 week Treatment Period. *The time from a subject's first received study medication to his/her last recorded visit is included in the pooled analysis.* At the end of the Stabilization Period 803 subjects were randomized as follows: 404 to metformin plus alogliptin 25 mg plus pioglitazone 30 mg, and 399 to metformin plus pioglitazone titrated from 30 to 45 mg. The trial had the following inclusion criteria: men or women aged 18 to 80, with BMI between 23 and 45 kg/m^2, with a diagnosis of T2DM, who were inadequately controlled under their current regimen. The study was conducted between January 2007 and June 2009.

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Study 003 is a Phase 2 study titled: "A Multicenter, randomized, double-blind, placebo-controlled comparison study to determine the efficacy and safety of SYR110322 in subjects with Type 2 Diabetes, who are either receiving no current treatment or currently treated with diet and exercise, a sulfonylurea, metformin, or a combination of a sulfonylurea and metformin." The primary efficacy endpoint was the change from Baseline (Day 1) in HbA1c on Day 85. The study consisted of either a 2-week Screening/Washout Period for subjects who had received prior antidiabetic treatment or a 1-week Screening Period for subjects who had not received prior Antidiabetic treatment, plus a 12-week Treatment Period, an End-of Treatment Visit, and a 2-week Follow-up Period for all subjects. *The time from a subject's first received study medication to his/her last recorded visit is included in the pooled analysis.* At the end of the Stabilization Period 259 subjects were randomized as follows: 44 to alogliptin 6.25 mg, 44 to alogliptin 12.5 mg, 45 to alogliptin 25 mg, 44 to alogliptin 50 mg, 45 to alogliptin 100 mg, and 43 to alogliptin placebo. The trial had the following inclusion criteria: men or women aged 18 to 75, with BMI between 23 and 45 kg/m^2, with a diagnosis of T2DM, who were inadequately controlled under their current regimen. The study was conducted between March 2005 and October 2005.

INS-011 is a Phase 3 study titled: "International, multicenter, randomized, double-blind, placebo-controlled, 3-treatment arm study to assess the efficacy and safety of 2 doses of SYR-322 in combination with insulin (with or without metformin) versus insulin alone (with or without metformin)." The primary efficacy endpoint was the change from Baseline (Day 1) in HbA1c at Week 26. The study consisted of Screening Period of up to 2 weeks, a 4-week Run-in/Stabilization Period, a 26-week Treatment Period followed by an end-of-treatment visit. At the end of the Treatment Period, subjects were allowed to enroll into an open-label extension study; subjects who did not enroll in the extension study had a 2-week Follow-up Period. *The time from a subject's first received study medication to his/her last recorded visit, not including the optional open-label study, is included in the pooled analysis.* Subjects who received metformin prior to randomization were allowed to continue receiving metformin after randomization. At the end of the Stabilization Period 390 subjects were randomized as follows: 131 to alogliptin 12.5 mg plus insulin (77 with metformin), 129 to alogliptin 25 mg plus insulin (72 with metformin), 130 to placebo plus insulin (79 with metformin). The trial had the following inclusion criteria: men or women aged 18 to 80, with BMI between 23 and 45 kg/m^2, with a diagnosis of T2DM, who were inadequately controlled under their current regimen. The study was conducted between February 2006 and May 2007.

MET-008 is a Phase 3 study titled: "International, multicenter, randomized, double-blind, placebo-controlled, 3-treatment arm study to assess the efficacy and safety of 2 doses of SYR-322 in combination with metformin versus metformin alone." The study consisted of a Screening Period of up to 2 weeks, a 4-week Run-in/Stabilization Period, a 26-week Treatment Period (or Early Termination visit) and a 2-week Follow-up Period. Eligible subjects were allowed to enter an open-label extension study. *The time from a subject's first received study medication to his/her last recorded visit, not including the optional open-label study, is included in the pooled analysis.* At the end of the Stabilization Period 427 subjects were randomized as follows: 213 to alogliptin 12.5 mg plus metformin, 207 to alogliptin 25 mg plus metformin, 104 to alogliptin placebo plus metformin. The trial had the following inclusion criteria: men or women aged 18 to 80, with BMI between 23 and 45 kg/m^2, with a diagnosis of T2DM, who were inadequately controlled with metformin alone. The study was conducted between March 2006 and June 2007.

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PLC-010 is a Phase 3 study. According to the Sponsor this is an: "International, multicenter, randomized, double-blind, placebo-controlled, 3-treatment arm study to assess the efficacy and safety of 2 dose levels of SYR-322 versus placebo." The primary efficacy endpoint was the change from Baseline (Day 1) in HbA1c at Week 26. The study included a Screening Period of up to 2 weeks, a 4-week Run-in/Stabilization Period, a 26-week Treatment Period followed by an End-of-Treatment visit, and a 2-week Follow-up Period. Eligible subjects were allowed to enter an open-label extension study. *The time from a subject's first received study medication to his/her last recorded visit, not including the optional open-label study, is included in the pooled analysis.* At the end of the Stabilization Period 329 subjects were randomized as follows: 133 to alogliptin 12.5 mg, 131 to alogliptin 25 mg, 65 to placebo. The trial had the following inclusion criteria: men or women aged 18 to 80, with BMI between 23 and 45 kg/m^2, with a diagnosis of T2DM, who were experiencing inadequate glycemic control; who had failed treatment with diet and exercise for at least 1 month prior to Screening; and who were receiving no current antidiabetic therapy. The study was conducted between February 2006 and July 2007.

SULF-007 is a Phase 3 study. According to the Sponsor this is an: "International, multicenter, randomized, double-blind, placebo controlled, 3-treatment arm study to assess the efficacy and safety of 2 dose levels of SYR-322 in combination with a sulfonylurea versus a sulfonylurea alone." The primary efficacy endpoint was the change from Baseline (Day 1) in HbA1c at Week 26. The study included a Screening Period of up to 2 weeks, a 4-week Run-in/Stabilization Period, a 26-week Treatment Period followed by an end-of-treatment visit, and a 2-week Follow-up Period. *The time from a subject's first received study medication to his/her last recorded visit, not including the optional open-label study, is included in the pooled analysis.* At the end of the Stabilization Period 500 subjects were randomized as follows: 203 to alogliptin 12.5 mg plus glyburide, 198 to alogliptin 25 mg plus glyburide, 99 to alogliptin placebo plus glyburide. The trial had the following inclusion criteria: men or women aged 18 to 80, with BMI between 23 and 45 kg/m^2, with a diagnosis of T2DM, who were inadequately controlled with a sulfonylurea alone. The study was conducted between April 2006 and June 2007.

TZD-009 is a Phase 3 study. According to the Sponsor this is an: "International, multicenter, randomized, double-blind, placebo-controlled, 3-treatment arm study to assess the efficacy and safety of 2 dose levels of SYR-322 in combination with pioglitazone (with or without metformin or a sulfonylurea) versus pioglitazone alone (with or without metformin or a sulfonylurea)." The primary efficacy endpoint was the change from Baseline (Day 1) in HbA1c at Week 26. The study consisted of a Screening Period of up to 2 weeks, a 4-week Run-in/Stabilization Period, a 26-week Treatment Period (or Early Termination visit), and a 2-week Follow-up Period. Eligible subjects were allowed to enter an open-label extension study. During the Run-in/Stabilization Period, eligible subjects treated with pioglitazone continued this medication at the same daily dose; subjects treated with rosiglitazone were switched to a comparable dose of pioglitazone. *The time from a subject's first received study medication to his/her last recorded visit, not including the optional open-label study, is included in the pooled analysis.* At the end of the Stabilization Period, 493 subjects were randomized as follows: 197 to alogliptin 12.5 mg plus pioglitazone (107 with metformin, 42 with sulfonylurea, and 48 with neither), 199 to alogliptin 25 mg plus pioglitazone (114 with metformin, 44 with sulfonylurea, and 41 with neither), 97 to placebo plus pioglitazone (56 with metformin, 18 with sulfonylurea, and 23 with neither). The trial had the

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following inclusion criteria: men or women aged 18 to 80, with BMI between 23 and 45 kg/m^2, with a diagnosis of T2DM, currently receiving treatment with a thiazolidinedione either alone or in combination with metformin or a sulfonylurea. The study was conducted between February 2006 and August 2007.

Study 301 is a Phase 3b study titled: "A multi-center, randomized, double-blind, placebo-controlled, parallel-group study comparing SYR-322 alone and combination SYR-322 with pioglitazone versus placebo on postprandial lipids in subjects with Type 2 Diabetes." The primary variable was the change from Baseline in postprandial incremental area under the curve (AUC) for total triglycerides at Week 16. After a Screening Period, 71 subjects were randomly assigned on Day 1 (Baseline) to the following treatment regimens: 24 to placebo, 25 to alogliptin 25 mg, 22 to alogliptin 25 mg plus pioglitazone 30 mg. Subjects returned to the clinic at Weeks 4, 8, and 16 for study assessments. At Week 16, subjects completed study treatment and returned to the clinic for a Follow-up Visit at Week 18. *The time from a subject's first received study medication to his/her last recorded visit is included in the pooled analysis.* The trial had the following inclusion criteria: men or women aged 18 to 70, with a diagnosis of T2DM and inadequate glycemic control, having either failed treatment with diet and exercise for 3 months prior to Screening or having received a stable dose of metformin, sulfonylurea, nataglinide, or repaglinide for more than 3 months prior to Screening. The study was conducted between July 2007 and December 2009. This is the smallest study included in the pooled analysis.

Study 303 is a Phase 3b study titled: "A multicenter, randomized, double-blind study to evaluate the efficacy and safety of alogliptin compared to glipizide in elderly subjects with Type 2 Diabetes." The primary efficacy variable evaluated glycemic control through HbA1c changes from Baseline at Week 52. Male or female subjects, between the ages of 65 and 90, with BMI between 23 and 45 kg/m^2, diagnosed with T2DM, were eligible for study participation if they had inadequate glycemic control with diet and exercise therapy alone (Schedule A), or failed treatment with oral monotherapy alone (Schedule B). All eligible subjects underwent a 2 week Screening Period. Subjects on Schedule B then underwent a 4-week Washout Period. All randomized subjects underwent a 52-week treatment period with 441 total randomized subjects, 222 randomized to alogliptin 25 mg, and 219 to glipizide 5-10 mg. *The time from a subject's first received study medication to his/her last recorded visit is included in the pooled analysis.* The study was conducted between June 2008 and August 2010.

Study 402 is an ongoing Phase 3b study titled: "A multicenter, randomized, double-blind, placebo-controlled study to evaluate cardiovascular outcomes following treatment with alogliptin in addition to standard care in subjects with Type 2 Diabetes and Acute Coronary Syndrome." The primary objective of Study 402 is to demonstrate that alogliptin is not associated with increased risk of MACE compared to placebo. According to the study protocol, the study consists of a Screening Period of 2-weeks, followed by randomization to alogliptin 25 mg (subjects with estimated glomerular filtration rate [eGFR] ≥50 mL/min at baseline), 12.5 mg (subjects with eGFR ≥30 and <50 mL/min), alogliptin 6.25 mg (subjects with eGFR < 30 mL/min), or placebo. According to the CSR for Study 402: "All subjects randomized to receive alogliptin, regardless of dose (6.25 mg, 12.5 mg, or 25 mg), are shown in the alogliptin 25 mg group due to similar exposure determined in the renal impairment pharmacokinetic study." Study 402 started in September 2009 and is currently ongoing. For the current submission, the data was

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locked on April 29, 2011; at that time, 1,058 subjects had been randomized to alogliptin and 1,076 to placebo. *The time from a subject's first received study medication to the first of his/her time of event, censoring, or April 29, 2011 is included in the pooled analysis.*

Study 402 is designed to conduct interim analyses in two stages. The first stage of the study is designed to rule out a hazard ratio (HR) of MACE of 1.8. The second stage is designed to rule out a HR of 1.3. A flowchart of Study 402 is found in the Appendix. The current submission includes data for the first interim analysis in the first stage of Study 402, which occurred after (b) (4) events. If Study 402 is able to rule out a HR of 1.8, the next interim analysis will be conducted after 550 observed MACE, at which point the HR for MACE associated with the use of alogliptin will be tested against a non-inferiority margin of 1.3. If Study 402 cannot rule out a HR of 1.8 after the first (b) (4) events, then the non-inferiority margin of 1.8 will be tested again at 100 events. The interim analysis of the primary variable was conducted using a Cox proportional hazards model.

Out of the 12 studies included in the pooled analysis, Study 402 is the only one specifically designed and powered to evaluate cardiovascular safety. The duration of the study will depend on the number of events. Subjects will be followed until the study is completed. The maximum length of follow-up for a subject is expected to be 4.75 years with a median of 2 years. The trial has the following inclusion criteria: men and women with T2DM who have a diagnosis of Acute Coronary Syndrome (ACS) 15 to 90 days prior to randomization. ACS is defined as myocardial infarction or unstable angina requiring hospitalization.

Reviewer's comment:
The consistent design of these studies suggests that an adequate pooled analysis can be performed to assess the cardiovascular risk of alogliptin in accordance to the Guidance for Industry. The inclusion criteria of Study 402 is consistent with the Guidance recommendation that "To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events".

3.1.2 Endpoints and Adjudication Methods

3.1.2.1 Primary Composite Endpoint

The primary endpoint is the time until first Major Adverse Cardiovascular Event (MACE), defined as any of the following adjudicated events: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

The time to event is calculated from the time of randomization to the occurrence of first MACE. Subjects without an observed MACE are censored at the time of their last recorded visit in the original controlled trial in which they enrolled. Subjects' time on open-label studies, if any, is not counted towards the primary endpoint. The dataset for Study 402 was locked on April 29, 2011 for this submission. All subjects enrolled in Study 402 at that date, who had not experienced an event while on the trial, are considered censored at that date.

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3.1.2.2 Secondary Composite Endpoint

The secondary endpoint, in Study 402 only, is the time from randomization to the first occurrence of any event in the adjudicated secondary MACE composite: CV death, nonfatal MI, nonfatal stroke, and urgent revascularization due to unstable angina. In this review, the secondary MACE composite will be referred to as MACE+.

3.1.2.3 Adjudication Methods

MACE was adjudicated prospectively in Study 402 and retrospectively in the other 11 trials in the pooled analysis. The secondary MACE+ endpoint was adjudicated in Study 402, but not in the other trials.

In Study 402, according to Takeda: "Potential CV events are identified by comparing all adverse event preferred terms to a pre-established list of MedDRA preferred terms." During Study 402, physicians review all SAE narratives to ensure potential CV events are not missed. An independent Cardiovascular Endpoints Committee (CEC) reviews reported terms not captured in a pre-specified Medical Query and evaluates if additional events should be considered as potential CV events. The CEC reviews and adjudicates both the primary MACE and secondary MACE+ endpoints in Study 402.

The same definition of MACE is used in the other 11 studies and retrospective adjudication by the same CEC was performed.

Reviewer's comment:
The formation of the CEC addresses the Guidance for Industry recommendation that reads: "Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials."

3.1.3 Statistical Methodologies

The following sections describe the statistical methodology used in the pooled analysis of MACE in the 12 trials, and the analysis of MACE in Study 402 alone.

3.1.3.1 Time to Event Analysis

The agreed upon primary pooled analysis compares the hazard ratio of MACE in subjects randomized to any dose of alogliptin (≥ 6.25 mg) vs. all subjects randomized to any treatment not containing alogliptin using a Cox proportional hazards model stratified by study. A one-sided 97.5% confidence interval for the hazard ratio will be calculated based on the robust, or sandwich, variance estimator of the Cox model. The stratified Cox model uses information from all strata (studies) with at least 1 event. Strata with zero events do not contribute information to the stratified Cox model.

The agreed upon primary analysis in Study 402 compares the hazard ratio of MACE in subjects randomized to alogliptin vs. subjects randomized to placebo. Alogliptin will be considered non-

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inferior to placebo in terms of risk of MACE if the upper bound of a one-sided 97.5% confidence interval for the HR is less than a non-inferiority margin of 1.8. The upper bound of the 1-sided repeated confidence interval for the hazard ratio is calculated using an O'Brien-Fleming-type spending function designed to preserve an overall one-sided alpha of 0.025 for ruling out a HR greater than or equal to 1.8. The confidence interval is constructed using a critical value of 2.796, corresponding to an O'Brien-Fleming-type spending function for a repeated confidence interval with a one-sided alpha of 0.00259.

The agreed upon secondary analysis in Study 402 compares the hazard ratio of the secondary MACE+ composite in subjects randomized to alogliptin vs. subjects randomized to placebo. The same statistical approach is used in the primary and secondary analyses.

Kaplan-Meier curves will be provided to compare the survival function of MACE in both treatment groups graphically in the pooled analysis of all trials, and in Study 402 alone. The proportional hazards assumption of the Cox model will be evaluated graphically by plotting the negative log-survival curve, and Schoenfeld residuals.

3.1.3.2 Secondary Time to Event Analysis

A secondary analysis compares the hazard ratio of each individual element of MACE (CV death, MI, and nonfatal stroke) in the stratified Cox model including all 12 trials in the pooled analysis, and in Study 402 alone.

A secondary analysis of interest compares the HR of MACE in subjects randomized to the combination alogliptin + pioglitazone to pioglitazone alone. Four trials randomized subjects to these treatment regimens: OPI-001, OPI-22, OPI-004 and TZD-009. Additionally Study 301 randomized subjects to alogliptin, alogliptin + pioglitazone, and placebo (but not to pioglitazone alone). Using these 5 trials, a Cox model stratified by study with terms for alogliptin, pioglitazone, and the interaction alogliptin x pioglitazone, will be fit to compare the HR of MACE associated with the combination alogliptin + pioglitazone vs. alogliptin alone, and to compare the HR of MACE of the combination alogliptin + pioglitazone vs. placebo. These analyses are not pre-specified in the SAP.

3.1.3.3 Analysis of Event Incidence

A secondary analysis will estimate the Mantel-Haenszel incidence rate ratio of MACE in the 12 trials. Both the primary stratified Cox proportional hazards model and the Mantel-Haenszel incidence rate ratio do not use information from trials with zero events. In order to use data from all trials, including those with zero events, the Mantel-Haenszel incidence rate difference will be estimated. These two analyses are not pre-specified in the SAP.

3.1.3.4 Evaluation of Heterogeneity between Trials

The stratified Cox model allows for different baseline hazards across strata, but assumes that the effect of treatment, the hazard ratio, is constant across strata. Testing for a difference in hazard ratio is equivalent to testing for an interaction of treatment by strata in the Cox model. Given that

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only Study 402 was powered to evaluate cardiovascular safety, few MACE are expected to be observed in each of the other 11 trials. Therefore a test for interaction of treatment by study in the primary Cox model would have effectively no power to detect differences in the hazard ratio between trials. Therefore, in this review we do not test for the interaction of treatment and strata, and assume that the hazard ratio between alogliptin and comparators is the same for all trials. Takeda's SAP does not propose testing for heterogeneity between trials.

3.1.3.5 Sensitivity Analyses

As a condition for enrollment, all subjects in Study 402 experienced an ACS event 15 to 90 days prior to randomization. It is possible that some of these subjects may experience MACE shortly after randomization as a consequence of their earlier ACS independently of their randomized treatment. In order to assess whether early events affect the estimate of the hazard ratio of MACE in Study 402, the review team at the FDA will fit the Cox model for MACE in Study 402 excluding all subjects' first 15 days after randomization, and first 30 days after randomization. Results of these analyses will be compared with results obtained using the full data available for Study 402. These sensitivity analyses are not pre-specified in Takeda's SAP and have been proposed after observing the distribution of time to MACE in Study 402.

3.1.4 Populations

According to Takeda's SAP, the analysis of MACE will be conducted on the Randomized Set consisting of all subjects who provided informed consent and were randomized in one of the Phase 2 and Phase 3 controlled studies summarized in Table 3. Subjects will be analyzed according to their randomized treatment assignment, regardless of treatment received. This Randomized Set is the primary, pre-specified and agreed upon population of the pooled analysis. The time contributed to the primary analysis by each subject is counted from the time of randomization until the subject's last recorded visit or adjudicated MACE. For subjects still participating in Study 402 at the time of its interim data cut, April 29, 2011, this date will be imputed for the date of last visit/contact. The Randomized Set for the 12 trials includes 5,226 subjects randomized to alogliptin and 2,936 subjects randomized to non-alogliptin comparators. The Randomized Set for Study 402 includes 1,058 subjects randomized to alogliptin and 1,076 subjects randomized to placebo.

3.1.5 Subject Disposition, Demographics and Baseline Characteristics

3.1.5.1 Characteristics of All Trials in the Pooled Analysis

Table 4 shows that baseline demographic characteristics were similar between subjects randomized to alogliptin and comparators in the 12 trials included in the pooled analysis. Approximately 46.9% of subjects randomized to alogliptin were female, compared to 43.3% among comparators. Subjects randomized to alogliptin were slightly younger on average: 56.5 years vs. 58.3 years on comparators. The mean BMI across all subjects and treatment groups was 30.8 with a standard deviation of 5.4. Approximately 71% of all subjects were White, 6% were

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Black or African-American, 14% were Asian, and the remaining 9% were either another race or multiracial. Among subjects randomized to alogliptin, 32.4% have been randomized in North America, compared to 26.2% among patients randomized to comparators. This slight imbalance appears to be due to chance.

Table 4. Demographics of All Trials in Pooled Analysis

	Alogliptin (*N =5226*)	**All Comparators** (*N =2936*)
Percent Female	46.9 %	43.3%
Age± SD (years)	56.5 ± 10.7	58.3 ± 10.7
≤ 50 years	28.6 %	23.3 %
51 – 65 years	50.0 %	50.3 %
66 - 75 years	18.3 %	21.8 %
> 75 years	3.1 %	4.6 %
BMI± SD (kg/m^2)	31.0 ± 5.4	30.5 ± 5.5
≤ 25	12.9 %	15.8 %
26-30	35.6 %	36.9 %
> 30	51.5 %	47.3 %
Race and Ethnicity		
White	71.8 %	69.5 %
Black	5.9 %	6.4 %
Asian	12.8 %	16.0 %
Other / Multiracial	9.5 %	8.1 %
Region		
North America	32.4 %	26.2 %
Latin America	26.1 %	25.1 %
Europe, Australia and Middle East	10.3 %	11.1 %
Rest of the World	31.2 %	37.6 %

Source: Created by reviewer. Dataset: d_demog.xpt

Table 5 shows baseline cardiovascular risk among subjects in the 12 trials included in the pooled analysis. The percentage of smokers and the average duration of diabetes were similar between alogliptin and comparators. Renal impairment is determined using the Modification of Diet in Renal Disease [MDRD] Formula. Subjects randomized to comparators appear to have slightly worse renal function, on average, than subjects randomized to alogliptin. Slight imbalances such as these are expected due to randomization.

Table 5. Cardiovascular Risk Factors in All Trials in Pooled Analysis

	Alogliptin (*N = 5226*)	**All Comparators** (*N = 2936*)
Renal Function		
Severely Impaired	0.6 %	1.0 %
Moderately Impaired	14.4 %	18.2 %
Mildly Impaired	65.7 %	62.9 %
Normal	19.3 %	17.9 %
Currently Smokes		
Yes	16.6 %	15.9 %
No	83.4 %	84.1 %

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Diabetes Duration		
≤ 3 years	32.3 %	30.0 %
3 – 10 years	43.8 %	42.7 %
> 10 years	23.9 %	27.3 %

Source: Created by reviewer. Dataset: d_demog.xpt

Table 6 shows the mean time of follow-up per subject, in days, in each of the 12 trials. Table 7 shows that so far, 940 total subjects have had follow-up of at least 360 days, all of them in 3 trials: OPI-004, 303 and 402.

Table 6. Days of Follow-up, by Trial. Mean (SD)

Trial	Alogliptin	All Comparators
OPI-001	170 (41)	156 (49)
OPI-002	165 (45)	161 (52)
OPI-004	315 (115)	293 (123)
003	80 (32)	62 (35)
INS-011	157 (48)	137 (54)
MET-008	168 (46)	158 (50)
PLC-010	166 (46)	150 (54)
SULF-007	167 (41)	157 (45)
TZD-009	167 (45)	159 (51)
301	126 (11)	128 (5)
303	299 (120)	283 (130)
402	169 (114)	166 (115)
Overall:	180 (90)	186 (110)

Table 7. Number of Subjects with at least 360 Days of Follow-up

Trial	Alogliptin	All Comparators
OPI-004	286	246
303	137	126
402	73	72
Total:	496	444

Figure 1 shows the rate of premature study discontinuation by trial and treatment arm. Overall, subjects randomized to comparators seem to have been more likely to discontinue their enrollment in these trials than subjects randomized to alogliptin. The reasons for trial discontinuation by trial and treatment arm are given in Table 8. The major difference between treatment arms in Table 8 is that subjects randomized to comparators seem to have been more likely to drop out due to lack of efficacy than subjects randomized to alogliptin.

Reviewer's comment:

Overall, the alogliptin and comparator arms appear balanced, with slight differences expected due to randomization, in terms of demographic characteristics and cardiovascular risk factors. Subjects on alogliptin have so far been less likely to discontinue participation in their

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corresponding studies. We found no major concerns in terms of baseline characteristics and subjects' disposition in these trials.

In the Complete Response Letter from the FDA to Takeda issued on June 2009 and discussed in Section 2.1, the FDA noted that: "Your complete response should contain controlled data for at least 500 patients with at least 1-year total exposure to alogliptin". In the current submission, there are 496 subjects randomized to alogliptin with at least 360 days of follow-up. The difference of 4 subjects between the required 500 and the observed 496 is not a source of concern for this review.

Figure 1. Percentage of Subjects with Premature Study Discontinuation by Trial and Treatment Group

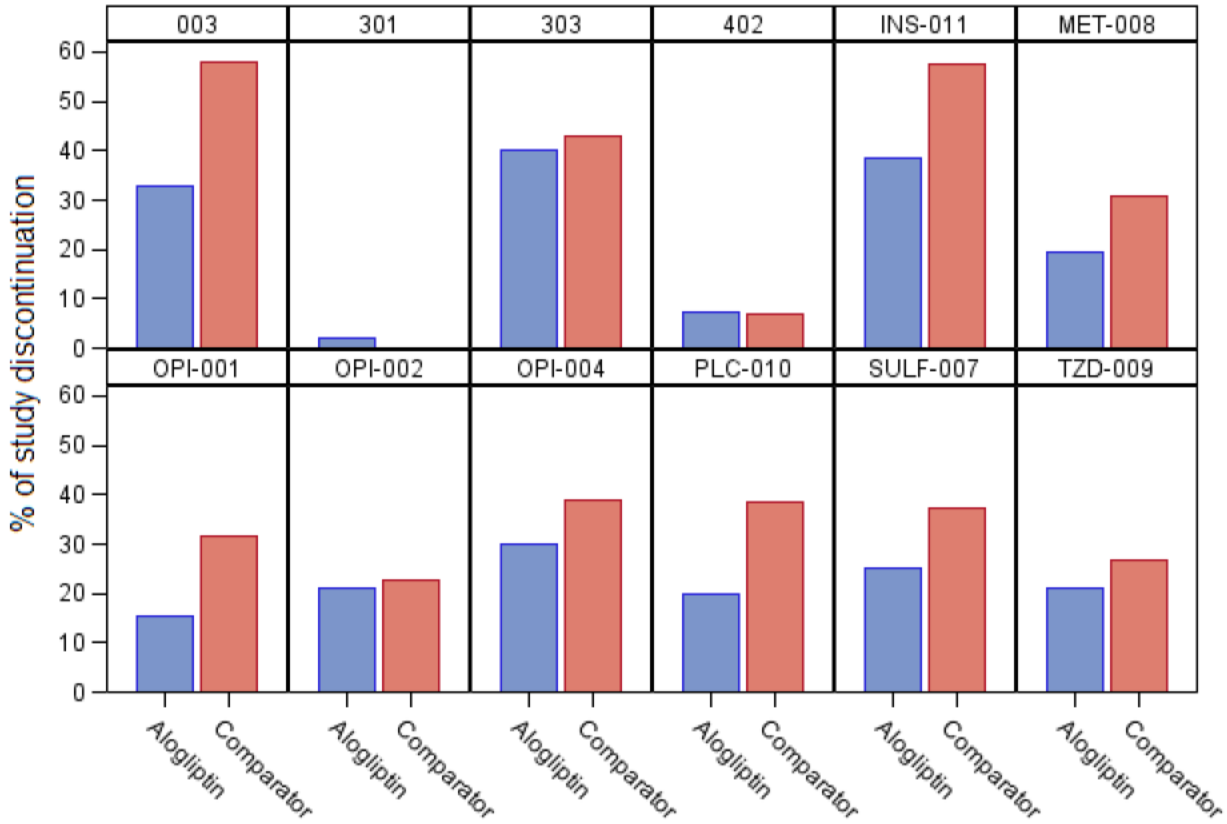

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Table 8. Trial Discontinuation Rates by Reason

Trial	Randomized Treatment	Sample Size	Reason for Discontinuation						
			Lack of Efficacy	Voluntary Withdrawal	Adverse Event	Major Protocol	PI Discretion	Lost to Follow-Up	Other
OPI-001	alogliptin	1037	62 (6.0%)	33 (3.2%)	17 (1.6%)	25 (2.4%)	10 (1.0%)	10 (1.0%)	2 (0.2%)
	pioglitazone	388	43 (11.1%)	15 (3.9%)	11 (2.8%)	18 (4.6%)	5 (1.3%)	9 (2.3%)	3 (0.8%)
	placebo	129	41 (31.8%)	5 (3.9%)	3 (2.3%)	2 (1.6%)	4 (3.1%)	4 (3.1%)	.
OPI-002	alogliptin	492	28 (5.7%)	23 (4.7%)	15 (3.0%)	15 (3.0%)	10 (2.0%)	12 (2.4%)	1 (0.2%)
	pioglitazone	163	10 (6.1%)	5 (3.1%)	8 (4.9%)	3 (1.8%)	4 (2.5%)	6 (3.7%)	1 (0.6%)
OPI-004	alogliptin	404	44 (10.9%)	25 (6.2%)	13 (3.2%)	25 (6.2%)	6 (1.5%)	6 (1.5%)	2 (0.5%)
	pioglitazone	399	87 (21.8%)	20 (5.0%)	16 (4.0%)	20 (5.0%)	8 (2.0%)	2 (0.5%)	3 (0.8%)
003	alogliptin	222	.	11 (5.0%)	6 (2.7%)	5 (2.3%)	5 (2.3%)	9 (4.1%)	37 (16.7%)
	metformin or sulfonylurea	43	.	2 (4.7%)	.	1 (2.3%)	1 (2.3%)	.	21 (48.8%)
INS-011	alogliptin	260	52 (20.0%)	8 (3.1%)	7 (2.7%)	9 (3.5%)	14 (5.4%)	7 (2.7%)	3 (1.2%)
	insulin	130	52 (40.0%)	3 (2.3%)	4 (3.1%)	3 (2.3%)	10 (7.7%)	2 (1.5%)	1 (0.8%)
MET-008	alogliptin	423	36 (8.5%)	16 (3.8%)	13 (3.1%)	6 (1.4%)	2 (0.5%)	7 (1.7%)	1 (0.2%)
	metformin	104	25 (24.0%)	2 (1.9%)	1 (1.0%)	2 (1.9%)	1 (1.0%)	1 (1.0%)	.
PLC-010	alogliptin	264	23 (8.7%)	15 (5.7%)	5 (1.9%)	1 (0.4%)	2 (0.8%)	6 (2.3%)	.
	placebo	65	19 (29.2%)	-	1 (1.5%)	1 (1.5%)	3 (4.6%)	.	1 (1.5%)
SULF-007	alogliptin	401	61 (15.2%)	19 (4.7%)	10 (2.5%)	4 (1.0%)	3 (0.7%)	3 (0.7%)	.
	sulfonylurea	99	28 (28.3%)	3 (3.0%)	2 (2.0%)	.	3 (3.0%)	1 (1.0%)	.
TZD-009	alogliptin	396	37 (9.3%)	19 (4.8%)	14 (3.5%)	3 (0.8%)	6 (1.5%)	4 (1.0%)	.
	pioglitazone	97	12 (12.4%)	2 (2.1%)	3 (3.1%)	1 (1.0%)	5 (5.2%)	3 (3.1%)	.
301	alogliptin	47	.	-	.	.	.	1 (2.1%)	.
	placebo	24	.	-	.	.	.	.	.
303	alogliptin	222	55 (24.8%)	12 (5.4%)	16 (7.2%)	4 (1.8%)	.	.	2 (0.9%)
	glipizide	219	47 (21.5%)	16 (7.3%)	20 (9.1%)	7 (3.2%)	.	4 (1.8%)	.
402	alogliptin	1058	.	25 (2.4%)	27 (2.6%)	.	3 (0.3%)	3 (0.3%)	4 (0.4%)
	placebo	1076	.	22 (2.0%)	31 (2.9%)	1 (0.1%)	2 (0.2%)	4 (0.4%)	5 (0.5%)

Source: Created by reviewer. Dataset: d_master.xpt

3.1.5.2 Characteristics of Study 402

Table 9 shows that baseline demographic characteristics were similar between subjects randomized to alogliptin and placebo in Study 402 up to the current submission database lock date of April 29, 2011. Approximately 30.3% of all subjects randomized so far are female, with a mean age of 60.9 years and a mean BMI of 29.4. Approximately 67.7% of randomized subjects are White, 24.1% Asian, 4.2% Black or African-American, and 4.1% were either another race or multiracial. The percentage of subjects randomized by geographical region is similar between subjects randomized to alogliptin and placebo.

Table 10 shows that baseline cardiovascular risks were similar between subjects randomized to alogliptin and placebo in Study 402. Subjects in Study 402 were more likely to have severe or moderately severe renal impairment compared to subjects in the 12 trials combined (Table 10 vs. Table 5); this is to be expected due to Study 402's inclusion criteria of subjects with higher CV risk and a recent ACS event. The time from ACS to randomization in Study 402 was similar between alogliptin and placebo, with an overall mean time of 47.1 days.

Table 8 and Figure 1 show that Study 402 has experienced a low study discontinuation rate in both treatment arms so far. There appears to be no difference between treatment arms in terms of reasons for discontinuation.

Table 9. Demographics of Study 402

	Alogliptin (*N =1058*)	**Placebo** (*N =1076*)
Percent Female	30.3 %	30.4 %
Age± SD (years)	60.9 ± 9.9	60.9 ± 10.1
≤ 50 years	14.4 %	15.7 %
51 – 65 years	52.7 %	52.7 %
66 - 75 years	25.0 %	23.8 %
> 75 years	7.9 %	7.8 %
BMI± SD (kg/m^2)	29.6 ± 5.7	29.3 ± 5.8
≤ 25	21.8 %	24.9 %
26-30	38.2 %	37.8 %
> 30	40.0 %	37.3 %
Race and Ethnicity		
White	67.9 %	67.4 %
Black	4.0 %	4.4 %
Asian	24.1 %	24.0 %
Other / Multiracial	4.0 %	4.2 %
Region		
North America	17.5 %	17.1 %
Latin America	25.7 %	26.1 %
Europe, Australia and Middle East	11.2 %	11.2 %
Rest of the World	45.6 %	45.6 %

Source: Created by reviewer. Dataset: d_demog.xpt

Reference ID: 3067406

Table 10. Cardiovascular Risk Factors in Study 402

	Alogliptin (*N =1058*)	Placebo (*N = 1076*)
Renal Function		
Severely Impaired	2.6 %	2.9 %
Moderately Impaired	27.4 %	29.5 %
Mildly Impaired	59.5 %	55.0 %
Normal	10.5 %	12.6 %
Currently Smokes		
Yes	11.3 %	11.9 %
No	88.7 %	88.1 %
Diabetes Duration		
≤ 3 years	28.5 %	26.9 %
3 – 10 years	33.5 %	35.2 %
> 10 years	38.0 %	37.9 %
Time from ACS to Randomization ± SD (days)	46.7 ± 29.8	47.5 ± 21.6
≤ 30 days	28.9 %	26.4 %
31 – 60 days	45.9 %	48.4 %
> 60 years	25.2 %	25.2 %

Source: Created by reviewer. Datasets: d_demog.xpt, d_cvhx.xpt

3.1.6 Analysis Results

3.1.6.1 Descriptive Statistics of Primary Composite MACE

(b) (4)

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5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

During the face-to-face meeting held between Takeda and the FDA on February 23rd, 2010, both parties agreed on a Statistical Analysis Plan (SAP) to assess the CV safety of alogliptin through a dedicated CV trial alone, and through a pooled analysis of all controlled Phase 2 and Phase 3 trials combined, including the dedicated CV trial. The agreed upon population of interest consists of all subjects randomized in these trials. The primary safety endpoint of interest is MACE, composed of cardiovascular death, myocardial infarction and non-fatal stroke.

The pooled analysis of 12 Phase 2 and Phase 3 clinical trials, including the dedicated cardiovascular trial, Study 402, evaluates the risk of MACE associated with alogliptin compared to all non-alogliptin comparator groups (including metformin, glipizide, other sulfonylurea products, insulin, pioglitazone, and placebo). A Cox proportional hazards model stratified by study is fit to estimate the hazard ratio of MACE associated with the use of alogliptin. Secondary analyses are fit to estimate the Mantel-Haenszel incidence rate ratio and the Mantel-Haenszel incidence rate difference. The incidence rate difference is the only method in this analysis to use information from trials with zero events.

The dedicated CV safety trial, Study 402, follows a sequential design with an overall one-sided Type-I error rate of 0.025 to demonstrate the non-inferiority of the hazard ratio of MACE associated with the use of alogliptin vs. placebo with a hazard ratio margin of 1.8. The trial is designed to conduct pre-specified interim analyses after 80, 100, 125 and 150 total MACE events have been observed. If at any of these analyses, the upper bound of the 95% confidence interval for the hazard ratio, constructed using an O'Brien-Fleming spending function, is less than or equal to a pre-specified hazard ratio margin of 1.8, then it will be concluded that the HR of MACE associated with the use of alogliptin is smaller than 1.8 and that alogliptin meets this pre-specified safety threshold. If the trial succeeds in proving non-inferiority with a HR margin of 1.8, the trial will continue to the next stage, where it will conduct interim analyses after 550, 600 and 650 events and will test for non-inferiority against a hazard ratio margin of 1.3. At each interim analysis for the primary MACE endpoint, analyses of a secondary MACE+ are conducted. The secondary MACE+ endpoint is composed of CV death, nonfatal MI, nonfatal stroke, and urgent revascularization due to unstable angina.

(b) (4)

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Reference ID: 3067406

(b) (4)

The primary analysis of MACE in the 12 Phase 2 and Phase 3 clinical trials and the primary analysis of MACE in Study 402 both show that the upper bound of the 95% confidence interval for the hazard ratio of MACE of alogliptin vs. all comparators is smaller than 1.8 and therefore meets the 1.8 non-inferiority margin set forth in the FDA Diabetes Guidance (2008)[1].

(b) (4)

(b) (4)

Overall, the results of the primary analysis in the 12 clinical trials, the results of the primary analysis in Study 402, and the results of all sensitivity analyses, were consistent and show that the upper bound of the 95% confidence interval for the hazard ratio of MACE of alogliptin vs. all comparators is smaller than the pre-specified 1.8. The hazard ratio of MACE by subgroups of renal function impairment should be investigated in future analyses of Study 402.

5.2 Conclusions and Recommendations

Takeda assessed the CV safety of alogliptin through a dedicated CV trial alone, and through a pooled analysis of all controlled Phase 2 and Phase 3 trials combined, including the dedicated CV trial, based on a Statistical Analysis Plan (SAP) agreed upon by the FDA on February 23rd, 2010. The agreed upon population of interest consisted of all subjects randomized in these trials. The primary safety endpoint was MACE, composed of cardiovascular death, myocardial infarction and non-fatal stroke. Events were adjudicated by an independent Cardiovascular Endpoints Committee (CEC) in accordance with the FDA Guidance[1].

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The criteria for adequate cardiovascular safety of new antidiabetic products set forth in the FDA Diabetes Guidance (2008)[1] reads:

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For completed studies, before submission of the new drug application (NDA)/biologics license application (BLA):

- *Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8.*

The upper-bound of the 95% confidence interval of the hazard ratio of MACE of alogliptin vs. all comparators meets the 1.8 non-inferiority hazard ratio margin. It is therefore our recommendation that alogliptin be considered safe with respect to the risk of major cardiovascular events for the purpose of approval for the treatment of T2DM, within the statistical bounds recommended in the aforementioned Diabetes Guidance.

Table 30. Summary of Primary Analysis Results

(b) (4)

[redacted]

6 References

1. Food and Drug Administration. Guidance for industry: Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. December 2008. (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf)

2. Breslow NE, Day NE (1994), *Statistical Methods in Cancer Research Volume II: The Design and Analysis of Cohort Studies,* IARC Scientific Publications, No. 82, New York: Oxford University Press, Inc.

3. Whitehead, Anne (2002), *Meta-analysis of Controlled Clinical Trials*. Chichester, England: John Wiley & Sons Inc.

4. Cleveland WS (1985). *The Elements of Graphing Data*. Summit, New Jersey: Hobart Press.

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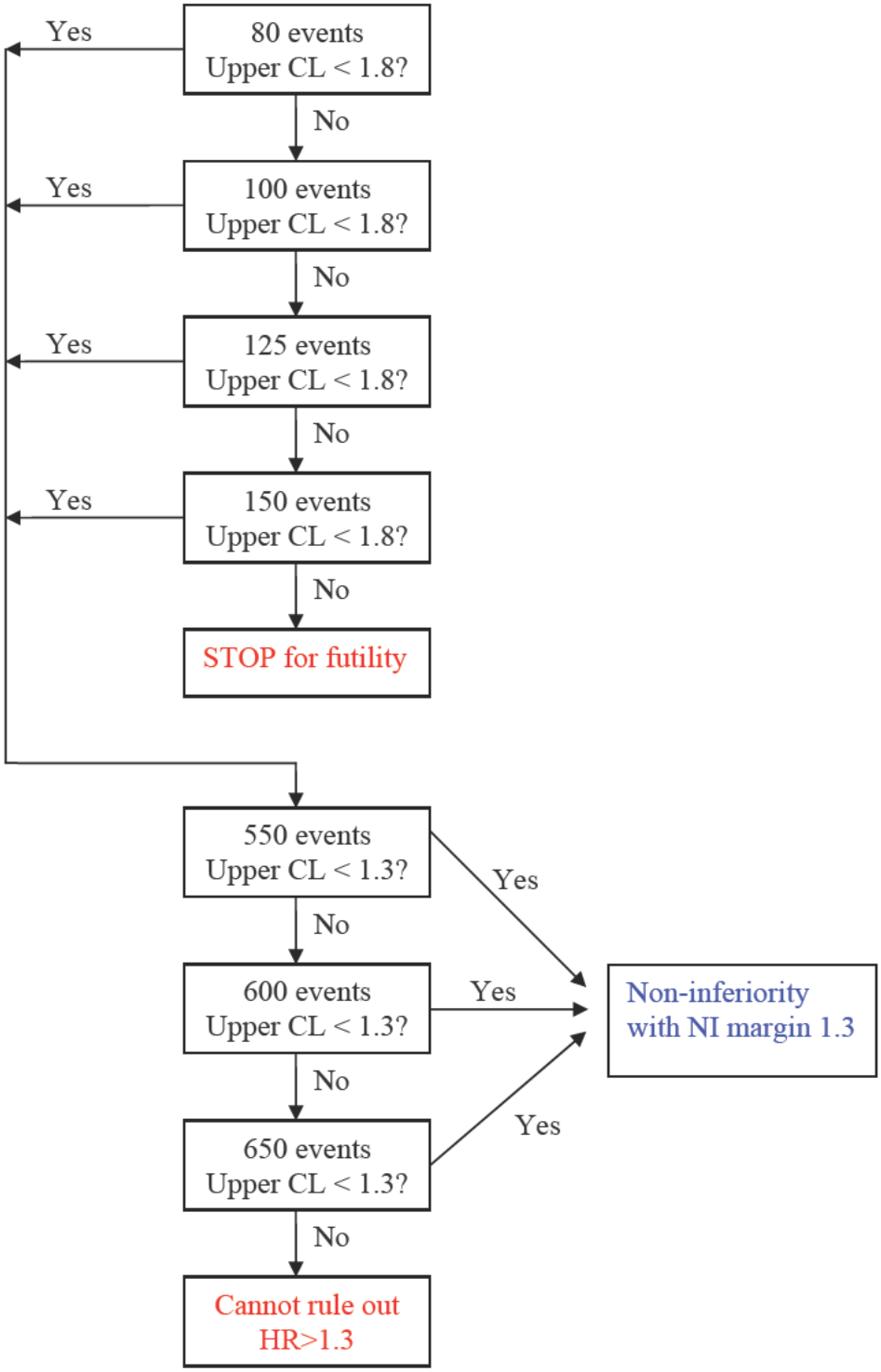
7 Appendix

A.1 Study 402 Flowchart



A.2 Assessment of Proportional Hazards

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Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 022271/0 NDA 022426/0
Drug Name:	Alogliptin (Nesina™) Alogliptin + Pioglitazone fixed dose combination (Oseni™)
Indication(s):	Treatment of type 2 diabetes
Applicant:	Takeda
Date(s):	Letter Date: 7/25/11 PDUFA Goal Date: 1/25/12
Date of this review:	11/18/11
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2
Statistical Reviewer:	Janice Derr, Ph.D.
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Medical Division:	Division of Metabolic and Endocrinology Products
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Keywords: NDA review, clinical studies

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1. Executive Summary

The statistical review focused on two Phase 3 clinical studies that are summarized in the proposed labels for Nesina™ (alogliptin) and Oseni™ (alogliptin + pioglitazone FDC) and had not been reviewed previously.

Study OPI-004 was a comparison of two therapies that were added on to a background therapy of pioglitazone 30 mg + metformin in adults with type 2 diabetes. All enrolled subjects were given this background therapy for four weeks, after which they were randomized to receive either (1) alogliptin 25 mg or (2) an additional 15 mg of pioglitazone, added to the ongoing therapy. The key statistical review issue was the non-inferiority margin of 0.3 that the applicant used to evaluate these two arms. This margin refers to the primary endpoints, HbA1c change from baseline at week 26 and at week 52. In my opinion, the margin of 0.3 is too large for the comparison of adding 25 mg of alogliptin vs. adding 15 mg of pioglitazone to the ongoing therapy. However, the study results supported the superiority of the alogliptin arm (TABLE 1). For this reason, I believe that these results are interpretable even with my concerns about the non-inferiority margin.

TABLE 1 Study OPI-004; HbA1c change from baseline at week 26 and at week 52

Analysis population Study week Treatment groups	N	Baseline mean (SD)	Adjusted mean change from baseline at endpoint ± SE[1]	Difference in adjusted mean change (95% CI) [1]	P-value
HbA1c change from baseline at week 26 (FAS/LOCF)					
Alogliptin 25 mg + Pioglitazone 30 mg + metformin	397	8.2 (0.9)	-0.85 ±0.04	-0.45 (-0.55, -0.35)	p<0.0001
Pioglitazone 45 mg + metformin	394	8.1 (0.8)	-0.40 ± 0.04		
HbA1c change from baseline at week 52 (FAS/LOCF)					
Alogliptin 25 mg + Pioglitazone 30 mg + metformin		as above	-0.69 ± 0.04	-0.40 (-0.51, -0.29)	p<0.0001
Pioglitazone 45 mg + metformin			-0.29 ± 0.04		

Study SYR-322_303 compared alogliptin 25 mg to glipizide (5 mg, with the option of titrating to 10 mg) in adults with type 2 diabetes who were 65 to 90 years old. The treatment period was 52 weeks. The key statistical review issue was the non-inferiority margin of 0.4. This margin refers to the primary endpoint, HbA1c change from baseline at week 52. In my opinion, this margin was too large, considering the elderly population in the study, the low dose of glipizide given in the study, and the low average HbA1c at baseline of 7.5. The observed results, with an upper confidence bound of 0.13, are consistent with a non-inferiority margin that is less than 0.4

(TABLE 2). I believe that the decision about whether or not non-inferiority has been demonstrated is a review issue. From my statistical perspective, I don't believe that this is a confirmatory finding of non-inferiority, because of the inadequacy of the pre-specified margin and the post-hoc nature of the decision. However, the upper confidence bound may be sufficiently less than 0.4, from the clinical perspective, to support a conclusion of non-inferiority.

TABLE 2 Study SYR-322_303; HbA1c change from baseline at week 52

Analysis population Study week Treatment groups	N	Baseline mean (SD)	Adjusted mean change from baseline at endpoint ± SE[1]	Difference in adjusted mean change (95% CI) [1]	P-value
HbA1c change from baseline at week 52 (FAS/LOCF)					
Alogliptin 25 mg	215	7.5 (0.7)	-0.13 ±0.06	-0.02 (-0.17, 0.13)	0.586
Glipizide 5 to 10 mg	214	7.5 (0.6)	-0.11 ± 0.06		

2. Introduction

2.1 Overview

This review covers two submissions submitted by the applicant on 7/25/11, one for alogliptin (NDA 022271) and one for the fixed dose combination (FDC) of alogliptin + pioglitazone (NDA 022426). These submissions are the applicant's response to Complete Response letters from the Division, issued in June 2009. Based on the review of the original submissions to these NDAs, and on recommendations from the Endocrine and Metabolism Drugs Advisory Committee in April 2009, the Division requested that the applicant conduct a cardiovascular safety trial for alogliptin. This request was based on recommendations in the 2008 guidance on evaluating cardiovascular risk in new antidiabetic therapies.[1]

The cardiovascular safety study, Study SYR-322_402 ("EXAMINE") is ongoing at the time of this review. The applicant is submitting results from an interim analysis of this study, because they believe that the results satisfy the criteria for new antidiabetic drugs that are described in the 2008 guidance. In addition, the applicant has submitted other information that has become available since the submission of the two original NDAs in 2007 (alogliptin) and 2008 (alogliptin + pioglitazone). This information includes the results from two additional Phase 3 clinical studies.

Dr. Eugenio Andraca-Carrera, of the Division of Biometrics 7, is reviewing the statistical results from the interim analysis of the cardiovascular safety study. In this review, I evaluate the two Phase 3 studies that had not been reviewed previously.[2]

[1] FDA Guidance for Industry: Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, December 2008.
[2] See the statistical review of alogliptin, NDA 022271/0 dated 9/2/08 and the statistical review of alogliptin + pioglitazone FDA, NDA 022426/0 dated 7/31/09.

2.1.1 Class and Indication

Nesina™ (alogliptin) 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. Other DPP-4 inhibitors have been approved in the U.S. for the treatment of type 2 diabetes, including sitagliptin (Januvia™; approved in 2006), saxagliptin (Onglyza™; approved in 2009) and linagliptin (Tradjenta™; approved in 2011).

Oseni™ is a fixed dose combination of alogliptin and pioglitazone. The applicant developed the combination because they believe that the two drugs could act in a complementary way. The two drugs have different mechanisms of action. Pioglitazone is a member of the thiazolidinedione class of oral anti-diabetic drugs. Pioglitazone increases insulin sensitivity in the peripheral tissue and liver, resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Pioglitazone (Actos™) was approved for the treatment of type 2 diabetes in the U.S. in 1999.

The applicant developed an orally available, immediate-release formulation of alogliptin + pioglitazone in six dosage strengths, combining alogliptin in two dosage strengths (12.5 mg and 25 mg) with pioglitazone in three dosage strengths (15, 30 and 45 mg).

2.1.2 Specific Studies Reviewed

This review will focus on two Phase 3 clinical studies that are summarized in the proposed labels and had not been reviewed previously.

Study OPI-004 (Study 004) compared the combination of alogliptin 25 mg + pioglitazone 30 mg to pioglitazone 45 mg. Both arms had a background therapy of metformin. This was a non-inferiority evaluation. The treatment period was 52 weeks. The applicant has included a description of Study 004 in Part 14 (Clinical Studies) of the labels of both Nesina and Oseni.

Study SYR-322_303 (Study 303) compared alogliptin 25 mg to glipizide (5 mg, with the option of titrating to 10 mg) in adults 65 to 90 years old. This was a non-inferiority evaluation. The treatment period was 52 weeks. The applicant has included a description Study 303 in Part 8.5 (Geriatric Use) of the Nesina label.

2.1.3 Major Statistical Issues

<u>Study 004</u>: The key statistical review issue in Study 004 is the non-inferiority margin of 0.3%. I believe that this margin is too large. In my opinion, the only reasonable comparison is a

superiority evaluation of alogliptin 25 mg in comparison with pioglitazone 15 mg, on a background therapy of pioglitazone 30 mg and metformin. However, the study results did support the superiority of the alogliptin arm to the pioglitazone arm (

TABLE **9**). For this reason, I believe that the results are interpretable even with my concerns about the non-inferiority margin.

Study 303: The key statistical review issue in Study 303 is the non-inferiority margin of 0.4%. The applicant did not provide a justification for this margin. I believe that the margin is likely to be too large, considering the elderly population in the study, the low dose of glipizide given in the study, and the low average HbA1c at baseline of 7.5. The alogliptin arm was not superior to the glipizide arm with respect to the mean change in HbAc from baseline at week 52 (TABLE 17). The observed results, with an upper confidence bound of 0.13, are consistent with a smaller non-inferiority margin than 0.4. I believe that the decision about whether or not non-inferiority has been demonstrated with an observed upper confidence bound of 0.13 is a review issue. From my statistical perspective, I don't believe that this is a confirmatory finding of non-inferiority, because of the inadequacy of the pre-specified margin and the post-hoc nature of the decision. However, the upper confidence bound may be sufficiently smaller than 0.4, from the clinical perspective, to support a conclusion of non-inferiority.

2.2 Data Sources

Submissions and data that I reviewed for these two NDA submissions are summarized in TABLE 3.

TABLE 3 Data sources for this submission

Number	Date	Description
\\cdesub1\evsprod\NDA 022271/0 Alogliptin		
0048	7/25/11	Response to Division's Complete Response letter
0051	10/5/11	Response to request for information concerning disposition in Studies 004 and 303
0053	10/11/11	Response to request for information concerning glipizide titration in Study 303
\\cdesub1\evsprod\NDA 022426/0 Alogliptin + Pioglitazone FDC		
0030	7/25/11	Response to Division's Complete Response letter

A. Study OPI-004

The primary objective of Study OPI-004 (Study 004) was to evaluate the efficacy of the addition of alogliptin (25 mg) compared to the titration of pioglitazone from 30 mg to 45 mg on HbA1c at week 26 and week 52.

3A. Statistical Evaluation

3.1A Data and Analysis Quality

I do not have review concerns about data and analysis quality in the parts of the submission that I reviewed.

3.2A Evaluation of Efficacy

3.2.1A Study Design and Endpoints

Design: Study 004 was an international, multicenter, randomized, double-blind, two-treatment arm study. The study was conducted in 803 type 2 diabetes subjects who were experiencing inadequate glycemic control on a current regimen of metformin (≥ 1500 mg) plus pioglitazone (30 mg). The time frame for Study 004 was January 30, 2007 to June 5, 2009.

Eligible subjects followed one of two study schedules, according to their background therapy:

Schedule A: Subjects with a screening HbA1c between 7.0% and 10% and a treatment regimen of metformin (≥ 1500 mg) plus pioglitazone (30 mg) completed the screening visit (up to two weeks) followed by a four-week stabilization period (FIGURE 1).

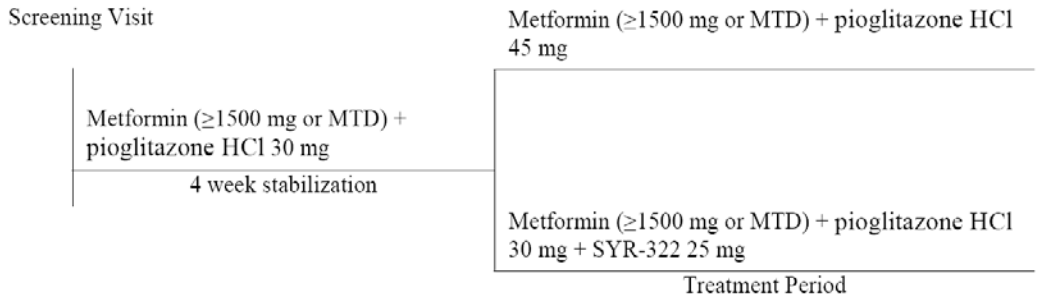
Schedule B: Subjects with a screening HbA1c > 8.0% and a treatment regimen of metformin and another oral antidiabetic agent (i.e., sulfonylureas, rosiglitazone, or pioglitazone 15 mg) entered a pre-screening period of up to two weeks. These subjects were then instructed to discontinue their previous combination therapy and start a regimen consisting of ≥ 1500 mg metformin and pioglitazone 30 mg. The subjects experienced this switch in treatment for 12 weeks, after which they returned for a screening visit to assess their glycemic control. If a subject had an HbA1c between 7.0% and 10.0%, they then entered a 4-week stabilization period (FIGURE 1).

At the conclusion of the stabilization period, subjects were randomized in a 1:1 ratio to either (1) the addition of alogliptin 25 mg, or (2) the titration of pioglitazone from 30 mg to 45 mg. Subjects were then treated for a total of 52 weeks.

FIGURE 1 Study 004: Schematic of the study design

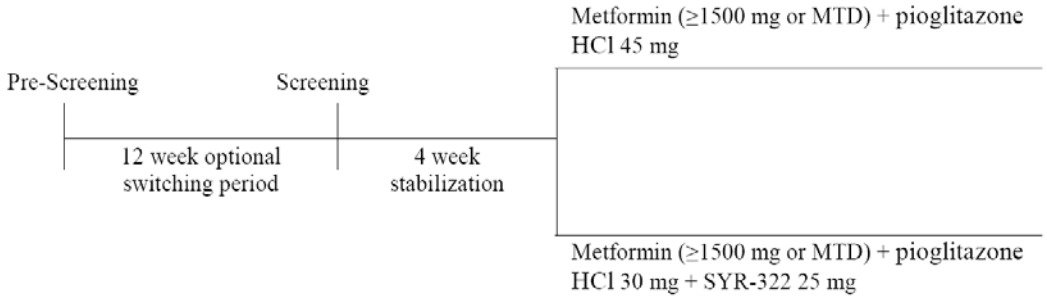
Study Schedule A

Assess-ments	Screening Period	Stabilization Phase				Treatment Period											Follow-Up
Week	-6 to -5	-4	-3	-2	-1	1	2	4	8	12	16	20	26*	34	42	52/ ET	54
Day	-42 to -29	-29	-22	-15	-8	1 (Base-line)	15	29	57	85	113	141	183	239	295	365	379



Study Schedule B

Pre-Screening Period (Up to 2 weeks)	Optional Switching Period 12 weeks	Screening Period (Up to 2 weeks)	Stabilization Phase				Treatment Period											Follow-Up
		-6 to -5	-4	-3	-2	-1	1	2	4	8	12	16	20	26*	34	42	52/ ET	54
	6 week Interim Lab Visit	-42 to -29	-29	-22	-15	-8	1 (Base-line)	15	29	57	85	113	141	183	239	295	365	379



Notes: * 6-month interim evaluation

Source: Study 004 clinical report, Figures 6.a and 6.b

Randomization: The balance of treatment assignments was randomized within the following stratification factors: (1) HbA1c at week -1 (HbA1c < 8.0%, ≥ 8.0%); (2) study schedule (schedule A, schedule B); and (3) region. The stratification regions were named "USA", "WEANZ" (Western Europe, Australia and New Zealand), and "ROW" (Rest of the World). The countries that were included in each stratification region are listed in TABLE 4.

Study sites: As described in the clinical report, Study 004 was conducted in a total of 235 study sites in 16 countries. However, this number is larger than the total that I obtained from summarizing the database. In terms of study sites with unique site IDs that enrolled subjects, I identified 196 sites in 17 countries that enrolled a total of 969 subjects. Of these, 347 subjects were enrolled in 102 sites in the US (TABLE 4). The enrollment refers to the initial 4-week stabilization period. Of the 969 enrolled subjects, 803 were randomized into the treatment period to receive double-blind study medication. The remaining 166 subjects were not randomized. The disposition of subjects from enrollment through to the end of the study is described in more detail in Part 3.2.2A, "Subject disposition, demographic and baseline characteristics."

TABLE 4 Study 004: Stratification region, country, investigative sites and number of subjects enrolled

Stratification Region[1]	Country	Number of investigative sites	Number of subjects enrolled, by country	Total number of subjects enrolled, by stratification region
USA	USA	102	347	347
WEANZ	Australia	6	22	
	Austria	3	12	
	Belgium	2	8	
	Denmark	1	2	
	Finland	5	16	
	France	3	7	
	Germany	2	3	
	Italy	2	6	
	New Zealand	8	28	
	Norway	3	4	
	Spain	4	28	
	UK	9	31	167
ROW	India	10	112	
	Romania	8	89	
	Russia	9	71	
	South Africa	19	183	455
Totals	17	196	969	969

Notes:
[1] "Stratification regions" were groupings of countries that the applicant used to stratify the randomization.
Source: Analysis by this reviewer

Criteria for hyperglycemic rescue: The protocol specified that if subjects met any of the following criteria, they were rescued:

- After more than 2 weeks (14 days) of treatment 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 5 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 5 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 5 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 a ≤ 0.5% reduction in HbA_{1c} as compared with the baseline HbA1c, confirmed by a second sample drawn within 5 days after the first sample and analyzed by the central laboratory.

Subjects who were rescued completed an end of treatment/early termination visit and a follow-up visit. Subjects who met the criteria for rescue were considered to have completed the study at time of rescue. For purposes of calculating the primary and secondary efficacy endpoints, the laboratory values collected at the early termination visit were carried forward to all subsequent visits through week 52.

Statistical power and the size of the study: The applicant calculated the number of subjects to be enrolled in the study with the following assumptions:

- The Per Protocol analysis set, consisting of approximately 75% of the randomized subjects
- Standard deviation of 1.1%
- A non-inferiority margin of 0.3%
- No difference between the treatment arms
- A one-sided α of 0.025 at week 26 and at week 52

Based on these assumptions, the applicant estimated that 760 subjects (380 per treatment arm) would provide at least 90% power to declare non-inferiority in mean change from baseline in HbA1c at either week 26 or week 52, and at least 80% power to declare non-inferiority at both week 26 and week 52.

The key statistical review issue with this calculation is the non-inferiority margin of 0.3%. I believe that this margin is too large. Moreover, I believe that a non-inferiority margin for the incremental effect of adding 15 mg to 30 mg of pioglitazone is probably too small to be evaluated in a study of reasonable size. In my opinion, the only reasonable comparison is a superiority evaluation of alogliptin 25 mg in comparison with pioglitazone 15 mg, on a background therapy of pioglitazone 30 mg and metformin.

The reasons for my opinion are the following:

1. The comparison in Study 004 is between adding 25 mg of alogliptin vs. adding 15 mg of pioglitazone on a background therapy of metformin and 30 mg of pioglitazone. The non-inferiority question is whether the addition of 25 mg of alogliptin is no worse by a pre-specified margin than the addition of 15 mg of pioglitazone to this background therapy. For this reason, we need to have an estimate of the effect of adding 15 mg of pioglitazone to a background therapy 30 mg of pioglitazone + metformin. Ideally, this would come from a study or studies with a comparator arm of placebo + 30 mg of pioglitazone + metformin. We may be able to approximate this effect from two studies of pioglitazone monotherapy that are described in the statistical review of the original submission of pioglitazone (NDA 021073/0). Studies 001 and 012 evaluated both the 30 mg and 45 mg doses of pioglitazone with a placebo comparator arm. By comparing the effect on HbA1c of the 45 mg dose arm with the 30 mg dose arm, we can obtain an approximate estimate of the incremental effect of adding 15 mg of pioglitazone to the 30 mg arm. The results do not support a margin as large as 0.3. The result from Study 001 has an upper 95% confidence limit of -0.1, and the result from Study 012 is not significant (TABLE 5).

2. Patients with a background therapy of metformin + 30 mg pioglitazone may experience a smaller effect of adding 15 mg pioglitazone compared to the results from the monotherapy studies 001 and 012. This prediction is based on the somewhat smaller effect of pioglitazone 30 mg when added to background metformin therapy, as depicted in a summary figure in the statistical review of the original pioglitazone application (FIGURE 2).

3. The higher baseline HbA1c of Studies 001 and 012 (approximately 10.0; TABLE 5) may have supported a larger incremental effect than would be likely to take place in Study 004 with its average baseline HbA1c of 8.2. The relationship between baseline HbA1c and change from baseline has been observed in many anti-diabetic drugs. In general, a higher level of baseline HbA1c is associated with a larger change from baseline.

4. The incremental effect on HbA1c, determined at 6 months in Studies 001 and 012 may decrease over time and be smaller when determined at 12 months in Study 004.

For these reasons, I don't believe that the non-inferiority comparison is meaningful in Study 004. I believe the applicant should have designed and powered Study 004 as a superiority comparison.

TABLE 5 HbA1c change from baseline in pioglitazone 30 mg and pioglitazone 45 mg monotherapy arms; from two clinical studies reported in the Actos™ label

Study 001 (monotherapy)	Placebo (n=79)	Pioglitazone 30 mg (n=85)	Pioglitazone 45 mg (n=76)
Baseline	10.4 ± 0.2	10.2 ± 0.2	10.3 ± 0.2
Week 26			
Mean HbA1c[1] ± SE	0.7 ± 0.2	-0.3 ± 0.2	-0.9 ± 0.2
Difference from placebo (95% CI)		-1.0 (-1.6, -0.4)	-1.6 (-2.2, -1.0)
Difference from pioglitazone 30 mg (approx 95% CI)[2]			-0.6 (-1.1, -0.1)
Study 012 (monotherapy)[3]	**Placebo (n=83)**	**Pioglitazone 7.5/15/30 mg (n=85)**	**Pioglitazone 15/30/45 mg (n=85)**
Baseline	10.8 ± 0.2	10.3 ± 0.2	10.8 ±0.2
Week 24			
Mean HbA1c ± SE	0.9 ± 0.2	-0.5 ± 0.2	-0.6 ± 0.2
Difference from placebo (95% CI)		-1.5 (-2.0, -1.0)	-1.5 (-2.0, -1.0)
Difference from pioglitazone 30 mg (approx 95% CI)			-0.1 (-0.6, 0.5)

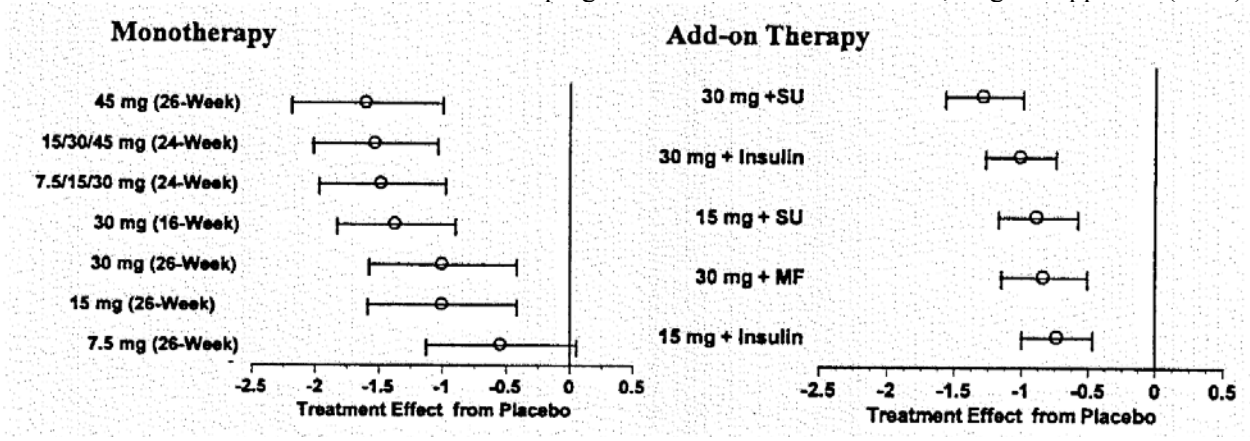
[1] HbA1c expressed as a change from baseline

[2] I calculated an approximate CI from $\overline{X} \pm \left(1.96 \times \sqrt{2} \times \text{the larger of the two SEs}\right)$

[3] Study 012 had two titration steps of four weeks each, and the final dose was given for 16 weeks.

Source: Statistical review of NDA 021073, 6/17/1999 (Pian, L-P), Table 5 and Table 20

FIGURE 2 Placebo-controlled studies of pioglitazone from NDA 021073/0, original approval (1999)



Notes: The graph depicts the least squares means and 95% confidence interval in HbA1c change from baseline. "MF" stands for metformin as background therapy.

Source: Statistical review of NDA 021073, 6/17/1999 (Pian, L-P), Figure 40.

Efficacy endpoints: The primary efficacy endpoint was the change from baseline in HbA1c at week 26 and at week 52. The protocol also identified the following secondary endpoints, to be evaluated at week 26, week 52 and at other intermediate time points during the study: HbA1c levels and categorical endpoints, fasting plasma glucose, proinsulin, insulin, proinsulin/insulin ratio, C-peptide, serum lipids, NMR lipid fractionation, free fatty acids, apolipoproteins and hsCRP, adiponectin, body weight, calculated HOMA insulin resistance and HOMA beta-cell function, incidence of marked hyperglycemia, and incidence of rescue.

3.2.2A Subject Disposition, Demographic and Baseline Characteristics

Disposition: The status of randomized subjects with respect to disposition is subdivided into three categories: completed, rescued for hyperglycemia, and discontinued. The majority of subjects in each arm completed the 52-week study; 70% in the alogliptin arm and 61% in the pioglitazone arm (TABLE 6). Fewer subjects were rescued for hyperglycemia in the alogliptin arm (11%) than in the pioglitazone arm (22%). Most of the hyperglycemic rescues took place from week 12 on (TABLE 6), which was the point at which the criteria for rescue changed from being based on FPG to being based on HbA1c.

Demographic and baseline characteristics are summarized in (TABLE 7).

TABLE 6 Study 004; Disposition of subjects

		Alogliptin 25 mg + Pio 30 mg + metformin	Pio 45 mg + metformin
Entered into stabilization period	N=969		
Randomized	N=803	404	399
Completed		283 (70.0%)	243 (60.9%)
Hyperglycemic rescue		44 (10.9%)	87 (21.8%)
Rescued before week 12		2	11
Rescued up until week 26		24	56
Rescued up until week 52		44	87
Discontinued		77 (19.1%)	69 (17.3%)
Discontinued before week 12		29	21
Discontinued up until week 26		53	50
Discontinued up until week 52		77	69
Primary reason for discontinuation			
Voluntary withdrawal		25 (6.2%)	20 (5.0%)
Major protocol deviation		25 (6.2%)	20 (5.0%)
Adverse Event		13 (3.2%)	16 (4.0%)
Investigator discretion		6 (1.5%)	8 (2.0%)
Lost to follow-up		6 (1.5%)	2 (0.5%)
Other		2 (0.5%)	3 (0.8%)

Source: Study 004 clinical report, Figure 10.a, and additional analysis by this reviewer

TABLE 7 Study 004; Demographic and baseline characteristics

	Alogliptin 25 mg + Pio 30 mg + metformin N=404	Pio 45 mg + metformin N=399	Total N=803
Sex			
Male	210 (52.0%)	204 (51.1%)	414 (51.6%)
Female	194 (48.0%)	195 (48.9%)	243 (55.1%)
Age (yr) [1]			
Mean (SD)	54.3 (9.9)	55.9 (9.9)	55.1 (9.9)
≥ 65 yrs	65 (16.1%)	79 (19.8%)	144 (17.9%)
Race			
White	242 (59.9%)	256 (64.2%)	498 (62.0%)
Asian	79 (19.6%)	78 (19.5%)	157 (19.6%)
Black or African American	41 (10.1%)	36 (9.0%)	77 (9.6%)
American Indian or Alaska Native	2 (0.5%)	0 (0.0%)	2 (0.2%)
Native Hawaiian or other Pacific Islander	2 (0.5%)	0 (0.0%)	2 (0.2%)
Other	38 (9.4%)	29 (7.3%)	67 (8.3%)

	Alogliptin 25 mg + Pio 30 mg + metformin N=404	Pio 45 mg + metformin N=399	Total N=803
Ethnicity			
Hispanic or Latino	30 (7.4%)	31 (7.8%)	61 (7.6%)
Not Hispanic or Latino	374 (92.6%)	368 (92.2%)	742 (92.4%)
Weight (kg)			
Mean (SD)	88.2 (18.9)	88.0 (19.3)	88.1 (19.1)
BMI (kg/m^2)			
Mean (SD)	31.5 (5.2)	31.6 (5.2)	31.6 (5.2)
Diabetes duration, yr			
Mean (SD)	7.5 (5.2)	6.9 (4.6)	7.2 (4.9)
HbA1c, %[1]	n=303	n=306	
Mean (SD)	8.3 (0.8)	8.1 (0.8)	
Baseline daily metformin use (mg)			
Median (range)	1700 (500-3400)	1700 (500-3000)	1700 (500-3400)

Note:
[1] The applicant reported baseline HbA1c values from the full analysis set

Source: Study 004 clinical report, Table 10.b and Table 11.c

3.2.3A Statistical Methodologies

The primary analysis model was an analysis of covariance model with the response variable of change from baseline in HbA1c at week 26 and, in a separate analysis, at week 52. The primary model included treatment arm, study schedule (schedule A or B), and geographic region (three regions: US, Western Europe / Australia / New Zealand, and Rest of the World) as class effects, and baseline metformin dose and baseline HbA1c as continuous covariates. In my opinion, this is a reasonable analysis model and is typical of the models used to evaluate the HbA1c endpoint in clinical studies with this design.

However, I had review concerns about other aspects of the primary efficacy analysis, and these concerns directed my review activities, as follows:

1. Analysis set used in the primary analysis: The applicant used the per protocol set for the primary analysis. However, the Agency recommends using the intention to treat (ITT) set, or a modified version of the ITT analysis set, for the primary analysis. This recommendation is described in the 2008 Diabetes Draft Guidance[3], as well as in the ICH-E9 guidance[4]. For this

[3] *2008 Draft Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Intervention*
[4] *1998 Guidance for Industry: ICH E9 Statistical Principles for Clinical Trials*

reason, I evaluated the analysis of the HbA1c endpoint in the full analysis set, which the applicant also provided as a supportive analysis.

The protocol defined the key analysis sets as follows:

a. Safety Set: All randomized subjects who took at least 1 dose of double-blind study drug.
b. Full analysis set (FAS): All subjects in the safety set. For a particular variable, the FAS analysis consisted of all subjects who have a baseline assessment and at least one post-baseline assessment for that variable.
c. Per protocol set (PPS): All FAS subjects who had no major protocol violations. The list of violations was finalized by the clinical science and biostatistics team as part of the masked final review prior to the interim database lock (for the week 26 analysis). This list was used to identify subjects with major protocol violations prior to the interim analysis and again prior to the final analysis. Subjects who had major protocol violations for the interim analysis were automatically considered as having major protocol violations for the final analysis.

A summary of the number of subjects in each of the key analysis sets, and in the stratification levels used in randomization, is given in (TABLE 8).

TABLE 8 Study 004; Number of subjects by stratification factors and analysis populations

	Alogliptin 25 mg + Pio 30 mg + metformin N=404	Pio 45 mg + metformin N=399	Total N=803
Geographic region			
United States	132 (32.7%)	125 (31.3%)	257 (32.0%)
Western Europe, Australia, New Zealand	72 (17.8%)	72 (18.0%)	144 (17.9%)
Rest of the world	200 (49.5%)	202 (50.6%)	402 (50.1%)
Baseline HbA1c			
< 8.0%	161 (39.9%)	163 (40.9%)	324 (40.3%)
≥ 8.0%	243 (60.1%)	236 (59.1%)	479 (59.7%)
Study Schedule			
A	176 (43.6%)	173 (43.4%)	349 (43.5%)
B	228 (56.4%)	226 (56.6%)	454 (56.5%)
Safety analysis set	404 (100%)	399 (100%)	803 (100%)
Full analysis set	404 (100%)	399 (100%)	803 (100%)
Per protocol analysis set	303 (75.0%)	306 (76.7%)	609 (75.8%)

Source: Study 004 clinical report, Table 10.a

2. The primary imputation method used in the primary analysis. The applicant used the last observation carried forward (LOCF) method to provide analysis values for subjects who did not complete the study or were rescued for hyperglycemia. This method is consistent with recommendations in the 2008 Diabetes Draft Guidance. However, the Office of Biometrics is currently evaluating methods for dealing with endpoints from subjects who discontinue or who receive additional therapies such as rescue therapy in the course of the study. In Study 004, a fairly substantial percentage of subjects either discontinued or were rescued, with twice as many subjects rescued in the pioglitazone arm than in the alogliptin arm (TABLE 6). Endpoints for these subjects come from LOCF imputation. For this reason, as a sensitivity analysis, I evaluated another version of the HbA1c endpoint, the yes/no occurrence of HbA1c < 7.0, for week 26 and also (separately) for week 52. This endpoint was identified by the clinical review team, Dr. Pratt and Dr. Joffe, as of greatest clinical interest from the several that the applicant constructed. I evaluated this endpoint in two ways with respect to classifying subjects who discontinued or who were rescued: (1) using the applicant's method of classifying them based on the last observation prior to discontinuation or rescue; and (2) classifying all discontinued or rescued subjects as non-responders ("HbA1c ≥ 7.0"). I conducted this analysis for week 52.

3. The non-inferiority evaluation of the alogliptin arm to the pioglitazone arm: The applicant used a non-inferiority margin of 0.3. However, as I described earlier in this review, I believe that this margin is too large for the comparison of adding 25 mg of alogliptin vs. adding 15 mg of pioglitazone, with the background therapy of pioglitazone 30 mg + metformin. In my opinion, a hypothetical margin for this comparison might actually be fairly small, may not be clinically important as an effect size, and may be difficult to determine from a clinical study. For this reason, I focused on the superiority evaluation of the alogliptin arm compared to the pioglitazone arm. Because this was a post-hoc decision, the Type I error associated with this evaluation is a review issue.

4. The gate-keeping sequence of tests for the primary efficacy analysis: The applicant constructed a gate-keeping sequence of tests to protect Type I error in the primary analysis. First, the alogliptin arm was evaluated for non-inferiority to the pioglitazone arm with respect to the HbA1c endpoint at week 26. If a conclusion of non-inferiority was supported, then two additional evaluations were conducted: (1) a superiority evaluation at week 26, and (2) a non-inferiority evaluation at week 52. If a conclusion of non-inferiority was supported for week 52, then a superiority evaluation was conducted for week 52. All evaluations were conducted at the 1-sided 0.025 level. This gate-keeping sequence does protect Type I error. However, as a consequence of my opinion that the non-inferiority evaluation was not useful, I focused on the superiority evaluation at week 26, followed by a superiority evaluation at week 52. This was a test sequence that was determined post-hoc, and for this reason, I believe that the protection of Type I error is a review issue.

With regard to secondary efficacy endpoints, the protocol described a large number of secondary endpoints and time periods for their evaluation. The analysis plan did not describe a set of key secondary evaluations, nor did it describe an approach for protecting type I error across these evaluations.

3.2.4A Results and Conclusions

The superiority of alogliptin 25 mg with background therapy of pioglitazone 30 mg + metformin compared to pioglitazone 45 mg with background therapy of metformin after 26 weeks and after 52 weeks of treatment was supported by the results from Study 004 (

TABLE **9**). In my opinion, the results from the pre-specified primary analysis and supportive analyses were sufficient to address the review concerns I had about the pre-specified statistical methodology, and to alleviate concerns about the post-hoc nature of the approach that I recommended. This approach was the following:

1. The analysis set used in the primary analysis should be the FAS, not the PPS: The results for the FAS and the PPS supported the superiority of the alogliptin arm compared to the pioglitazone arm (

TABLE **9**). I confirmed the results from the FAS set for week 26 and week 52. The low p-values associated with the analysis of the primary endpoint, for both the FAS and the PPS, alleviated my concerns about the post-hoc nature of the change in focus on the FAS instead of the PPS.

2. The LOCF imputation method is currently under review by the Office of Biometrics and should be evaluated for each application: Results from the responder endpoint "HbA1c < 7.0 (yes/no)" also supported the superiority of the alogliptin arm compared to the pioglitazone arm (TABLE 11). In addition, an analysis of the week 52 endpoint using the imputation method of classifying subjects who discontinued or were rescued as "non-responders" (HbA1c ≥ 7.0) supported the superiority of the alogliptin arm (TABLE 11). This method resulted in a greater percentage of non-responders compared to the LOCF method, due to the difference in imputation for subjects who discontinued. Subjects who were rescued were classified as non-responders according to both imputation methods (TABLE 10).

3. The non-inferiority evaluation should be replaced by a superiority evaluation: The conclusion of superiority at week 26 and at week 52 in the primary endpoint, along with support from sensitivity analyses, alleviated my concerns about omitting the non-inferiority evaluation.

4. The sequence of tests for the primary efficacy endpoint should omit the non-inferiority gate-keeping steps: The low p-values associated with the superiority evaluation of the primary endpoint alleviated my concerns about the post-hoc nature of the change in gate-keeping sequence which bypassed the non-inferiority evaluation.

The time course of HbA1c through the 52-week period is depicted in FIGURE 7 for the PPS/LOCF population, and for the FAS/LOCF population. We typically prefer to depict the longitudinal course of HbA1c response in the population of completers. However, this study had a fairly high percentage of subjects who experienced hyperglycemic rescue in this study, and this percentage was greater in the alogliptin + pioglitazone arm (11%) than in the pioglitazone arm (22%; TABLE 6). For this reason, the longitudinal profile of completers may not be a useful illustration of the effect of the alogliptin + pioglitazone arm in comparison with the pioglitazone arm. In this situation, the PPS/LOCF and FAS/LOCF populations may be a reasonable enough illustration of the comparison between the two arms. However, I do not believe that a figure of the longitudinal course of HbA1c response should be included in the Nesina label, and I note that the applicant did not include a figure of this type in the proposed label.

The results for fasting plasma glucose also supported the superiority of the alogliptin arm to the pioglitazone arm (TABLE 11). Neither arm appeared to have an appreciable effect on body weight (TABLE 11).

TABLE 9 Study 004; HbA1c change from baseline at week 26 and at week 52

Analysis population Study week Treatment groups	N	Baseline mean (SD)	Adjusted mean change from baseline at endpoint ± SE[1]	Difference in adjusted mean change (95% CI) [1]	P-value
FAS/LOCF; Week 26					
Alogliptin 25 mg + Pioglitazone 30 mg + metformin	397	8.2 (0.9)	-0.85 ±0.04	-0.45 (-0.55, -0.35)	p<0.0001
Pioglitazone 45 mg + metformin	394	8.1 (0.8)	-0.40 ± 0.04		
FAS/LOCF; Week 52					
Alogliptin 25 mg + Pioglitazone 30 mg + metformin		as above	-0.69 ± 0.04	-0.40 (-0.51, -0.29)	p<0.0001
Pioglitazone 45 mg + metformin			-0.29 ± 0.04		

PPS/LOCF; Week 26					
Alogliptin 25 mg + Pioglitazone 30 mg + metformin	303	8.3 (0.8)	-0.89 ± 0.04	-0.47 (-0.59, -0.35)	p<0.0001
Pioglitazone 45 mg + metformin	306	8.1 (0.8)	-0.42 ± 0.04		
PPS/LOCF; Week 52					
Alogliptin 25 mg + Pioglitazone 30 mg + metformin		as above	-0.70 ± 0.05	-0.42 (-0.56, -0.28)	p<0.0001
Pioglitazone 45 mg + metformin			-0.29 ± 0.05		

Note:
[1] The adjusted mean change from baseline at week 26 and the difference in the adjusted mean change were estimated from the primary analysis of covariance model, with treatment, study schedule and geographic region as class variables, and baseline metformin dose and baseline HbA1c as covariates.

Sources: Study 004 clinical report, Table 11.b, Table 15.2.1.1.1a, Table 15.2.1.1.2a, and additional analysis by this reviewer

TABLE 10 Study 004; HbA1c < 7.0% at week 52 by disposition status (discontinued, rescued or completed)

Alogliptin 25 mg + Pioglitazone 30 mg + metformin	Discontinued	Rescued	Completed	Totals
HbA1c ≥ 7.0% at week 52; "non-responders"	48	44	171	
HbA1c < 7.0% at week 52; "responders"	22	0	112	
Totals	70	44	283	397
Pioglitazone 45 mg + metformin				
HbA1c ≥ 7.0% at week 52; "non-responders"	53	86	170	
HbA1c < 7.0% at week 52; "responders"	12	0	73	
Totals	65	86	243	394

Source: Analysis by this reviewer

TABLE 11 Study 004; Results from additional efficacy endpoints (HbA1c < 7%, FPG, and body weight)

1. The proportion of subjects achieving HbA1c < 7% in the FAS[1]

A. At week 26 with LOCF imputation

	n	Proportion with HbA1c < 7%	Alo25+Pio30 vs. Pio45 Adjusted odds ratio	P-value[2]
Alogliptin 25 mg + Pioglitazone 30 mg + metformin	397	158 (39.8%)	2.7 (1.9, 3.9)	< 0.001
Pioglitazone 45 mg + metformin	394	103 (26.1%)		

B. At week 52 with LOCF imputation

Alogliptin 25 mg + Pioglitazone 30 mg + metformin	397	134 (33.8%)	2.4 (1.7, 3.4)	< 0.001
Pioglitazone 45 mg + metformin	394	85 (21.6%)		

C. At week 52 with non-responder ("HbA1c ≥ 7") imputation for subjects who discontinued or were rescued

Alogliptin 25 mg + Pioglitazone 30 mg + metformin	397	112 (28.2%)	2.1 (1.4, 3.0)	< 0.001
Pioglitazone 45 mg + metformin	394	73 (18.5%)		

2. Change from baseline in fasting plasma glucose concentration (mg/dL)

A. At week 26

	n	Baseline mean FPG (SD)	Adjusted mean change from baseline at Week 24 ± SE[3]	Alo25+Pio30 vs. Pio45 Difference in adjusted mean change (95% CI)	P-value
Alogliptin 25 mg + Pioglitazone 30 mg + metformin	399	161.8 (41.8)	-17.1 ± 1.8	-12.2 (-17.2, -7.3)	< 0.001
Pioglitazone 45 mg + metformin	396	162.2 (42.7)	-4.9 ± 1.8		

B. At week 52

Alogliptin 25 mg + Pioglitazone 30 mg + metformin	As above	-14.6 ± 1.9	-10.9 (-16.2, -5.7)	< 0.001
Pioglitazone 45 mg + metformin		-3.7 ± 1.9		

3. Change from baseline in weight (kg)

A. At week 26

	n	Baseline mean FPG (SD)	Adjusted mean change from baseline at Week 24 ± SE[3]	Alo25+Pio30 vs. Pio45 Difference in adjusted mean change (95% CI)	P-value
Alogliptin 25 mg + Pioglitazone 30 mg + metformin	395	87.9 (18.4)	0.7 ± 0.2	-0.2 (-0.7, 0.2)	0.252
Pioglitazone 45 mg + metformin	394	88.5 (19.2)	1.0 ± 0.2		

B. At week 52

Alogliptin 25mg + Pioglitazone 30 mg + metformin	As above	1.1 ± 0.2	-0.5 (-1.0, 0.0)	0.071
Pioglitazone 45 mg + metformin		1.6 ± 9.2		

Notes:

[1] Subjects who did not complete the scheduled week 26 or week 52 visit were assessed based on their response at the time of discontinuation or rescue. The applicant calculated the percentage of subjects with HbA1c < 7.0 on the basis of the total number in the FAS (404 for the alogliptin arm, 399 for the pioglitazone arm). I re-calculated these on the basis of the total number in the FAS who had post-baseline levels of HbA1c. This is the same number as are in the FAS for the primary HbA1c analysis.

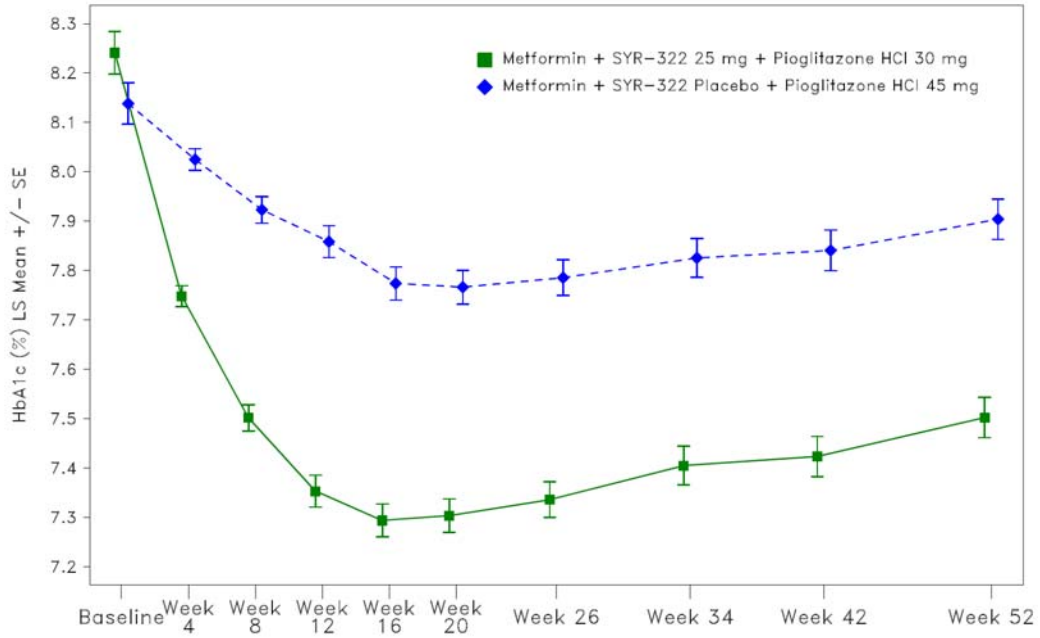
[2] The p-values and corresponding odds ratio and 95% confidence interval were from a logistic regression model with effects for treatment, study schedule, geographic region, baseline metformin dose and baseline HbA1c.

[3] The p-values and adjusted (least squares) means were from an analysis of covariance model with treatment, study schedule and geographic region as class variables, and baseline metformin dose and baseline fasting plasma glucose (for FPG analysis) or baseline weight (for weight analysis) as covariates.

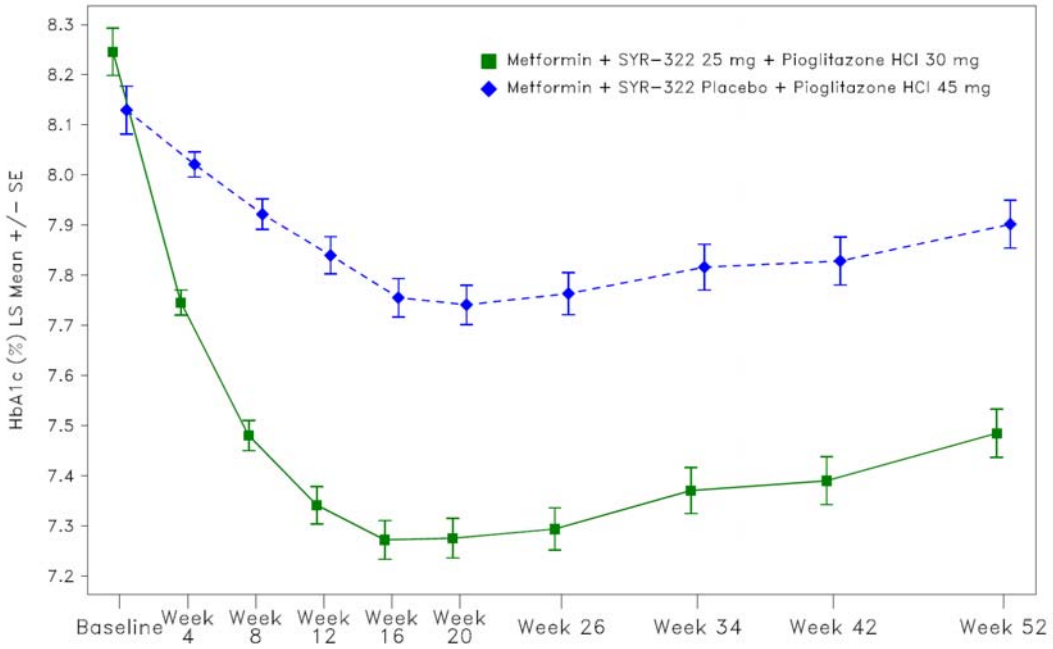
Source: Study 004 clinical report:
1A, B and C: Table 15.2.26, and additional analysis by this reviewer.
2A and B: Table 15.2.2.1
3A and B: Table 15.2.7.1

FIGURE 3 Study 004; Mean HbA1c by clinic visit

A. FAS/LOCF



B. PPS/LOCF



Note: The profile lines connect the LS Mean ± SE for each arm.

Source: Study 004 clinical report, Figure 11.b, Figure 15.2.1.10 and Figure 15.2.1.11

3.3A Evaluation of Safety

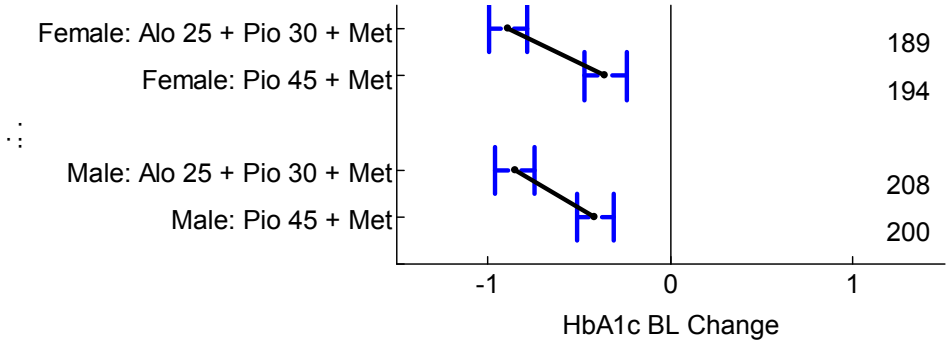
An evaluation of the safety of alogliptin and the alogliptin + pioglitazone combination product is included in the clinical review by Dr. Valerie Pratt. Dr. Eugenio Andraca-Carrera of the Division of Biometrics 7 is conducting a statistical review of cardiovascular safety of alogliptin.

4A. Findings in Gender, Race, Age, and Geographic Region

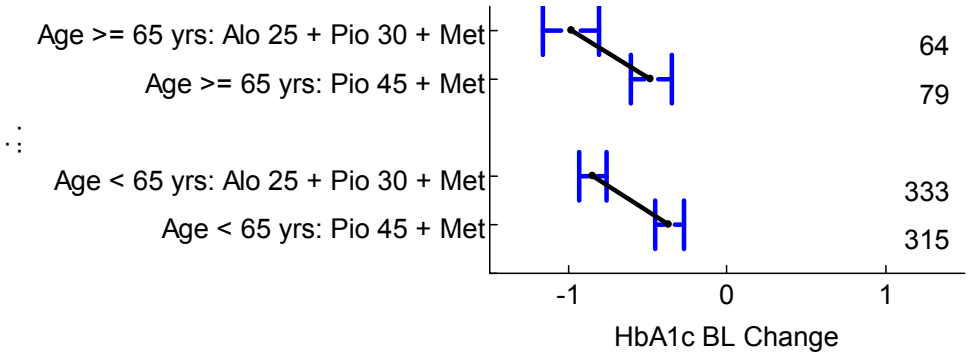
The comparison between the alogliptin and pioglitazone arms did not appear to be appreciably affected by sex, age group (< 65 and ≥ 65 years of age), race (4 subgroups: white, black, Asian and all others), ethnicity (Hispanic / Latino or not Hispanic / Latino), or region (U.S. or outside the U.S.), at week 26 and at week 52 (FIGURE 4, FIGURE 5).

FIGURE 4 Study 004; The effects of subgroups on HbA1c change from baseline at week 26

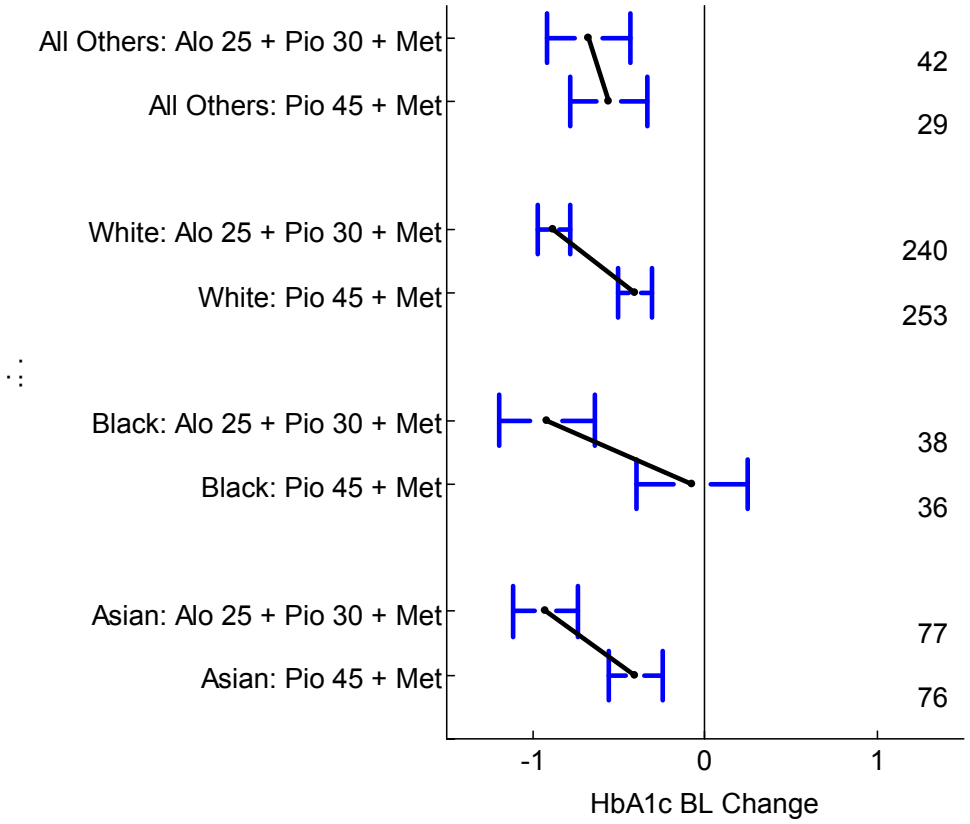
A. Sex; p-value of sex by treatment arm interaction is 0.2205



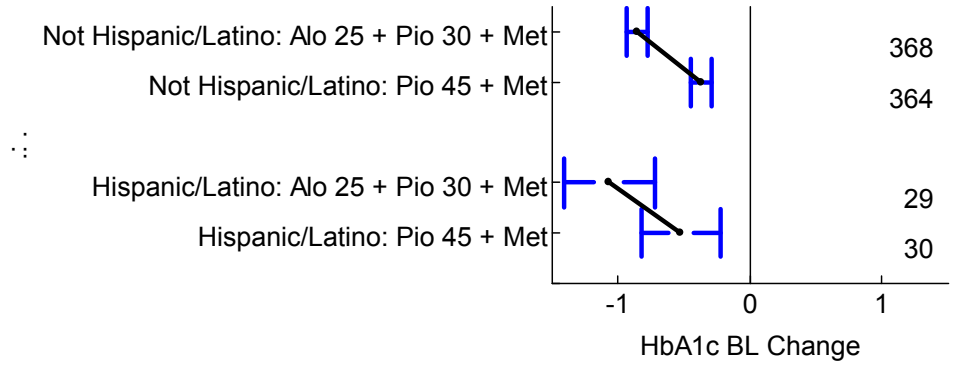
B. Age group; p-value of age group by treatment arm interaction is 0.7062



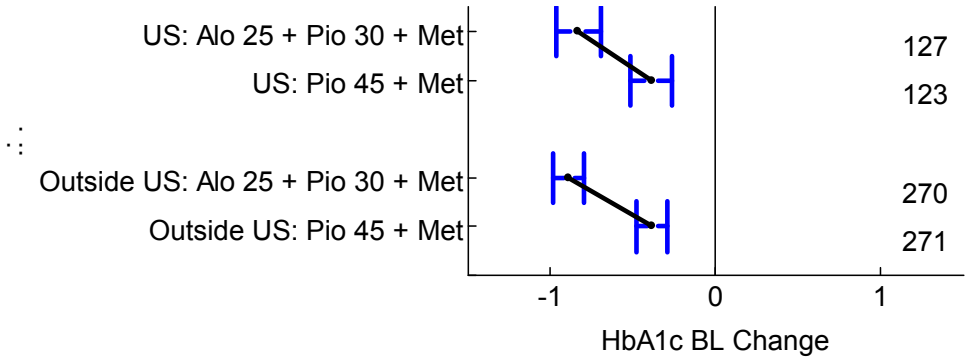
C. Race; p-value of race by treatment arm interaction is 0.1900



D. Ethnicity; p-value of ethnicity by treatment arm interaction is 0.5494



E. Region; p-value of region by treatment arm interaction is 0.5620

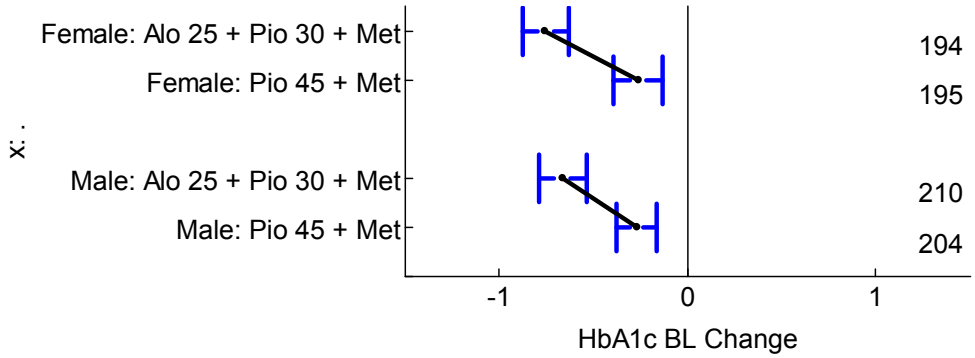


Notes: A separate analysis of covariance model was evaluated for each subgroup. The FAS/LOCF analysis population was used for the analysis. The analysis model was based on the primary analysis model, with fixed effect terms added for the subgroup and the interaction of the subgroup with the treatment arm.

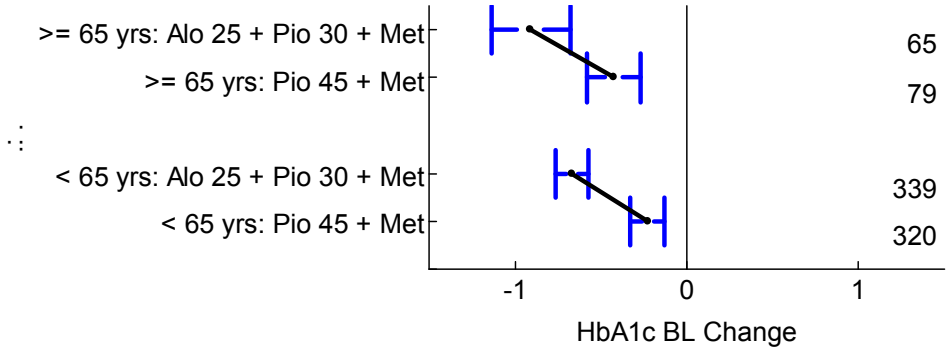
Source: Analysis by this reviewer

FIGURE 5 Study 004; The effects of subgroups on HbA1c change from baseline at week 52

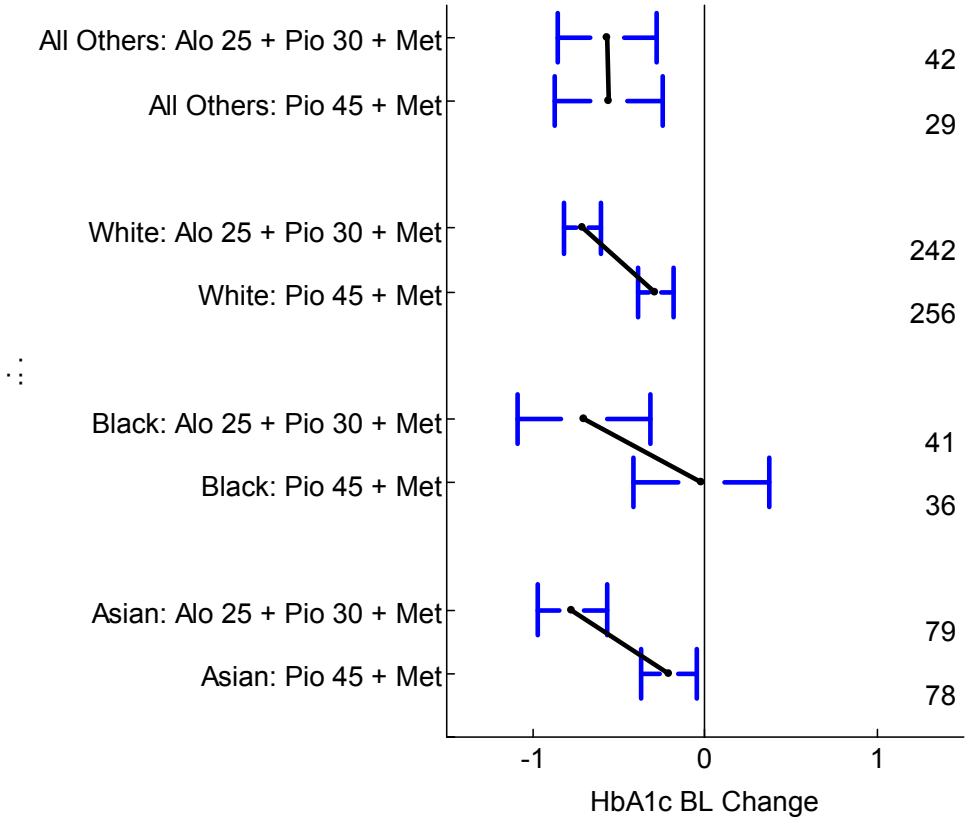
A. Sex; p-value of sex by treatment arm interaction is 0.2555



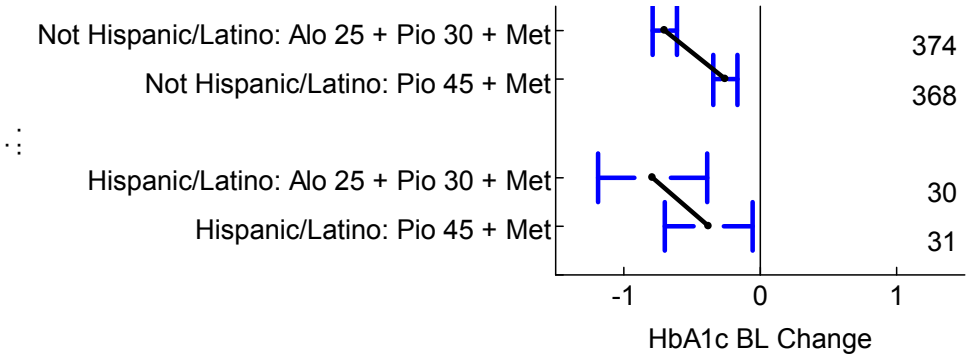
B. Age group; p-value of age group by treatment arm interaction is 0.5579



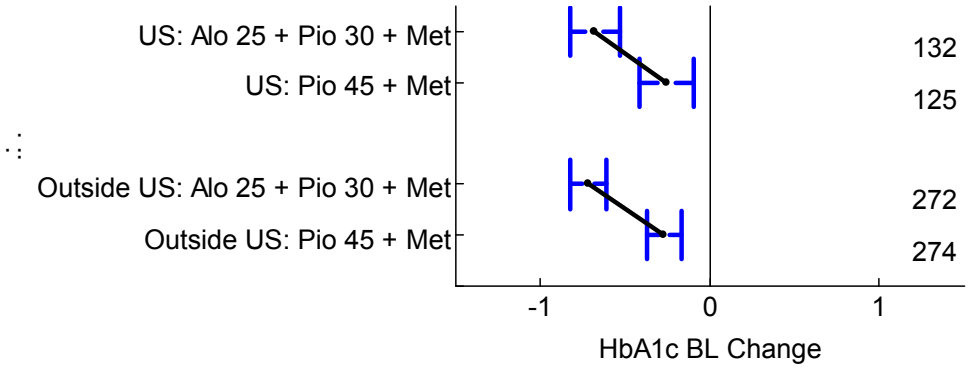
C. Race; p-value of race by treatment arm interaction is 0.7419



D. Ethnicity; p-value of ethnicity by treatment arm interaction is 0.8844



E. Region; p-value of region by treatment arm interaction is 0.8058



Notes: A separate analysis of covariance model was evaluated for each subgroup. The FAS/LOCF analysis population was used for the analysis. The analysis model was based on the primary analysis model, with fixed effect terms added for the subgroup and the interaction of the subgroup with the treatment arm.

Source: Analysis by this reviewer

B. Study SYR-322_303

3B. Statistical Evaluation

3.1B Data and Analysis Quality

I do not have review concerns about data and analysis quality in the parts of the submission that I reviewed.

3.2B Evaluation of Efficacy

The purpose of Study SYR-322_303 (Study 303) was to evaluate the efficacy and safety of alogliptin monotherapy compared to glipizide monotherapy over a 52-week period in an older subject population (aged 65-90 years) with type 2 diabetes.

3.2.1B Study Design and Endpoints

Design: Study 303 was a randomized, double-blind, active-controlled, two treatment arm study of alogliptin (25 mg once daily) versus glipizide (5 mg titrated for inadequate control to 10 mg once daily). Eligible subjects with type 2 diabetes were aged 65 to 90 years, who during the two months prior to screening had either failed diet and exercise therapy alone (defined as HbA1c 6.5% - 9.0%; "Schedule A"), or had been receiving oral antidiabetic monotherapy, yet their

diabetes remained inadequately controlled (defined as HbA1c 6.5% - 8.0%, "Schedule B"). Study 303 was conducted from June 25, 2008 to August 30, 2010.

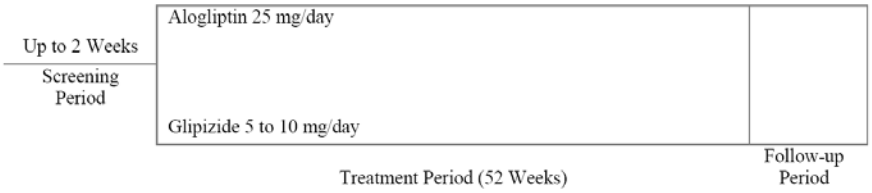
Subjects following Schedule A had a screening period of up to two weeks, a treatment period of 52 weeks, followed by a week 52 visit (or early termination visit) and a follow-up visit two weeks after the week 52 visit (FIGURE 6).

Subjects following Schedule B had a screening period of up to two weeks and a washout period of 4 weeks. During the washout period, subjects stopped taking their antidiabetic medication. They visited the study center at weeks -4, -3 and -1 for assessments and procedures that are described in more detail in the study protocol. After the washout period, subjects were eligible for randomization if their HbA1c concentration was between 6.5% and 9.0%. Randomization took place on Day 1, after which the study schedule was the same as was described for Schedule A (FIGURE 6).

FIGURE 6 Study 303: Schematic of the study design

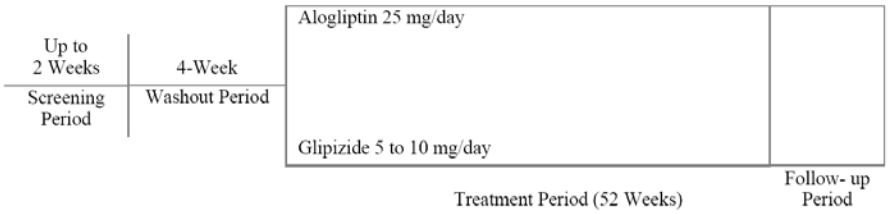
Schedule A subjects

Assessments	Screening Period (Up to 2 weeks)	Treatment Period (Day 1 through Week 52 after Randomization)											Follow-up Period
Week	-2 to 0	Baseline Visit (Day 1)	2	4	8	12	16	20	26	34	42	52 (or ET)	54 (or 2 weeks after ET visit)



Schedule B subjects

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



ET=early termination.

Source: Study 303 clinical report, Figures 9.a and 9.b

Randomization: At randomization (Day 1), eligible subjects were randomly assigned in a 1:1 ratio to alogliptin 25 mg or glipizide 5 mg. The balance of randomized treatment assignments was managed within the following stratification factors: (1) HbA1c at week -1 (HbA1c < 8.0%, ≥ 8.0%); (2) study schedule (Schedule A, Schedule B); and (3) geographic region (USA, Europe/Rest of the World, and Latin America (TABLE 4).

Study sites: A total of 438 subjects were randomized in 79 study sites in 11 countries worldwide (TABLE 4). Of these, 126 were in 32 study sites in the USA.

TABLE 12 Study 303: Stratification region, country, investigative sites and number of subjects randomized

Stratification Region[1]	Country	Number of investigative sites	Number of subjects enrolled, by country	Total number of subjects enrolled, by stratification region
USA	USA	32	126	126
Europe, Rest of World	Hungary	3	29	200
	Israel	5	39	
	India	4	35	
	Poland	3	6	
	Romania	6	36	
	Russia	3	9	
	Ukraine	2	6	
	Zambia	5	40	
Latin America	Mexico	10	55	112
	Peru	6	57	
Totals		79	438	438

Notes:
[1] "Stratification regions" were groupings of countries that the applicant used to stratify the randomization.
Source: Analysis by this reviewer

Criteria for study medication dose titration and hyperglycemic rescue: Doses of glipizide (or matching placebo) were increased from 5 to 10 mg for subjects with fasting plasma glucose (FPG) ≥ 250 mg/dL after at least one week of treatment and prior to week 12. Any subject who continued to experience hyperglycemia following this dose titration was rescued per the following criteria:

- At least 1 week post-titration and before week 12: Subjects whose glipizide (or matching placebo) doses were titrated up to 10 mg, yet their FPG was still ≥ 250 mg/dL, confirmed by a repeat test within 7 days after the first sample (both analyzed by the central laboratory).

- Following week 12 through week 52: Subjects whose HbA1c was ≥ 8.0, confirmed by a second sample drawn within 7 days after the first sample (both analyzed by the central laboratory).

All rescued subjects underwent the assessments scheduled for the early termination visit and the follow-up visit. The reason for withdrawal was documented as hyperglycemic rescue (lack of efficacy).

Statistical power and the size of the study: The applicant determined that 430 subjects (215 per treatment arm) would provide at least 90% power for a non-inferiority evaluation at week 52 between the alogliptin 25 mg arm and the glipizide arm, based on the following assumptions:

- A standard deviation of 1.1% of the HbA1c endpoint (change from baseline at week 52)
- A non-inferiority margin of 0.4%
- No difference between the treatment arms
- Use of the per protocol set and an evaluability rate of 75% (i.e., the percentage of randomized subjects who are included in the per protocol set)
- A one-sided α of 0.025

The key assumption is the non-inferiority margin of 0.4%. The applicant did not provide a justification for this margin. I believe that the margin is likely to be too large, considering the elderly population in the study, the low dose of glipizide given in the study, and the low average HbA1c at baseline of 7.5. However, information concerning an appropriate margin is indirect and not definitive, as summarized below:

1. *Information that supports a non-inferiority margin of 0.4*: This perspective is supported by the following considerations:

    a. A margin of 0.4 may be supported by placebo-controlled studies of sulfonylurea drugs. The Glucotrol™ (glipizide) label does not provide a summary of clinical study results. However, it may be reasonable to extend the results of placebo-controlled studies of Amaryl™ (glimepiride), another sulfonylurea drug, to the non-inferiority margin of glipizide. A meta-analysis of three placebo-controlled studies of glimepiride produced an estimated effect size of -1.6 with 95% confidence interval of (-1.9, -1.3), referring to HbA1c change from baseline[5].

    b. The 2008 Draft Diabetes Guidance states: "Typically, we accept a noninferiority margin of 0.3 or 0.4 HbA1c percentage units provided this is no greater than a suitably conservative estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled trials."

[5] The results of the meta-analysis of glimepiride are not described further in this review but are available on request.

2. *Information that supports a smaller non-inferiority margin than 0.4*: This perspective is supported by the following considerations:

   a. The low dose of glipizide used in Study 303, 5 to 10 mg, may result in a smaller change from baseline in HbA1c compared to the full dose range of 5-40 mg. The Glucotrol (glipizide) label advises caution in selecting a dose for an elderly patient. The selection of a dose should begin at the low end of the dose range (TABLE 13). The Glucotrol label also notes that the effect of glipizide in elderly patients has not been fully characterized (TABLE 13). In addition to the effect of the lower dose, the older age may also contribute to a smaller effect of glipizide on HbA1c.

   b. The low average baseline HbA1c of 7.5 in Study 303 may also contribute to a lower HbA1c response compared to the placebo-controlled studies of glimepiride. The average or median baseline HbA1c reported in these studies ranged from 7.7 to 9.0. The relationship between baseline HbA1c and change from baseline has been observed in many anti-diabetic drugs. In general, a lower level of baseline HbA1c is associated with a smaller change from baseline.

TABLE 13 Glucotrol™ label, excerpts pertaining to geriatric use (glipizide; approved in 1984)

Geriatric Use: A determination has not been made whether controlled clinical studies of GLUCOTROL included sufficient numbers of subjects aged 65 and over to define a difference in response from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

…

DOSAGE and ADMINISTRATION

…

Initial Dose: The recommended starting dose is 5 mg, given before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg.

Titration: Dosage adjustments should ordinarily be in increments of 2.5–5 mg, as determined by blood glucose response. At least several days should elapse between titration steps. If response to a single dose is not satisfactory, dividing that dose may prove effective. The maximum recommended once daily dose is 15 mg. Doses above 15 mg should ordinarily be divided and given before meals of adequate caloric content. The maximum recommended total daily dose is 40 mg.

Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15

> mg should ordinarily be divided. Total daily doses above 30 mg have been safely given on a b.i.d. basis to long-term patients. In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions (see **PRECAUTIONS** section).

Considering the issues surrounding the non-inferiority margin, I believe that the most interpretable conclusion from this study is either superiority or inferiority. This conclusion refers to the difference between the alogliptin arm and the glipizide arm in the average HbA1c change from baseline at week 52, and the associated 95% confidence interval of this difference. If the study results are in the range of non-inferiority, with an upper 95% confidence bound within the interval of ≥ 0.0 but ≤ 0.4, then I believe that the conclusion of non-inferiority is a review issue.

Efficacy endpoints: The primary efficacy endpoint was the change from baseline of HbA1c at week 52. Missing values were imputed using last observation carried forward (LOCF). The study protocol also lists 15 secondary endpoints, most of which were evaluated at multiple time points. The protocol does not describe a plan for protecting type I error in a subset of key secondary endpoints.

3.2.2B. Subject Disposition, Demographic and Baseline Characteristics

Disposition: The status of randomized subjects with respect to disposition is subdivided into three categories: completed, rescued for hyperglycemia, and discontinued. Approximately 60% of subjects in each arm completed the 52-week study (TABLE 14). The remaining 40% were either were rescued due to hyperglycemia or else discontinued for other reasons. In the alogliptin arm, a greater percentage (25%) were rescued for hyperglycemia than were discontinued for other reasons (15%), compared to the glipizide arm, where 22% were rescued for hyperglycemia and 22% were discontinued for other reasons (TABLE 14). The two classifications, “hyperglycemic rescue” and “discontinued” were mutually exclusive groups.

The dynamics of disposition were affected by the protocol for up-titration of glipizide and the criteria for hyperglycemic rescue. These both changed at week 12: Prior to week 12, glipizide (or placebo) could be up-titrated from 5 mg to 10 mg. Also prior to week 12, subjects could be rescued for hyperglycemia, after up-titration of the glipizide dose, if FPG were ≥ 250 mg/dl. Few subjects experienced hyperglycemic rescue in either arm prior to week 12 (TABLE 14). From week 12 on, subjects could no longer have an up-titration of the glipizide dose, and the criterion for hyperglycemic rescue changed to HbA1c ≥ 8.0. Most of the hyperglycemic rescues took place from week 12 on, and the percentage of rescues was fairly similar in each arm (TABLE 14). The percentage of subjects who discontinued for other reasons was fairly similar before and after week 12 in both arms.

Because of the interplay between the up-titration of the glipizide dose and hyperglycemic rescue, the Division requested an additional summary of the number of subjects who experienced

different combinations of these outcomes. The two arms had a fairly similar distribution of subjects across the key combinations of up-titration and hyperglycemic rescue (TABLE 15):

- The majority in each arm, approximately 70%, did not experience either up-titration or rescue for hyperglycemia (158/219 in the glipizide arm and 156/222 in the alogliptin arm).
- Approximately 20% of the subjects in each arm who were not up-titrated were subsequently rescued (40/198 in the glipizide arm and 47/203 in the alogliptin arm).
- A small number of subjects in each arm, approximately 10%, experienced up-titration. Of these, about half did not require rescue for hyperglycemia: (10/21 in the glipizide arm and 11/19 in the alogliptin arm).
- Only 6 subjects experienced a down-titration, of which 4 were in the alogliptin arm (and therefore the down-titration was of the placebo dose).

Demographic and baseline characteristics: Eligible subjects were between 65 and 90 years of age in Study 303, and the majority in the study were between 65 and 75 years old (TABLE 16). The eligible range of HbA1c was 6.5 to 9.0%, while receiving no antidiabetic treatment within 2 months prior to screening (Schedule A), or 6.5% to 8.0% within 2 months prior to screening for subjects on oral monotherapy alone (Schedule B). The average baseline HbA1c of 7.5% reflects these eligibility criteria (TABLE 16).

TABLE 14 Study 303; Disposition of subjects

		Alogliptin	Glipizide
Screened	N=957[1]		
Randomized	N=441	222	219
Completed (without hyperglycemic rescue)		133 (59.9%)	125 (57.1%)
Hyperglycemic rescue		55 (24.8%)	47 (21.5%)
Rescued before week 12		4 (1.8%)	1 (0.5%)
Rescued from week 12 on		51 (23.0%)	46 (21.0%)
Discontinued		34 (15.3%)	47 (21.5%)
Discontinued before week 12		14 (6.3%)	23 (10.5%)
Discontinued from week 12 on		20 (9.0%)	24 (11.0%)
Primary reason for discontinuation			
Adverse Event		16 (7.2%)	20 (9.1%)
Voluntary withdrawal		12 (5.4%)	16 (7.3%)
Major protocol deviation		4 (1.8%)	7 (3.2%)
Lost to follow-up		0 (0.0%)	4 (1.8%)
Other		2 (0.9%)	0 (0.0%)

Note:
[1] Of the 519 subjects who were not randomized, 9 subjects entered the study through Schedule B but did not meet the additional entry criteria following the washout period

Source: Study 303 clinical report, Figure 10.a, and additional analysis by this reviewer

TABLE 15 Study 303; Titration of glipizide (and placebo), hyperglycemic rescue, and completion of study

	Ran-dom-ized	Up titra-tion (Y/N)	Down titra-tion (Y/N)	Res-cue (Y/N)	Com-pleted (Y/N)
A. Glipizide arm (+ alogliptin placebo)	219				
1. Not uptitrated		N:198			
i. Not rescued				N:158	
- Completed the study					Y:114
- Discontinued the study					N: 44
ii. Rescued				Y: 40	
2. Uptitrated to glipizide 10 mg (in weeks 1-12)		Y: 21			
a. Not downtitrated			N: 19		
i. Not rescued				N: 12	
- Completed the study					Y: 10
- Discontinued the study					N: 2
ii. Rescued				Y: 7	
b. Downtitrated (any time from the uptitration week through week 52)			Y: 2		
i. Not rescued				N: 2	
- Completed the study					Y: 1
- Discontinued the study					N: 1
ii. Rescued				Y: 0	
B. Alogliptin arm (+ glipizide placebo)	222				
1. Not uptitrated		N:203			
i. Not rescued				N:156	
- Completed the study					Y:126
- Discontinued the study					N: 30
ii. Rescued				Y: 47	
2. Uptitrated to glipizide placebo 10 mg (in weeks 1-12)		Y: 19			
a. Not downtitrated			N: 15		
i. Not rescued				N: 9	
- Completed the study					Y: 6
- Discontinued the study					N: 3
ii. Rescued				Y: 6	
b. Downtitrated (any time from the uptitration week through week 52)			Y: 4		
i. Not rescued				N: 2	
- Completed the study					Y: 1
- Discontinued the study					N: 1
ii. Rescued				Y: 2	

Source: Submission 0053 by applicant to NDA 022271, 10/11/21

TABLE 16 Study 303; Demographic and baseline characteristics

	Alogliptin N=222	Glipizide N=219	Total N=441
Sex			
Male	102 (45.9%)	96 (43.8%)	198 (44.9%)
Female	120 (54.1%)	123 (56.2%)	243 (55.1%)
Age (yr) [1]			
Mean ± SD	70.1 ± 4.4	69.8 ± 4.1	69.9 ± 4.2
≥ 75 yrs	36 (16.2%)	26 (11.9%)	62 (14.1%)
Race			
White	169 (76.1%)	154 (70.3%)	323 (73.2%)
Asian	19 (8.6%)	26 (11.9%)	45 (10.2%)
Black or African American	16 (7.2%)	20 (9.1%)	36 (8.2%)
American Indian or Alaska Native	12 (5.4%)	13 (5.9%)	25 (5.7%)
Multiracial	6 (2.7%)	6 (2.7%)	12 (2.7%)
Ethnicity			
Hispanic or Latino	79 (35.6%)	70 (32.0%)	149 (33.8%)
Not Hispanic or Latino	143 (64.4%)	149 (68.0%)	292 (66.2%)
Weight (km)			
Mean ± SD	78.6 ± 14.8	78.8 ± 15.2	78.7 ± 15.0
BMI (kg/m^2)			
Mean ± SD	29.6 ± 4.3	30.0 ± 4.5	29.8 ±4.4
Diabetes duration, yr			
Mean ± SD	6.3 ± 6.3	5.9 ± 6.3	6.1 ± 6.3
HbA1c, % [2]	n=215	n=214	
Mean ± SD	7.5 ± 0.7	7.5 ± 0.6	

Note:
[1] All subjects enrolled in Study 303 were 65 years or older (the enrollment range was 65 to 90 years of age)
[2] The applicant reported baseline HbA1c values from the full analysis set

Source: Study 303 clinical report, Table 10.b

3.2.3B Statistical Methodologies

The primary analysis model was an analysis of covariance model with change from baseline in HbA1c at week 52 as the response variable. The primary model included treatment arm, study schedule (schedule A or B), and geographic region (three regions: US, Europe + Rest of the World, and Latin America) as class effects, and baseline HbA1c as a continuous covariate. In my opinion, this is a reasonable analysis model and is typical of the models used to evaluate the HbA1c endpoint in clinical studies with this design.

However, I had review concerns about certain aspects of the primary efficacy analysis. These are summarized below:

1. The analysis set used in the primary analysis: The applicant defined the Full Analysis Set (FAS) as all randomized subjects who took at least one dose of double-blind study medication. The Per Protocol Set (PPS) included all FAS subjects who had no major protocol violations. The applicant designated the PPS as the analysis set for the primary analysis of the change from baseline in HbA1c at week 52. However, we typically recommend using the FAS population for the primary analysis.

2. The primary imputation method used in the primary analysis. The applicant used the last observation carried forward (LOCF) method to provide analysis values for subjects who did not complete the study or were rescued for hyperglycemia. This imputation method was applied to the FAS and the PPS, and was used in the primary efficacy analysis. This method is consistent with recommendations in the 2008 Diabetes Draft Guidance, as I have discussed in the review of Study 004. To gain additional perspective on the primary results, I also evaluated the percentage of subjects who met the clinical endpoint of HbA1c ≤ 7.0% at week 52.

3. The non-inferiority evaluation of the alogliptin arm to the pioglitazone arm: The applicant used a non-inferiority margin of 0.4. However, as I described earlier in this review, I believe that this margin is too large for the comparison of alogliptin 25 mg to glipizide 5 to 10 mg in this population of elderly subjects. For this reason, I focused on the superiority evaluation of the alogliptin arm compared to the glipizide arm. Because this was a post-hoc decision, the Type I error associated with this evaluation is a review issue.

4. The gate-keeping sequence of tests for the primary efficacy analysis: The applicant tested for superiority of the alogliptin arm compared to the glipizide arm, conditional on a conclusion of non-inferiority, with respect to the change in HbA1c from baseline at week 52. Because I did not agree with the non-inferiority margin, I believe that the gate-keeping sequence is not operable in this study.

3.2.4B Results and Conclusions

The alogliptin 25 mg arm of Study 303 resulted in a fairly similar change from baseline in HbA1c at week 52 as the glipizide 5 to 10 mg arm (TABLE 17). Neither arm had a very large average change from baseline at week 52. The net change in HbA1c at week 52 compared to baseline was in the direction of improvement, but the magnitude of improvement was greatest in weeks 12 and 16 (FIGURE 7). The longitudinal time course of average HbA1c showed a similar pattern in both arms.

The alogliptin arm was not superior to the glipizide arm with respect to the mean change in HbAc from baseline at week 52 (TABLE 17). The observed results, with an upper confidence bound of 0.13, were in the range that may support a conclusion of non-inferiority, ≥ 0.0 and ≤ 0.4. The decision about whether or not non-inferiority has been demonstrated with an observed upper confidence bound of 0.13 is a review issue. From my statistical perspective, I don't

believe that this is a confirmatory finding of non-inferiority, because of the inadequacy of the pre-specified margin and the post-hoc nature of the decision. However, the upper confidence bound may be sufficiently small, relative to the pre-specified margin of 0.4, to support a conclusion of non-inferiority from the clinical perspective. Part 5.3 of this review includes my recommendations regarding the applicant's proposed summary of Study 303 in Part 8.5 (Geriatric Use) of the Nesina label.

TABLE 17 Study 303; HbA1c change from baseline at week 52

Analysis population Study week Treatment groups	N	Baseline mean (SD)	Adjusted mean change from baseline at endpoint ± SE[1]	Difference in adjusted mean change (95% CI) [1]	P-value
1. HbA1c change from baseline at week 52					
A. FAS/LOCF					
Alogliptin	215	7.5 (0.7)	-0.13 ±0.06	-0.02 (-0.17, 0.13)	0.586
Glipizide	214	7.5 (0.6)	-0.11 ± 0.06		
B. PPS/LOCF					
Alogliptin	180	7.5 (0.7)	-0.14 ± 0.06	-0.05 (-0.23, 0.13)	0.794
Glipizide	162	7.5 (0.6)	-0.09 ± 0.07		
2. HbA1c ≤ 7.0; Week 52; FAS/LOCF					
		n (%)		Odds Ratio[2] (95% CI)	
Alogliptin	222	105 (48.8%)		1.19 (0.63, 2.25)	0.593
Glipizide	219	97 (45.3%)			

Notes:

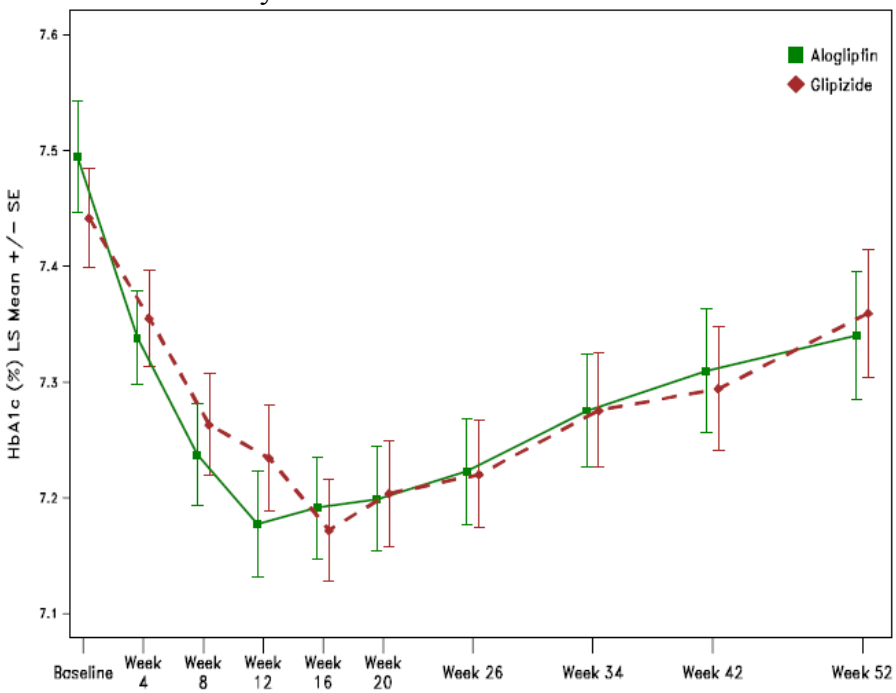
[1] The adjusted mean change from baseline at week 26 and the difference in the adjusted mean change were estimated from the primary analysis of covariance model, with treatment, study schedule and geographic region as class variables, and baseline HbA1c as a covariate.

[2] The logistic regression model included effects for treatment, geographic region, study schedule and baseline HbA1c.

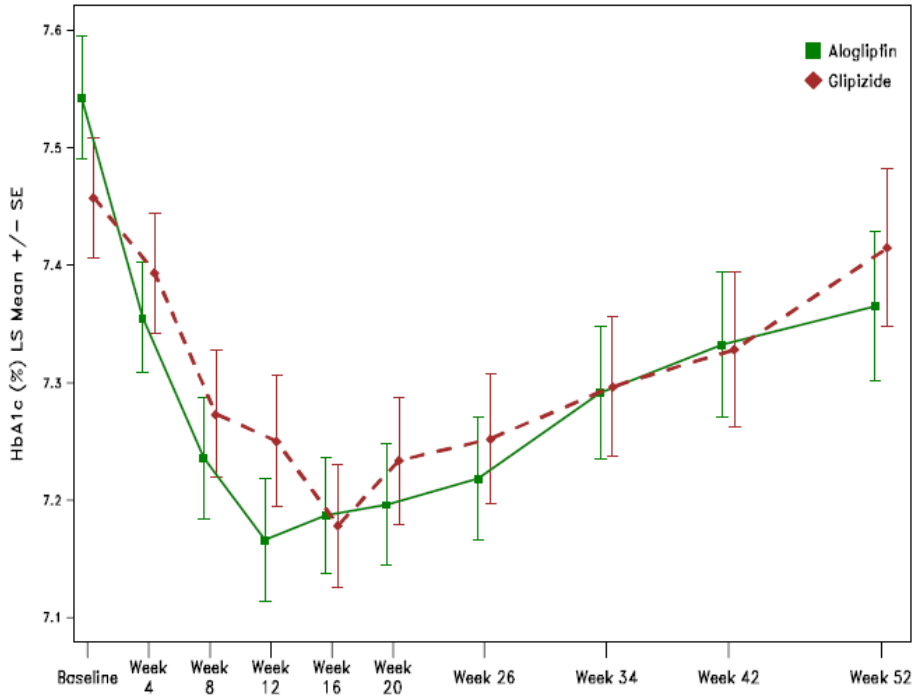
Sources: Study 303 clinical report; Table 11.b, Table 11 hand additional analysis by this reviewer

FIGURE 7 Study 303; HbA1c by study week

A. FAS/LOCF analysis set



B. PPS/LOCF analysis set



Source: Study 303 clinical report, Figure 15.2.1.10 and Figure 15.2.1.11

3.3B Evaluation of Safety

An evaluation of the safety endpoints from Study 303 is included in the clinical review by Dr. Valerie Pratt.

4B. Findings in Special / Subgroup Populations

I did not evaluate the results from this study further by subgroup. If an evaluation by subgroups is needed for purposes of summarizing results about subgroups in the label for Nesina™, this will be included in an addendum to this review.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

An important statistical issue in this review was the non-inferiority margin in Study 004 and in Study 303. The margin was not justified in either study, and I believe that both margins were too large. This issue led to post-hoc review decisions about the primary efficacy evaluation in each study. The outcome of these review decisions is not likely to affect regulatory decisions about Nesina and Oseni. However, I am also concerned that these studies may serve as precedents for future studies that may play a more pivotal role in a regulatory decision. A study with a poorly designed non-inferiority margin may produce uninterpretable results. For this reason, I believe that an adequate and well-controlled study has an appropriate and justified non-inferiority margin, when the design calls for an active control arm with a non-inferiority comparison.

5.2 Conclusions and Recommendations

Study 004: The superiority of alogliptin 25 mg with background therapy of pioglitazone 30 mg + metformin compared to pioglitazone 45 mg with background therapy of metformin after 26 weeks and after 52 weeks of treatment was supported by the results from Study 004. In my opinion, the results from the pre-specified primary analysis and supportive analyses were sufficient to address the review concerns I had about the pre-specified statistical methodology, and to alleviate concerns about the post-hoc nature of the approach that I recommended.

Study 303: The alogliptin 25 mg arm of Study 303 resulted in a fairly similar change from baseline in HbA1c at week 52 as the glipizide 5 to 10 mg arm. Neither arm had a very large average change from baseline at week 52. The observed results, with an upper confidence bound of 0.13, are consistent with a non-inferiority margin that is smaller than 0.4. The decision about whether or not non-inferiority has been demonstrated with an observed upper confidence bound of 0.13 is a review issue. From my statistical perspective, I don't believe that this is a confirmatory finding of non-inferiority, because of the inadequacy of the pre-specified margin

and the post-hoc nature of the decision. However, the upper confidence bound may be sufficiently small, from the clinical perspective, to support a conclusion of non-inferiority.

5.3 Recommendations for the Label

This portion of this review includes recommendations for two labels, the one for use with Nesina (alogliptin; NDA 022271) and the one for use with Oseni (alogliptin + pioglitazone combination; NDA 022426). These recommendations are summarized in TABLE 18.

TABLE 18 Recommendations for label summary of Study 303 (Nesina label, Part 8.5; Geriatric Use) and Study 004 (Nesina and Oseni labels, Part 14; Clinical Studies)

Proposed Label Summary	Statistical Review Comments
8.5 Geriatric Use [Proposed for the Nesina label]	
Of the total number of patients (b) (4) in clinical safety and efficacy studies treated with NESINA (b) (4) patients were 65 years and older and (b) (4) patients were 75 years and older. No overall differences in safety or effectiveness were observed between patients 65 years and over and younger patients. While this (b) (4) not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be (b) (4)	No statistical review comments
(b) (4)	1. (b) (4) 2. (b) (4) I suggest that the study results be summarized more descriptively, (b) (4)
14 CLINICAL STUDIES [Proposed for the Nesina label and the Oseni label]	

Proposed Label Summary	Statistical Review Comments
14.2 Combination Therapy	
[redacted] (b) (4)	No statistical review comments
Add-on Combination Therapy with Pioglitazone and Metformin 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 were randomized to either receive the addition of NESINA 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 (mean dose = (b) (4) mg).	In the Oseni (alogliptin + pioglitazone FDC) label, the mean baseline A1c is reported as 8.1% and the mean dose of metformin is (b) (4) mg. The summary statistics should be the same for both labels.
In combination with pioglitazone and metformin, NESINA 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 (Table 9).	First sentence: replace final phrase with "at week 26 and at week 52 (Table 9)." Second sentence: Omit.
(b) (4) [redacted]	Third sentence: Replace with (b) (4) [redacted]

Proposed Label Summary	Statistical Review Comments
(b) (4) [redacted]	First sentence: No changes Second and third sentence: Replace with (b) (4) [redacted] First sentence: Replace with (b) (4) [redacted] Second sentence: No changes

Proposed Label Summary	Statistical Review Comments

Table 9. Glycemic Parameters in a 52-Week, Controlled Study of NESINA as Add-On Combination Therapy With Pioglitazone and Metformin

(b) (4)

[redacted]

Statistical Review Comments for Table 9:

For A1C and FPG: Report the results from the intent-to-treat population using last observation on study, and note this in the first footnote. The fourth footnote can be omitted and the same symbol used to reference all three endpoints shown in the table.

For A1C and FPG change from baseline: The difference from placebo (adjusted mean) should also show the 95% confidence interval.

For % of patients achieving A1C < 7%: Omit the symbols related to statistical significance.

Final footnote: Replace with "p<0.001 compared to pioglitazone 45 mg + metformin"

CHECK LIST

Number of Pivotal Studies:

Trial Specification

Protocol Number (s):	OPI-004	303
Phase:	Phase 3	Phase 3
Control:	active control	active control
Blinding:	double-blind	double-blind
Number of Centers:		78 sites
Region(s) (Country):		USA, Hungary, Israel, India, Poland, Romania, Russia, Ukraine, Zambia, Mexico, Peru
Duration:	52 weeks	52 weeks
Treatment Arms:	(1) alogliptin 25 mg; (2) up-titration of pioglitazone to 45 mg; both with background therapy of metformin (≥ 1500 mg) and pioglitazone 30 mg	(1) alogliptin 25 mg/day; (2) glipizide 5 to 10 mg/day
Treatment Schedule:		
Randomization:		
Ratio:	1:1	1:1
Method of Randomization:	randomization by stratified permuted block schedule; generated by SAS PROC PLAN, and deployed with an IVRS	randomization by stratified permuted block schedule; generated by SAS PROC PLAN, and deployed with an IVRS
If stratified, then the Stratification Factors:	(1) screening HbA1c (< 8.0, ≥ 8.0); (2) study schedule (A, B), (3) 3 geographic regions (USA, Western Europe / Australia / New Zealand, Rest of World)	(1) screening HbA1c; (2) study schedule (A,B) (3) 3 Geographic regions (USA, Europe/Rest of World, Latin America
Primary Endpoint:	HbA1c change from baseline at week 26 and at week 52	HbA1c change from baseline at week 52
Primary Analysis Population:	Per Protocol (pre-specified by applicant)	Per Protocol (pre-specified by applicant)

Protocol Number (s):	OPI-004	303
Statistical Design:	non-inferiority	non-inferiority
If non-inferiority or equivalence: Was the non-inferiority margin calculated based on historical data?	Based on typical margin from 2008 Draft Diabetes Guidance	Based on typical margin from 2008 Draft Diabetes Guidance
Margin =	0.3	0.4
%Retained =	A review issue	A review issue
Adaptive Design?	No	No
Primary Statistical Methodology:	ANCOVA	ANCOVA
Interim Analysis?	No	No
If yes, No. of Times:		
Method:		
α Adjustment: Yes/No		
α Spending Function:		
DSMB?	No	No
Sample Size:		
Sample size determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable?	Yes	Yes
Statistic =	z-test statistic	z-test statistic
Power =	90%	90%
Δ =	NI margin of 0.3	NI margin of 0.4
α =	0.025 (one-tailed)	0.025 (one-tailed)
• Was there an alternative analysis in case of violation of assumption; e.g., Lack of normality, proportional hazards assumption violation?	No	No
• Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable?	No	No
• Were the covariates pre-specified in the protocol?	Yes	Yes
• Did the applicant perform sensitivity analyses?	Yes	Yes
• How were the missing data handled?	LOCF	LOCF
• Was there a multiplicity involved?	Yes	No
If yes, multiple arms?	No	No
Multiple endpoints?	Yes, HbA1c and week 26 and at week 52	No
Which method was used to control for type I error?	Gate-keeper	N/A
• Multiple secondary endpoints: Are they being included in the label? If yes, method to control for type 1 error.	Yes, no method for controlling type I error	Yes, no method for controlling type I error

Protocol Number (s):	OPI-004	303
• Were subgroup analyses performed?	Yes	Yes
• Were there any discrepancies between the protocol / statistical analysis plan vs. the study report?	No	No
• Overall, was the study positive?	Yes (superiority was demonstrated)	Yes (conclusion of NI was supported)

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JANICE A DERR
11/18/2011

JON T SAHLROOT
11/18/2011
concur

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Today's date: 8/8/11

NDA Number: 022271/0, 022426/0 **Applicant:** Takeda **Stamp Date:** 7/25/11

Drug Name: Alogliptin **NDA/BLA Type:** standard review **PDUFA goal date:** 1/25/12

Filing Date:

The purpose of these two NDA submissions is to provide a response to the Division's complete response from the review of the initial NDA submission for both alogliptin (NDA 022271) and alogliptin + pioglitazone fixed dose combination (NDA 022426). There is only one Phase 3 study, reported in both NDAs, that has not received a statistical review. This is Study OPI-004. The other Phase 3 studies were reviewed from the original submissions in 2008. The filing review focuses on Study OPI-004.

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

	Content Parameter	Study OPI-004
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 was included. This is 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 OPI-004
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

Phase 3 studies described in Part 14 of either one or both of the proposed labels for alogliptin and alogliptin + pioglitazone FDC:

Study number	Brief description	Status with respect to statistical review
010	Monotherapy (placebo-controlled); 26 weeks; 329 subjects, randomized to 3 arms: (1) alogliptin 12.5 mg; (2) alogliptin 25 mg; or (3) placebo	Reviewed under NDA 022271/0
OPI-002	Monotherapy (combination study, no placebo control); 26 weeks; 655 subjects, randomized to 4 arms: (1) alogliptin 25 mg; (2) pioglitazone; (3) alogliptin 12.5 mg + pioglitazone 30 mg; (4) alogliptin 25 mg + pio 30 mg	Reviewed under NDA 022426/0
008	Add-on combination therapy to metformin; 26 weeks; 527 subjects, randomized to 3 arms with background therapy of metformin; (1) alogliptin 12.5 mg; (2) alogliptin 25 mg; (3) placebo.	Reviewed under NDA 022271/0
OPI-001	Combination study with background therapy of metformin; 26 weeks; 1554 subjects, randomized to 12 arms: (1) placebo; (2) alogliptin 12.5 mg; (3) alo 25 mg; (4) pioglitazone 15 mg; (5) pio 30 mg; (6) pio 45 mg; (7) alo 12.5 mg + pio 15 mg; (8) alo 12.5 mg + pio 30 mg; (9) alo 12.5 mg + pio 45 mg; (10) alo 25 mg + pio 15 mg; (11) alo 25 mg + pio 30 mg; (12) alo 25 mg + pio 45 mg.	Reviewed under NDA 022426/0
009	Add-on combination therapy to a thiazolidinedione (TZD) alone or in combination with metformin or a sulfonylurea; 26 weeks; 493 subjects, randomized to 3 arms: (1) placebo; (2) alogliptin 12.5 mg; (3) alo 25 mg. The TZD used was pioglitazone during the study (mean dose of 35 mg).	Reviewed under NDA 022271/0 and covered again in NDA 022426/0.
OPI-004	Add-on combination therapy with pioglitazone and metformin; 52 weeks; 803 subjects, background therapy of pioglitazone 30 mg and metformin; randomized to 2 arms; (1) alogliptin 25 mg; (2) titration of pioglitazone 30 mg to 45 mg.	This study has not yet received a statistical review.
007	Add-on therapy to a sulfonylurea (SU); 26 weeks; 500 subjects randomized to 3 arms; (1) placebo; (2) alogliptin 12.5 mg; (3) alogliptin 25 mg. During the treatment period, the SU (glyburide) was maintained at a stable dose, mean dose of 12 mg.	Reviewed under NDA 022271/0
011	Add-on therapy to insulin; 26 weeks; 390 subjects, background therapy either insulin or insulin + metformin; randomized to 3 arms; (1) placebo; (2) alogliptin 12.5 mg; (3) alogliptin 25 mg.	Reviewed under NDA 022271/0

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JANICE A DERR
08/08/2011

JON T SAHLROOT
08/08/2011

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	022271/0
Drug Name:	Nesina™ (alogliptin; SYR-322) tablets
Indication(s):	Treatment of type 2 diabetes mellitus
Applicant:	Takeda Global Research & Development Center, Inc.
Date(s):	Letter date December 21, 2007
	PDUFA Goal Date October 27, 2008
	Statistical review completed 9/2/08
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2
Statistical Reviewer:	Janice Derr, Ph.D.
Concurring Reviewers:	J. Todd Sahlroot, Team Leader and Deputy Division Director
	Thomas Permutt, Division Director
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Joanna K. Zawadski, M.D., Medical Reviewer
	Hylton Joffe, M.D., Medical Team Leader
	Mary H. Parks, M.D., Division Director
Project Manager:	Julie Marchick

Keywords: clinical studies, NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Efficacy Conclusions: Based on an evaluation of the five key Phase 3 studies, I conclude that the efficacy results for alogliptin demonstrated statistically significant net reductions in HbA1c at week 26 relative to baseline, when compared to a placebo. This conclusion is based on studies that were designed for a superiority comparison of alogliptin against placebo, either as a monotherapy, or as an add-on therapy to sulfonylurea, metformin, pioglitazone or insulin. Results from a sensitivity analysis of the HbA1c endpoint supported the efficacy of alogliptin 12.5 mg and 25 mg. The efficacy of alogliptin was also supported by a greater average decrease in fasting plasma glucose (FPG) at week 26 relative to baseline, when compared to a placebo.

The net effect of alogliptin 25 mg was an average improvement of 0.6% (absolute) in comparison to placebo as monotherapy, 0.5% as an add-on to sulfonylurea or metformin, and 0.6% as an add-on to pioglitazone or insulin (TABLE 7). The net effect of alogliptin 12.5 mg was an improvement of 0.5% in comparison to placebo as monotherapy, 0.4% as an add-on to sulfonylurea, 0.5% as an add-on to metformin or pioglitazone, and 0.5% as an add-on to insulin. The net effect of alogliptin of the 12.5 mg dose and the 25 mg dose was very similar and would not be separable statistically (this was not an objective of the studies).

The greater incidence of "rescue" in the placebo arm compared to the alogliptin arms in each study also supports the efficacy of alogliptin. "Rescue" refers to intervention with additional diabetes medication based on criteria for hyperglycemia (fasting plasma glucose in weeks 1-12) or inadequate glycemic control (HbA1c in weeks 12-26). The insulin add-on study was different from the other four studies in the larger overall percentage of subjects in each arm who were rescued or discontinued (57.4% in the placebo add-on arm compared to 36.6% and 40.3% in the alogliptin add-on arms). In my opinion, the large percentage of subjects who were rescued or discontinued makes it difficult to get an unbiased estimate of the effect of alogliptin as an add-on to insulin in this patient population.

The average HbA1c response in the younger and older age groups (< 65 and ≥ 65 years) and in males and females were relatively similar. Most subjects were Caucasian in each of the five key studies. The numbers of subjects in the other identified race categories were small and did not support an evaluation of potential race-related difference in HbA1c reduction. In two studies with reasonable representation in the Hispanic/Latino ethnicity category, the average HbA1c response was relatively similar in the non-Hispanic/Latino and the Hispanic/Latino ethnicity categories.

The large majority of subjects in each study, 84% to 94%, stayed within ± 5% of their baseline body weight at week 26. Four studies had no apparent difference among the alogliptin and placebo arms in the pattern of weight change. The add-on to sulfonylurea study showed a net

average weight gain of 0.8 kg in the alogliptin 12.5 mg arm and 0.9 kg in the alogliptin 25 mg arm relative to placebo, with p-values < 0.05.

Safety Conclusions: Conclusions regarding the safety of alogliptin are addressed in the clinical review by Dr. Joanna Zawadski.

Recommendations: I believe that the use of HbA1c as a criterion for hyperglycemic rescue in the latter half of each study created complications in estimating the placebo-adjusted effect of alogliptin on HbA1c, the primary efficacy endpoint. I recommend that careful consideration be given to the study objectives and the criteria for hyperglycemic rescue in future studies of anti-diabetic products. This review (section 5.3) also includes general recommendations for the labeling text.

1.2 Brief Overview of Clinical Studies

The clinical development of alogliptin included efficacy studies of alogliptin monotherapy and add-on combination therapy with other common oral anti-diabetic drugs (sulfonylurea, metformin or pioglitazone) or insulin. Two general populations of subjects with type 2 diabetes mellitus were examined. A monotherapy phase 3 study was performed in subjects who had never received pharmacologic therapy or had received only minimal therapy. Add-on combination therapy trials were performed in subjects inadequately controlled by their existing therapy. The Phase 3 studies had a similar design, with a treatment period of 26 weeks and three arms: alogliptin 25 mg, alogliptin 12.5 mg and placebo. In the combination therapy trials, the designated background therapy was included in all three arms.

The primary efficacy criterion in all major studies was the change from baseline to study endpoint (week 26) in glycated hemoglobin (HbA1c). Fasting plasma glucose was a secondary efficacy endpoint. A total of 2239 subjects were randomized in five Phase 3 clinical studies. These five key studies are the focus of this statistical review.

1.3 Statistical Issues and Findings

Alogliptin produced statistically significant net reductions in HbA1c when compared with placebo as a monotherapy, and when given as an add-on to sulfonylurea, metformin, pioglitazone or insulin. Results from the sensitivity analysis of the HbA1c endpoint supported the efficacy of alogliptin 12.5 mg and 25 mg. The results from analyzing the Per Protocol population were very similar to the results from the Full Analysis Set population. The results from analyzing subjects who completed the study (with no hyperglycemic rescue) were also supportive in showing a net improvement in HbA1c in the alogliptin arms compared to the placebo arm in each study.

A design issue that affected the estimation of the placebo-adjusted effect of alogliptin is the relationship between the primary efficacy endpoint and the criteria used to intervene with additional diabetes medication. In my opinion, the estimate based on the Full Analysis Set (Intention-to-Treat) population using HbA1c carried forward from the point of rescue or discontinuation is a reasonable estimate of the placebo-adjusted effect of alogliptin. My reasoning is as follows:

- The criteria for "rescue" is based directly or indirectly on the primary efficacy endpoint, HbA1c. "Rescue" refers to intervention based on criteria for hyperglycemia (fasting plasma glucose in weeks 0-12) or inadequate glycemic control (HbA1c in weeks 12-26). Because the criteria for intervention involve the primary efficacy endpoint, either directly or indirectly, the incidence of rescue becomes a *de facto* efficacy endpoint as well.

- A substantial percentage of patients were rescued or discontinued in each study. The percentage of subjects who did not complete the study, either because of rescue or for other reasons, ranged from 21% to 45% (TABLE 4). These percentages are large enough to influence the estimation of the effect of alogliptin.

- More patients were rescued or discontinued in the alogliptin arms than in the placebo arm in each study. Efficacy of alogliptin is supported by a greater incidence of rescue in the placebo arm than in the alogliptin arms of a study. The odds of rescue or discontinuation for other reasons[1] were approximately twice as great in the placebo arm as in the alogliptin arms in four of the five studies, and were somewhat lower but still greater than 1.0 in the other study (TABLE 13). For this reason, the evaluation of a subset of the full analysis set consisting only of subjects who completed the study creates a selection bias between alogliptin and placebo arms.

- Rescue was more likely to occur in patients with higher baseline HbA1c than in patients with lower baseline HbA1c (TABLE 27). This differential also contributes to a selection bias between alogliptin and placebo arms in the completers subset of the full analysis set. In my opinion, the full analysis set is a more appropriate analysis population for the estimate of the placebo-adjusted effect of alogliptin.

- The last observation carried forward (LOCF) method permits the use of the full analysis set to estimate the placebo-adjusted effect of alogliptin. In my opinion, the LOCF method, while it can be criticized, is less problematic than other approaches in this situation. For example:

[1] I combined the occurrence of rescue with discontinuation for other reasons in order to distinguish these two outcomes from the outcome of completing a study without being rescued. Because the occurrence of discontinuation was relatively similar among and between studies, the differences among arms in the percentage of cases with the combined rescue/discontinuation outcome are mainly due to the rescue outcome. See Sections 3.1.1 and 3.1.6 for additional information.

a) The LOCF method can be viewed as conservative with respect to a hypothetical study with no rescue, as long as we assume that the rate of increase in HbA1c would have been the same or greater in the placebo arm than the alogliptin arm in this hypothetical study. This is due to the differential rescue rate between the placebo and the alogliptin arms, and to the tendency for the HbA1c levels of subjects who discontinued or were rescued to be higher than the HbA1c levels of subjects who completed the study (FIGURE 3).

b) A mixed model repeated measures (MMRM) analysis of the observed data (with no imputation) is an alternative method of estimation. However, the occurrence of rescue is based on HbA1c and is related both to the baseline level of HbA1c and to the rate of change in HbA1c. Under these circumstances, the assumptions of the MMRM estimation may not be met.

c) A rank-based method that adjusts for rescue by assigning a "bad" underlying outcome to rescued patients and uses rank-based methods of analysis is discussed in White, et al., (2001)[2]. This method may also produce conservative results in the sense that the HbA1c criterion for hyperglycemic rescue does not necessarily signal a bad underlying outcome.

d) A regression approach with rescue as a time-dependent covariate was also proposed by White, et al., (2001). This approach may be useful in a situation where the rescued patients continued in the study. However, in the five studies discussed in this review, subjects who were rescued were not continued.

Across the five key studies, subjects in subgroups with higher baseline HbA1c values generally had a greater average reduction in HbA1c compared to subjects in subgroups with lower baseline HbA1c values in the alogliptin arms compared to placebo. This relationship is illustrated not only in the alogliptin groups, but also in the placebo groups, and has also been demonstrated in clinical studies of other diabetes drugs. (b) (4)

The effect of alogliptin appears to be established by week 12, after which time the placebo-adjusted effect of alogliptin remained relatively constant, even though the average change from baseline decreased from week 12 through week 26 in the alogliptin arms and in the placebo arm This decrease in average change from baseline in all arms may represent the progression of diabetes over the time course of the studies. However, the dynamics of disposition has also contributed to this apparent stabilization of response by week 12. In four of the five studies, a substantial proportion of rescues/discontinuations took place from weeks 12 through 16,

[2] White, I.R., et al. 2001. Randomized clinical trials with added rescue medication: some approaches to their analysis and interpretation. Statistics in Medicine 20: 2995-3008.

following the change in criteria for hyperglycemic rescue from fasting plasma glucose to HbA1c at week 12 (FIGURE 2). The proportion of cases with HbA1c levels carried forward from weeks 12 through 16 contributes to the apparent stabilization of HbA1c response by week 12.

2. INTRODUCTION

2.1 Overview

Type 2 diabetes mellitus (diabetes) is a complex metabolic disorder characterized by abnormal insulin secretion and glucose homeostasis, resulting from impaired β-cell function and insulin resistance in target tissues. Diet and exercise are important and effective measures for maintaining glycemic control in individuals with insulin resistance, impaired glucose tolerance, and overt diabetes, and are particularly effective in the early stages of disease progression. In cases where diet and exercise alone fail to adequately maintain glycemic control, oral anti-diabetic drugs can be used. Five major classes of oral antidiabetic drugs that are currently available are biguanides, sulfonylureas, α-glucosidase inhibitors, thiazolidinediones and meglitinides[3].

Alogliptin (SYR-322) is a member of an additional class of oral antidiabetic drug intended for the treatment of diabetes. Alogliptin selectively inhibits the enzymatic activity of dipeptidyl peptidase IV (DPP-4) and is referred to as a DPP-4 inhibitor. DPP-4 inhibitors augment active levels of the incretin hormones glucagon like peptide-1 and glucose-dependent insulinotropic polypeptide following a meal. This enhances glucose-dependent insulin secretion from pancreatic β-cells and glucagon suppression from α-cells, resulting in improved peripheral glucose disposal and suppression of endogenous glucose production. The net effect of these two actions is to limit postprandial glucose excursions[4]. At the time of this review, one DPP-4 inhibitor, sitagliptin (Januvia™) has been approved by the Agency.

Scope of Statistical Review: Pivotal Efficacy and Safety Studies

The statistical review covers five key Phase 3 studies that were designed to assess the efficacy and safety of alogliptin 12.5 mg and 25 mg qd for the treatment of diabetes, either as monotherapy adjunct to diet and exercise, or as add-on therapy to other antidiabetic medications including a sulfonylurea, metformin, TZD, or insulin.

The five studies were similar in design: the studies were multicenter, randomized, double-blind, parallel-group and placebo-controlled. Each study evaluated alogliptin at doses of 12.5 and 25 mg qd. The studies had a placebo-controlled stabilization period for four weeks prior to randomization followed by a 26-week treatment period. The study design for all five studies is

[3] The source of this paragraph (paraphrased) is Harrison's Principles of Internal Medicine, 16th Ed, Part Fourteen: Endocrinology and Metabolism; Section 1; Endocrinology; Diabetes Mellitus (2005; from online.statref.com),
[4] The source of this paragraph is Section 2.5 Clinical Overview, Parts 1.1 and 4.2 (paraphrased).

depicted in FIGURE 1. The primary efficacy endpoint in these studies was the change from baseline in HbA1c at week 26.

FIGURE 1 General study design for five key Phase 3 studies

Screening and Washout Weeks -6 through -5 Prior to Randomization	Run-in/Stabilization Weeks -4 through -1 Prior to Randomization				Treatment Period Weeks 1-26 After Randomization								End-of-treatment	Follow-up Period
Week														
Screening Visit	-4	-3	-2	-1	Baseline Visit (Day 1)	1	2	4	8	12	16	20	26	28

Source: CTD 2.7.3 Summary of Clinical Efficacy, Figure 2.a

All subjects entering into these studies were required to have type 2 diabetes with inadequate glycemic control prior to randomization. Key inclusion criteria specific to each study are summarized below:

Study 010 (Alogliptin monotherapy)
- HbA1c between 7.0% and 10.0%, inclusive
- Subject had failed treatment with diet and exercise for at least 1 month prior to screening
- Subject had received < 7 days of any antidiabetic therapy within the 3 months prior to screening

Study 007 (Alogliptin as add-on to sulfonylurea)
- HbA1c between 7.0% and 10.0%, inclusive
- Subject received sulfonylurea for at least the 3 months prior to screening
- Subject maintained a stable sulfonylurea dose equivalent to at least 10 mg of glyburide for at least 8 weeks prior to randomization
- No treatment with antidiabetic agents other than a sulfonylurea within 3 months prior to screening

Study 008 (Alogliptin as add-on to metformin)
- HbA1c between 7.0% and 10.0%, inclusive
- Subject received metformin monotherapy for at least the 3 months prior to screening
- Subject maintained a stable metformin dose ≥ 1500 mg for at least 8 weeks prior to randomization
- No treatment with antidiabetic agents other than metformin within the 3 months prior to screening

Study 009 (Alogliptin as add-on to pioglitazone)
- HbA1c between 7.0% and 10.0%, inclusive

- Subject received TZD therapy (rosiglitazone or pioglitazone) either alone or in combination with metformin or a sulfonylurea for at least the 3 months prior to screening
- Only subjects who were receiving a minimum 30 mg daily dose of pioglitazone at the start of the run-in / stabilization period (following conversion from rosiglitazone, if applicable) were eligible to participate in the study
- No treatment with antidiabetic agents other than a TZD alone or in combination with either rmetformin or a sulfonylurea within the 3 months prior to screening

Study 011 (Alogliptin as add-on to insulin)

- HbA1c between 8.0% and 10.0%, inclusive
- Subjects received insulin therapy either alone or in combination with metformin for at least the 3 months prior to screening
- The insulin dose must have been ≥ 15 units and ≤ 100 units per day for at least 8 weeks prior to randomization; a dose of insulin that varied by up to 15% of the mean was considered stable
- If receiving metformin, subject maintained a stable metformin dose for at least 8 weeks prior to randomization
- No treatment with antidiabetic agents other than insulin alone or in combination with metformin within the 3 months prior to screening

The balancing of treatment assignments was managed within the following stratification factors:

- HbA1c at week -1 (HbA1c < 8.0%, HbA1c ≥ 8.0% for all studies except for Study 011, where the stratification factor was HbA1c < 9.0%, HbA1c ≥ 9.0%).

- Geographic region (as designated in TABLE 1):

TABLE 1 Levels of geographic region in the stratified randomization of five Phase 3 studies

	Geographic Region			
Study	**USA**	**Mexico and Central/South America**	**Western Europe, Australia, New Zealand**	**Rest of World**
010	USA	Argentina, Brazil, Dominican Republic, Guatemala, Mexico, Peru	Australia, Netherlands, New Zealand, United Kingdom	Hungary, India, Poland, South Africa
007	USA	Argentina, Brazil, Chile, Dominican Republic, Guatemala, Mexico, Peru	Australia, Netherlands, New Zealand, United Kingdom	India, Poland, South Africa
008	USA	Brazil, Chile, Guatemala, Mexico	Australia, Germany, Netherlands, New Zealand, Spain, United Kingdom	Hungary, India, Poland, South Africa
009	USA	Argentina, Brazil, Guatemala, Peru	Australia, Germany, Netherlands, New Zealand, Spain	Hungary, India, South Africa
011	USA	Brazil, Chile, Guatemala, Mexico	Australia, Germany, Netherlands, New Zealand	Hungary, India, Poland, South Africa

Source: CTD 2.7.3, Part 2.1.1

- Baseline treatment regimen for two studies: For study 009: pioglitazone alone, pioglitazone plus metformin, or pioglitazone plus a sulfonylurea. For study 010: insulin, and insulin plus metformin.

The five key studies involved 2239 randomized subjects, of whom 994 (44.4%) were enrolled at sites in the U.S. (TABLE 2). The numbers of subjects, centers and countries for each study are summarized in TABLE 2.

TABLE 2 Number of randomized subjects and sites by country for each of the five Phase 3 studies

	Study 010 (monotherapy)		**Study 007 (add-on to sulfonylurea)**		**Study 008 (add-on to metformin)**		**Study 009 (add-on to pioglitazone)**		**Study 011 (add-on to insulin)**	
Region[1]	***# sites***	**# pts.**	***# sites***	**# pts.**	***# sites***	**# pts.**	***# sites***	**# pts.**	***# sites***	**# pts.**
US/Canada		**172**		**136**		**210**		**331**		**145**
US	*54*	172	*47*	136	*45*	210	*73*	331	*43*	145
Europe / Aus. / NZ		**36**		**29**		**80**		**56**		**35**
Australia	*4*	10	*5*	11	*6*	9	*4*	11	*7*	12
Germany					*5*	16	*6*	15	*3*	8
Great Britain	*4*	10	*3*	3	*6*	21				
Netherlands	*2*	3	*2*	2	*3*	5	*1*	1	*2*	5
New Zealand	*4*	13	*3*	4	*2*	17	*3*	21	*4*	10
Spain			*1*	9	*1*	12	*2*	8		
Latin America		**58**		**213**		**116**		**60**		**107**
Argentina	*2*	3	*6*	63			*5*	13		
Brazil	*6*	20	*6*	18	*6*	35	*4*	23	*5*	48
Chile			*3*	7	*7*	20			*5*	25
Dom. Rep.	*1*	1	*1*	8						
Guatemala	*2*	3	*3*	27	*3*	12	*2*	10	*2*	10
Mexico	*2*	9	*6*	55	*5*	49			*3*	24
Peru	*4*	22	*6*	35			*3*	14		
Rest of the World		**63**		**122**		**121**		**46**		**103**
Hungary	*2*	8			*2*	21	*1*	6	*2*	13
India	*5*	23	*6*	54	*6*	36	*5*	32	*5*	30
Poland	*3*	7	*7*	40	*5*	23			*5*	22
South Africa	*5*	25	*4*	28	*4*	41	*2*	8	*6*	38
Totals	***100***	**329**	***109***	**500**	***106***	**527**	***111***	**493**	***92***	**390**

Note:
[1] *The applicant used "Region" as a stratification factor in the randomization. For purposes of this stratification, Australia and New Zealand were included in the region with Western Europe*

Sources:
CTD 2.7.3 Part 2.0 (Summary of results of individual studies), and DEMOG.xpt files for Studies 007, 008, 009, 010 and 011

The sample size for each study, approximately 500 subjects total to be randomized, with a 2:2:1 allocation to the alogliptin 25 mg: alogliptin 12.5 mg: placebo arms, was calculated with the following assumptions:

- a standard deviation of the primary endpoint (change in HbA1c between week 26 and baseline) of 0.8 in the per protocol set, based on estimates from previous studies with SYR-322 and one published study with the DPP-IV inhibitor LAF237 (vildagliptin[5])
- at least 80% of randomized subjects in the per protocol set
- a gate-keeper strategy for testing the 12.5 mg alogliptin arm against placebo contingent on a statistically significant result for the comparison of the 25 mg alogliptin arm against placebo
- a two-tailed α of 0.05 for both comparisons

Based on these assumptions, the applicant calculated that each study would have at least 95% power to detect a treatment group difference in HbA1c change from baseline as small as 0.4% in the per protocol set. I confirmed this calculation. In addition, I calculated the study power based on the intention-to-treat population, a standard error of 1.1, and a 10% attrition rate from the number of randomized subjects and the number of subjects in the intention-to-treat population. These assumptions reflect a more typical approach to calculating the number of subjects in diabetes clinical studies. With these assumptions, 500 randomized subjects in the study with a 2:2:1 allocation would have 90% power to detect a treatment group difference as small as 0.5% in the intention-to-treat set. I note that the estimates of standard deviation from the five clinical studies ranged from 0.8 to 0.9.

At the time of the submission of this NDA, an additional, long-term, open-label extension study was being conducted in subjects with type 2 diabetes who were enrolled from any of the five key studies, as well as two coadministration studies being conducted to support the alogliptin/pioglitazone fixed-dose combination program (IND 73193). Subjects who required protocol-defined hyperglycemic rescue from any of the phase 3 studies received alogliptin 25 mg qd, while subjects who completed any of the studies were randomized to receive either alogliptin 12.5 mg or 25 mg qd at a 1:1 ratio. Safety was evaluated by monitoring adverse events, clinical laboratory variables (hematology, serum chemistry and urinalysis), ECGs, vital signs, physical examination findings (including clinical examination of skin and digits), and incidence of hypoglycemic events.

2.2 Data Sources

[5] Ahren, Bo, et al., 2004. Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. *Diabetes Care* 27: 1874-2880.

The applicant submitted this NDA including the data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown in TABLE 3. Individual study reports were submitted for each study.

TABLE 3 Data sources for studies

Document: NDA 022271.0
CDER EDR link: \\CDSESUB1\N022271\
Company: Takeda
Drug: Alogliptin
Stamp date: January 27, 2007

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1. Subject disposition

All five studies had a similar overall pattern of disposition, with a greater percentage of subjects who were rescued in the placebo arm compared to the alogliptin arms (TABLE 4). "Rescue" refers to intervention with additional diabetes medication based on criteria for hyperglycemia (Weeks 0-12) or inadequate glycemic control (Weeks 12-26). The HbA1c at this early termination visit was used as the study endpoint for the rescued subject. The criteria for rescue are shown in EXHIBIT 1. The percentage of subjects who discontinued for reasons other than rescue was relatively similar among the arms of a study and did not differ greatly among studies (TABLE 4). For purposes of analysis, I combined the subjects who were rescued and who discontinued, in order to distinguish these outcomes from subjects who completed the study and were not rescued.

EXHIBIT 1 Criteria for rescue

Weeks 0-12: Fasting Plasma Glucose (FPG) criteria were applied during weeks 0-12:

- Following 1 week of treatment but prior to week 4 visit: For Studies 007, 008, 009 and 010: Single FPG ≥275 mg/dL (≥15.27 mmol/L); for Study 011: FPG ≥300 mg/dL (≥16.65 mmol/L)
- From week 4 visit but prior to week 8 visit: For Studies 007, 008, 009 and 010: Single FPG ≥250 mg/dL (≥13.88 mmol/L); for Study 011: FPG ≥275 mg/dL (≥15.27 mmol/L);
- From week 8 visit but prior to week 12 visit: For Studies 007, 008, 009 and 010: Single FPG ≥225 mg/dL (≥12.49 mmol/L); for Study 011: FPG ≥250 mg/dL (≥13.88 mmol/L)

Weeks 12-26: HbA1c criteria were applied from weeks 12-26: For Studies 007, 008, 009 and 010: HbA1c concentration ≥8.5% and ≤0.5% reduction in HbA1c as compared with Baseline; for Study 011: HbA1c concentration ≥8.7%)

The dynamics of disposition reflects the criteria for hyperglycemic rescue. Three studies show a marked increase in rescues/discontinuations in weeks 12 through 16; the monotherapy study 010, the add-on to sulfonylurea study 007 and the add-on to insulin study 010 (FIGURE 2). The add-on to metformin study 008 had a steadier drop in rescues/discontinuations in weeks 12-16. The add-on to pioglitazone study 009 appeared to have a more constant rate of rescues/discontinuations throughout the study. These differences in the dynamics of disposition may reflect differences in the study population.

The pattern of disposition has an impact on the efficacy evaluation, for two reasons:

(1) The criteria for rescue in weeks 12-26 directly involve the primary efficacy endpoint, HbA1c. The criteria for rescue in weeks 1-12 involve fasting plasma glucose, which is correlated with HbA1c. For example, the correlation coefficient between HbA1c and fasting plasma glucose at baseline was 0.68 in Study 010. For these reasons, the difference between the alogliptin arms and the placebo arm in the percentage of subjects who were rescued reflects the efficacy of alogliptin. As a sensitivity analysis to the primary efficacy evaluation, I compared the alogliptin arms to the placebo arm in the percentage of subjects who were rescued or discontinued in each study. The results of this analysis are summarized in section 3.1.7.

(2) In subjects who were rescued or discontinued, the HbA1c level at the last study visit (or at the early termination visit) was used in the primary efficacy analysis. These early termination levels of HbA1c tended to be larger than the HbAlc levels obtained at week 26 from subjects who completed a study (FIGURE 1). This is a consequence of the criteria for rescue. As a sensitivity analysis to the primary efficacy analysis, I estimated the placebo-adjusted effect of alogliptin separately from subjects who completed a study and from subjects who were rescued/discontinued. The results of these analyses are summarized in see section 3.1.6.

TABLE 4 Subject disposition

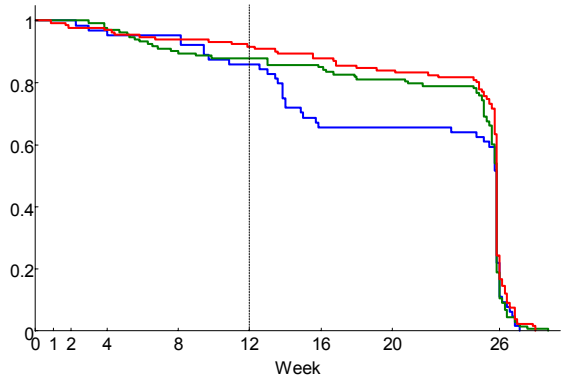
Monotherapy: Study 010	**placebo**	**alogliptin 12.5 mg**	**alogliptin 25 mg**	**Total**
Randomized	65	133	131	329
Full Analysis Set	64	133	131	328
Completed	40 (62.5%)[1]	105 (78.9%)	107 (81.7%)	304 (76.8%)
Rescued or Discontinued[2]	24 (37.5%)	28 (21.1%)	24 (18.3%)	76 (23.2%)
• Rescued[3]	19 (29.7%)	13 (9.8%)	10 (7.6%)	42 (11.1%)
FPG criteria (Weeks 0-12)	*7 (10.9%)*	*8 (6.0%)*	*3 (2.3%)*	*18 (4.7%)*
HbA1c criteria (Weeks 12-26)	*12 (18.8%)*	*5 (3.8%)*	*7 (5.3%)*	*24 (6.3%)*
• Discontinued	5 (7.8%)	15 (11.3%)	14 (10.7%)	34 (8.9%)
Add-on therapy: Study 007 (sulfonylurea)	**SU + placebo**	**SU + alogliptin 12.5 mg**	**SU + alogliptin 25 mg**	**Total**
Randomized	99	203	198	500
Full Analysis Set	99	203	198	500
Completed	62 (62.6%)	153 (75.4%)	148 (74.7%)	363 (72.6%)
Rescued or Discontinued	37 (37.4%)	50 (24.6%)	50 (25.3%)	137 (27.4%)
• Rescued	28 (28.3%)	30 (14.8%)	31 (15.7%)	89 (17.8%)
FPG criteria (Weeks 0-12)	*1 (1.0%)*	*7 (3.4%)*	*4 (2.0%)*	*12 (2.4%)*
HbA1c criteria (Weeks 12-26)	*27 (27.3%)*	*23 (11.3%)*	*27 (13.6%)*	*77 (15.4%)*
• Discontinued	9 (9.1%)	20 (9.9%)	19 (9.6%)	48 (9.6%)
Add-on therapy: Study 008 (metformin)	**metformin + placebo**	**metformin + alogliptin 12.5 mg**	**metformin + alogliptin 25 mg**	**Total**
Randomized	104	213	210	527
Full Analysis Set	104	212	207	523
Completed	72 (69.2%)	176 (83.0%)	165 (79.7%)	413 (79.0%)
Rescued or Discontinued	32 (30.8%)	36 (17.0%)	42 (20.3%)	110 (21.0%)
• Rescued	25 (24.0%)	19 (9.0%)	17 (8.2%)	61 (11.7%)
FPG criteria (Weeks 0-12)	*11 (10.6%)*	*3 (1.4%)*	*6 (2.9%)*	*20 (3.8%)*
HbA1c criteria (Weeks 12-26)	*14 (13.5%)*	*16 (7.5%)*	*11 (5.3%)*	*41 (7.8%)*
• Discontinued	7 (6.7%)	17 (8.0%)	25 (12.1%)	49 (9.4%)

Add-on therapy: Study 009 (pioglitazone)	**pioglitazone + placebo**	**pioglitazone + alogliptin 12.5 mg**	**pioglitazone + alogliptin 25 mg**	**Total**
Randomized	97	197	199	493
Full Analysis Set	97	197	199	493
Completed	71 (73.2%)	153 (77.7%)	160 (80.4%)	384 (77.9%)
Rescued or Discontinued	26 (26.8%)	44 (22.3%)	39 (19.6%)	109 (22.1%)
• Rescued	12 (12.4%)	19 (9.6%)	18 (9.0%)	49 (9.9%)
FPG criteria (Weeks 0-12)	*4 (4.1%)*	*9 (4.6%)*	*4 (2.0%)*	*17 (3.4%)*
HbA1c criteria (Weeks 12-26)	*8 (8.2%)*	*10 (5.1%)*	*14 (7.0%)*	*32 (6.5%)*
• Discontinued	14 (14.4%)	25 (12.7%)	21 (10.6%)	60 (12.2%)
Add-on therapy: Study 011 (insulin)	**insulin + placebo**	**insulin + alogliptin 12.5 mg**	**insulin + alogliptin 25 mg**	**Total**
Randomized	130	131	129	390
Full Analysis Set	129	131	129	389
Completed	55 (42.6%)	83 (63.4%)	77 (59.7%)	215 (55.3%)
Rescued or Discontinued	74 (57.4%)	48 (36.6%)	52 (40.3%)	174 (44.7%)
• Rescued	52 (40.3%)	27 (20.6%)	25 (19.4%)	104 (26.7%)
FPG criteria (Weeks 0-12)	*7 (5.4%)*	*7 (5.3%)*	*2 (1.6%)*	*16 (4.1%)*
HbA1c criteria (Weeks 12-26)	*45 (34.9%)*	*20 (15.3%)*	*23 (17.8%)*	*88 (22.6%)*
• Discontinued	22 (17.1%)	21 (16.0%)	27 (20.9%)	70 (18.0%)

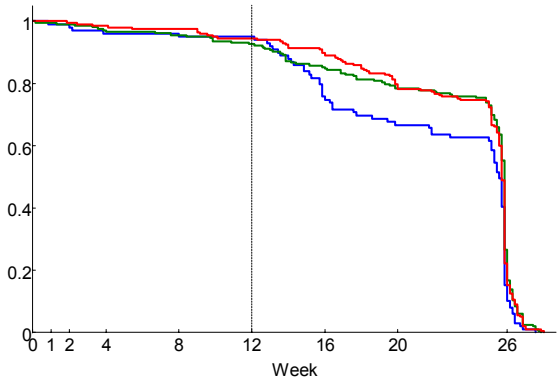
Notes:
[1] Percents are based on the FAS population
[2] The status of "rescued" was a separate category from other discontinuations. The reason for "rescue" was designated as "lack of efficacy." No other types of early discontinuation were designated as lack of efficacy.
[3] Criteria for rescue: See Exhibit 1.
Sources: Clinical Study Reports for Studies 007, 008, 009 and 010 (Section 10.1, Disposition of Subjects), and additional analyses of the disposition databases for each study by this reviewer.

FIGURE 2 Disposition by week on study; Kaplan-Meier plots

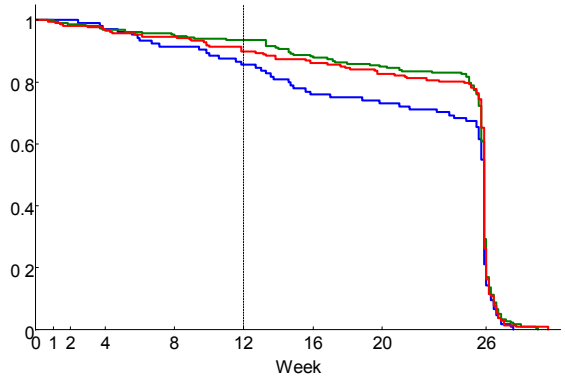
Study 010 (monotherapy)



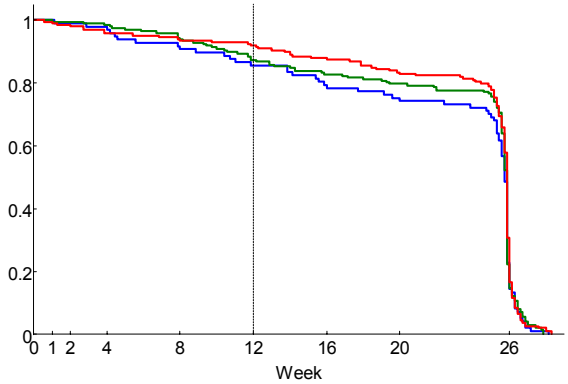
Study 007 (add-on to sulfonylurea)



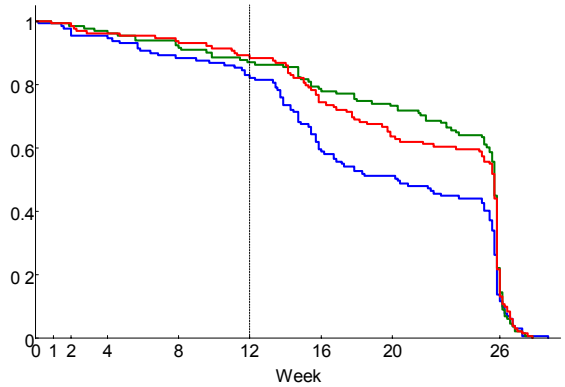
Study 008 (add-on to metformin)



Study 009 (add-on to pioglitazone)

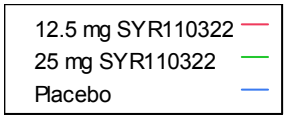


Study 011 (add-on to insulin)



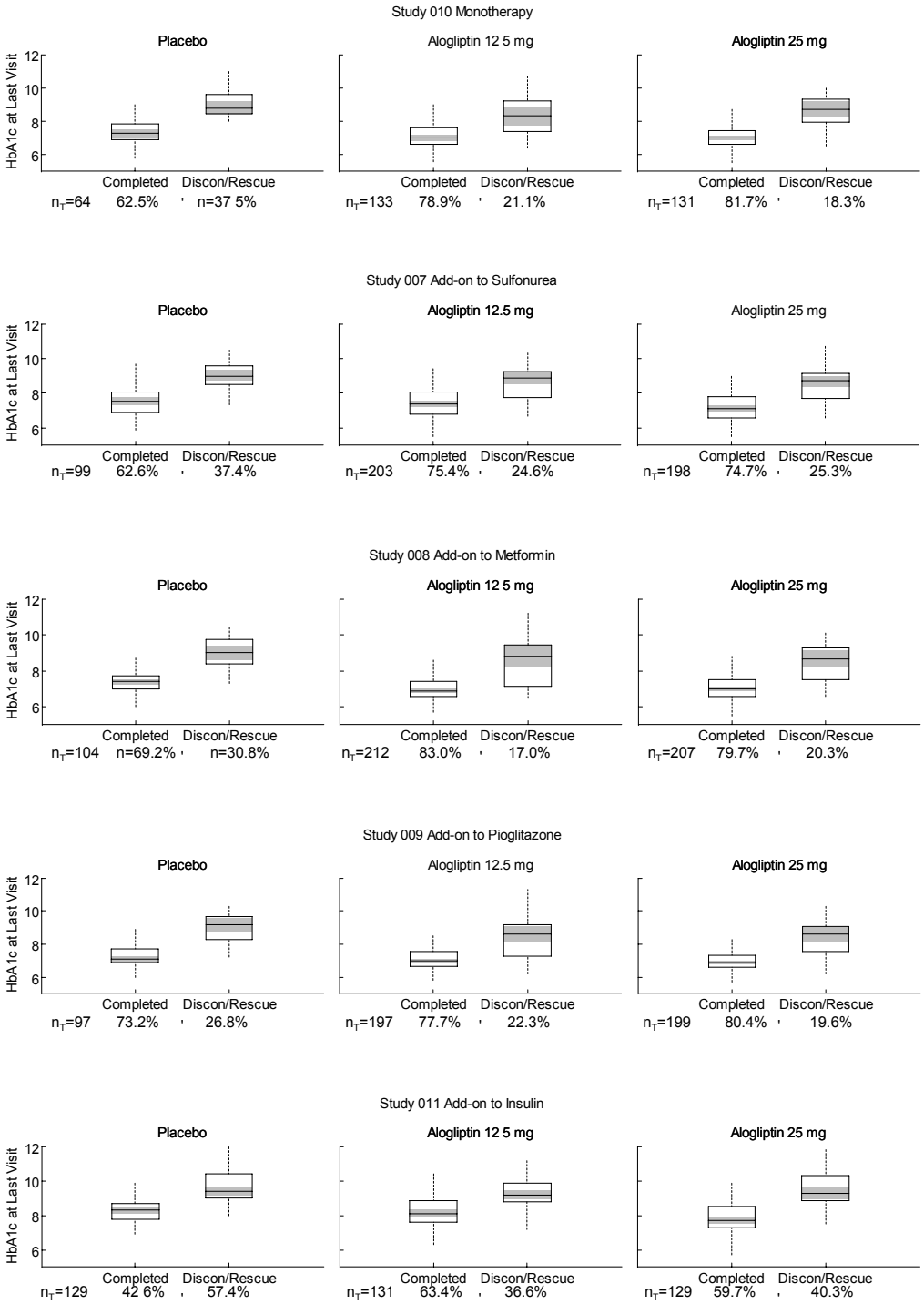
Notes:

- The vertical axis depicts the proportion of randomized patients remaining in the treatment arm.
- From weeks 0-12, the criteria for hyperglycemic rescue were based on fasting plasma glucose. From weeks 12-26, the criteria were based on HbA1c.



Source: Analysis by this reviewer

FIGURE 3 Distribution of HbA1c levels at last visit in subjects who completed a study (Week 26) and in subjects who discontinued or were rescued



Source: Analysis by this reviewer; n_T is the total number randomized in each arm

The five studies differed in the overall extent of rescue or discontinuation, and in the extent of the difference between the placebo and the alogliptin arms in the percentage of subjects who were rescued based on HbA1c criteria in weeks 12-26. These differences across studies may reflect differences in the subject population with respect to the progression of diabetes. Three studies were relatively similar in this pattern of disposition. These studies were the monotherapy study (Study 010), the sulfonylurea add-on study (Study 007) and the metformin add-on study. In these studies, around 30-40% of subjects were rescued or discontinued in the placebo arm, and around 20-30% of subjects were rescued or discontinued in the alogliptin arms (TABLE 4). The difference between placebo and alogliptin arms was largely attributable to the greater percentage of rescues based on HbA1c criteria in weeks 12-26 in the placebo arm compared to the alogliptin arms. Of these three studies, the sulfonylurea add-on study had the largest percentage of HbA1c rescues in the placebo add-on arm (27.3%). The percentage of HbA1c rescues was 11.3% and 13.6% in the sulfonylurea add-on arms (TABLE 4).

The pioglitazone add-on study (Study 009) reflected this pattern of disposition also, but to a lesser extent. The percentage of subjects who either were rescued or discontinued in the three arms was more similar, with 26.8% in the placebo add-on arm and 22.3% and 19.6% in the pioglitazone add-on arms, and a relatively similar percentage of subjects in each arm who were rescued based on the HbA1c criteria (TABLE 4). The insulin add-on study (Study 011) also reflected the pattern of greater percentage of rescue due to HbA1c criteria in the placebo arm (34.9%) compared to the alogliptin add-on arms (15.3% and 17.8%; TABLE 4).

The insulin add-on study was different from the other four studies in the larger overall percentage of subjects in each arm who were rescued or discontinued (57.4% in the placebo add-on arm compared to 36.6% and 40.3% in the alogliptin add-on arms; TABLE 4). In my opinion, the large percentage of subjects who were rescued or discontinued makes it difficult to get an unbiased estimate of the effect of alogliptin as an add-on to insulin in this patient population.

3.1.2. Subject demographic and baseline characteristics

Certain subject demographic and baseline characteristics were relatively similar across studies and among treatment groups within studies (TABLE 5). Four of the five studies had a somewhat greater percentage of males than females, ranging from 50.3% to 58.2%. The majority of subjects in each study were Caucasian, ranging from 65.4% to 77.4%. The majority of subjects in each study were younger than 65 years, ranging from 74.0% to 83.8% in the five studies (TABLE 5).

Differences among studies in other subject characteristics may reflect differences in the target populations for each study in the progression of diabetes. The largest percentage of subjects with baseline HbA1c < 8.0% was in the monotherapy study (59.9%), and the smallest percentage in this baseline HbA1c category was in the insulin add-on study (41.5%; TABLE 5). The shortest mean duration of diabetes at baseline was in the monotherapy study (3.2 years) and the longest

mean duration was in the insulin add-on study (12.6 years; TABLE 5). Studies also differed in the percentage of subjects who reported Hispanic/Latino ethnicity, from 16.2% in the pioglitazone add-on Study 009 to 49.8% in the sulfonylurea add-on Study 007 (TABLE 5). This difference may reflect regional differences among the studies. Study 009 randomized a smaller percentage of subjects from Latin America (12.2%) than Study 007 (42.6%; TABLE 2). Within each study, the distribution of baseline HbA1c levels was relatively similar among study arms, as was the percentage of cases in the HbA1c stratification categories (TABLE 5).

TABLE 5 Subject demographic and baseline characteristics in the randomized subjects in each of the five key studies

	Study 010 (mono-therapy) n=329	**Study 007 (add-on to sulfonylurea) n=500**	**Study 008 (add-on to metformin) n=527**	**Study 009 (add-on to pioglitazone) n=493**	**Study 011 (add-on to insulin) n=390**
Age (years)					
Mean ± SD	53.4 ± 11.1	56.6 ± 11.1	54.7 ± 10.6	55.4 ± 10.0	55.4 ± 10.2
Range	24 to 80	21 to 80	22 to 80	24 to 80	23 to 80
≥ 65 years (n, %)	55 (16.7%)	130 (26.0%)	92 (17.5%)	85 (17.2%)	63 (16.2%)
Sex					
Male (n, %)	175 (53.2%)	261 (52.2%)	265 (50.3%)	287 (58.2%)	161 (41.3%)
Female (n, %)	154 (46.8%)	239 (47.8%)	262 (49.7%)	206 (41.8%)	229 (58.7%)
Race					
Caucasian	220 (66.9%)	354 (70.8%)	408 (77.4%)	366 (74.2%)	255 (65.4%)
Black	27 (8.2%)	22 (4.4%)	24 (4.6%)	45 (9.1%)	54 (13.8%)
Asian	39 (11.9%)	58 (11.6%)	42 (8.0%)	53 (10.8%)	46 (11.8%)
Native American	1 (0.3%)	0 (0.0%)	3 (0.6%)	3 (0.6%)	1 (0.3%)
Pacific Islander	1 (0.3%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	2 (0.5%)
Other	41 (12.5%)	66 (13.2%)	49 (9.3%)	25 (5.1%)	32 (8.2%)
Ethnicity[1]					
Hispanic/Latino	87 (26.4%)	249 (49.8%)	159 (30.2%)	80 (16.2%)	129 (33.1%)
Not Hispanic/Latino	242 (73.6%)	251 (50.2%)	368 (69.8%)	413 (83.8%)	261 (66.9%)
Diabetes duration (yr)					
Mean ± SD	3.2 ± 3.9	7.7 ± 5.9	6.1 ± 4.9	7.6 ± 5.7	12.6 ± 6.9
Range	0.1 to 28.0	0.4 to 41.3	0.3 to 29.8	0.4 to 37.0	0.1 to 36.1
BMI (kg/m^2)					
Mean ± SD	32.0 ± 5.6	30.1 ± 4.9	31.8 ± 5.4	32.8 ± 5.7	32.5 ± 5.8
Range	22.6 to 45.4	22.3 to 45.1	22.6 to 45.0	23.0 to 45.3	22.0 to 45.5
HbA1c at baseline					
Mean ± SD	7.9 ± 0.8	8.1 ± 0.9	7.9 ± 0.8	8.0 ± 0.9	9.3 ± 1.1
Range	6.4 to 10.3	6.5 to 10.3	6.3 to 10.4	6.6 to 12.7	7.5 to 13.8
< 8.0%[2]	197 (59.9%)	221 (44.2%)	301 (57.1%)	252 (51.1%)	< 9.0%: 162 (41.5%)
≥ 8.0%	132 (40.1%)	279 (55.8%)	226 (42.9%)	241 (48.9%)	≥ 9.0%: 228 (58.5%)

Notes:
[1] Hispanic/Latino status was coded in an ethnicity category separately from the race category.
[2] The stratification cutpoint for baseline HbA1c was 8.0% for Studies 007, 008, 009 and 010, and 9.0% for Study 011
Sources: Table 10.c in the clinical report of each study, and additional analysis by this reviewer

TABLE 6 Baseline levels of HbA1c by study arm for the five key studies

	Placebo	Alogliptin 12.5 mg	Alogliptin 25 mg
Study 010 (monotherapy)			
n[1]	64	133	131
Mean ± SD	8.0 ± 0.9	7.9 ± 0.8	7.9 ± 0.8
Median	7.9	7.7	7.8
Range	6.7 to 10.0	6.6 to 10.2	6.4 to 10.3
< 8.0%	38 (59.4%)	79 (59.4%)	79 (60.3%)
≥ 8.0%	26 (40.6%)	54 (40.6%)	52 (39.7%)
Study 007 (add-on to sulfonylurea)			
n	97	201	197
Mean ± SD	7.9 ± 0.8	8.1 ± 0.8	8.1 ± 0.9
Median	7.9	7.9	8.0
Range	6.5 to 10.1	6.5 to 10.3	6.6 to 10.1
< 8.0%	43 (44.3%)	88 (43.8%)	87 (44.2%)
≥ 8.0%	54 (55.7%)	113 (56.2%)	110 (55.8%)
Study 008 (add-on to metformin)			
n	103	210	203
Mean ± SD	8.0 ± 0.9	7.9 ± 0.7	7.9 ± 0.8
Median	7.8	7.7	7.7
Range	6.7 to 10.4	6.3 to 10.2	6.6 to 10.1
< 8.0%	57 (55.3%)	122 (58.1%)	120 (59.1%)
≥ 8.0%	46 (44.7%)	88 (41.9%)	83 (49.9%)
Study 009 (add-on to pioglitazone)			
n	97	197	199
Mean ± SD	8.0 ± 0.8	8.1 ± 0.9	8.0 ± 0.8
Median	8.0	7.9	7.8
Range	6.6 to 10.3	6.8 to 12.7	6.8 to 10.3
< 8.0%	47 (48.5%)	100 (50.8%)	105 (52.8%)
≥ 8.0%	50 (51.5%)	97 (49.2%)	94 (47.2%)
Study 011 (add-on to insulin)			
n	129	131	129
Mean ± SD	9.3 ± 1.1	9.3 ± 1.1	9.3 ± 1.1
Median	9.1	9.1	9.1
Range	7.7 to 13.8	7.5 to 13.6	7.7 to 12.9
< 9.0%[2]	54 (41.9%)	54 (41.2%)	54 (41.9%)
≥ 9.0%	75 (58.1%)	77 (58.8%)	75 (58.1%)

Source: Analysis by this reviewer.

Notes:

[1] The number of cases comes from the totals in the FAS database developed by this reviewer for baseline HbA1c as a stratification variable (i.e., the number of cases with baseline HbA1c < 8.0% and the number of cases with HbA1c ≥ 8.0%). There are minor differences in these totals from the number of cases reported for the FAS database for the HbA1c endpoint.

[2] The stratification cutpoint for baseline HbA1c was 8.0% for Studies 007, 008, 009 and 010, and 9.0% for Study 011

3.1.3. Analysis populations

All five studies used the same definitions for the analysis populations, as follows:

Full Analysis Set (FAS): The FAS included all randomized subjects who had a baseline assessment and at least one post baseline assessment for the efficacy variable being analyzed. In FAS efficacy summaries, subjects were analyzed according to their randomized treatment assignment. Subjects who discontinued early had their HbA1c level in the last assessment carried forward to the study endpoint. Similarly, subjects who met the criteria for hyperglycemia rescue had the HbA1c level in the last assessment prior to rescue carried forward to the study endpoint.

Per Protocol Set (PPS): The PPS included all FAS subjects who had no major protocol violations. Subjects were analyzed according to the randomized treatment assignment.

Safety sets: The Enrolled Safety Set included all subjects who received at least one dose of single-blind placebo during the run-in/stabilization period. The Safety Set included all subjects who took at least one dose of double-blind study drug. In safety summaries, subjects were analyzed according to the most frequent treatment they received.

3.1.4. Primary efficacy variable

The primary efficacy variable in all five studies was the difference in HbA_{1c} at study endpoint (after 26 weeks of treatment) compared to baseline.

3.1.5. Statistical analysis methods for primary efficacy endpoint

Primary analysis method: The primary analysis was performed for the FAS using analysis of covariance (ANCOVA). The primary model included study treatment and geographic region as class variables, and diabetes duration and baseline HbA1c as continuous covariates. Supportive analyses were conducted using the PPS and the same ANCOVA model. Parameters in the ANCOVA models were estimated using SAS PROC MIXED using only fixed effects options. The F tests based on Type III sums of squares were used for all hypothesis testing.

For the primary analysis, the 25 mg dose was compared with placebo at the 2-sided 0.05 significance level using a contrast derived from the primary model. If this test was statistically significant, the 12.5 mg dose was to be evaluated in a similar fashion. Using this step-down strategy, no significance level adjustment was necessary for the multiple comparisons.

Empirical evaluations of change from baseline in HbA1c were conducted for subgroups defined by sex, age, race, ethnicity and baseline BMI. The applicant also evaluated the consistency of

the treatment effect across subgroups determined by region, by duration of diabetes, and by baseline HbA1c.

The biometrics review team concurred with the statistical methods proposed for the primary analysis of HbA1c (see the minutes to the November 28, 2005 end of phase 2 meeting). The review team suggested an additional sensitivity analysis, consisting of an analysis of subgroups defined by rescue status. The applicant did not conduct this sensitivity analysis, but I did so and have reported the results in Part 3.1.6 of this review. The review team also suggested that the applicant conduct additional exploratory analyses based on the methods described in White et al, *Statistics in Medicine*, 2001, 20: 2995-3008 ("Randomized clinical trials with added rescue medication: some approaches to their analysis and interpretation"). This reference describes alternative methods of accounting for patients who required hyperglycemic rescue therapy. The applicant did not present the results of these analyses in this submission. I did not conduct additional exploratory analyses for this review; however, a brief discussion of these methods is in Part 1.3.

3.1.6. Results of the statistical analysis of efficacy

HbA1c at week 26 – baseline: Alogliptin 12.5 mg and 25 mg produced statistically significant net reductions in HbA1c at week 26 compared to baseline, when compared with placebo as a monotherapy, and when given as an add-on to a sulfonylurea, metformin, pioglitazone, and to insulin (TABLE 7). The net effect of alogliptin 12.5 mg ranged from an average improvement in HbA1c of 0.4 to 0.5 across the five studies. The net effect of alogliptin 25 mg ranged from an average improvement of 0.5 to 0.6 across the five studies (TABLE 7). I confirmed the results for the primary analysis of HbA1c. The net effect of alogliptin of the 12.5 mg dose and the 25 mg dose was very similar and would not be separable statistically (this was not an objective of the studies).

Results from the sensitivity analysis of the HbA1c endpoint supported the efficacy of alogliptin 12.5 mg and 25 mg. The results from analyzing the Per Protocol population were very similar to the results from the FAS population (TABLE 8-TABLE 12). The results from analyzing subjects who completed the study (with no rescue) were supportive in showing a net improvement in HbA1c in the alogliptin arms compared to the placebo arm in each study (TABLE 8-TABLE 12). The results from analyzing subjects who did not complete the study because they were discontinued or rescued were supportive in general, although the smaller numbers of subjects in this subgroup meant that the 95% confidence interval of the placebo-adjusted effect of alogliptin included 0 in several of these comparisons (TABLE 8-TABLE 12). Estimates of the placebo-adjusted effect of alogliptin from the two subsets of completers and non-completers are influenced by the differential rescue rate in the alogliptin arms compared to the placebo arm, and for this reason these estimates are challenging to interpret. The most useful estimates of the placebo-adjusted effect of alogliptin come from the primary efficacy analysis in the FAS population.

The effect of alogliptin appears to be established by week 12, after which time the placebo-adjusted effect of alogliptin remained relatively constant, even though the average change from baseline decreased from week 12 through week 26 in the alogliptin arms and in the placebo arm (FIGURE 4-FIGURE 8). This decrease in average change from baseline in all arms may represent the progression of diabetes over the time course of the studies. However, the dynamics of disposition has also contributed to this apparent stabilization of response by week 12. In four of the five studies, a substantial proportion of rescues/discontinuations took place from weeks 12 through 16, following the change in criteria for hyperglycemic rescue from fasting plasma glucose to HbA1c at week 12 (FIGURE 2). The proportion of cases with HbA1c levels carried forward from weeks 12 through 16 has contributed to the apparent stabilization of HbA1c response by week 12.

TABLE 7 Changes in HbA1c in the five key studies (primary efficacy FAS population with LOCF) at week 26

Study **Treatment groups**	**N**	**Baseline mean ± SE**	**Adjusted mean change from baseline at Week 26 endpoint ± SE[1]**	**Difference in adjusted mean change (95% CI)[1]**	**P-value vs. control**
Study 010 (monotherapy)					
Alogliptin 25mg	128	7.91 ± 0.07	-0.59 ±0.07	-0.57 (-0.80, -0.35)	<0.001
Alogliptin 12.5 mg	131	7.91 ± 0.07	-0.56 ± 0.07	-0.54 (-0.76, -0.31)	<0.001
Placebo	63	8.03 ± 0.11	-0.02 ± 0.09		
Study 007 (add-on to sulfonylurea)					
Alogliptin 25mg	197	8.09 ± 0.06	-0.52 ± 0.06	-0.53 (-0.73, -0.33)	<0.001
Alogliptin 12.5 mg	201	8.08 ± 0.06	-0.38 ± 0.06	-0.39 (-0.59, -0.19)	<0.001
Placebo	97	8.15 ± 0.09	0.01 ± 0.08		
Study 008 (add-on to metformin)					
Alogliptin 25mg	203	7.93 ± 0.06	-0.59 ± 0.05	-0.48 (-0.67, -0.30)	<0.001
Alogliptin 12.5 mg	210	7.89 ± 0.05	-0.61 ± 0.05	-0.50 (-0.68, -0.32)	<0.001
Placebo	103	8.01 ± 0.09	-0.10 ± 0.08		
Study 009 (add-on to pioglitazone)					
Alogliptin 25mg	195	8.01 ± 0.06	-0.80 ± 0.06	-0.61 (-0.80, -0.41)	<0.001
Alogliptin 12.5 mg	196	8.08 ± 0.07	-0.66 ± 0.06	-0.47 (-0.67, -0.28)	<0.001
Placebo	95	7.97 ± 0.08	-0.19 ± 0.08		
Study 011 (add-on to insulin)					
Alogliptin 25mg	126	9.27 ± 0.10	-0.71 ± 0.08	-0.59 (-0.80, -0.37)	<0.001
Alogliptin 12.5 mg	130	9.29 ± 0.09	-0.63 ± 0.08	-0.51 (-0.72, -0.30)	<0.001
Placebo	126	9.28 ± 0.10	-0.13 ± 0.08		

Note:
[1] The adjusted mean change from baseline at week 26 and the difference in the adjusted mean change were estimated from the primary Analysis of Covariance model
Sources: Table 11.a in the clinical report of each study

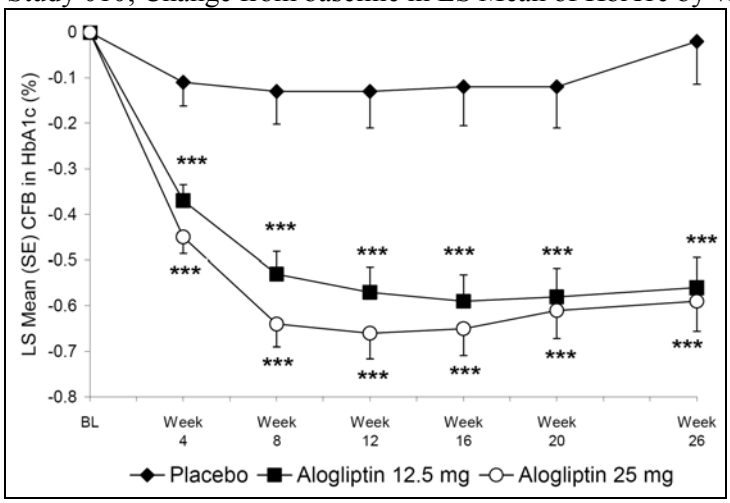
TABLE 8 Study 011; Results of primary and sensitivity analysis of HbA1c (change from baseline)

Study 010 (monotherapy) Treatment groups	**N**	**Baseline mean ± SE**	**Adjusted mean change from baseline at Week 26 endpoint ± SE**	**Difference in adjusted mean change (95% CI)**	**P-value vs. control**
Primary FAS population (LOCF)					
Alogliptin 25mg	128	7.91 ± 0.07	-0.59 ±0.07	-0.57 (-0.80, -0.35)	<0.001
Alogliptin 12.5 mg	131	7.91 ± 0.07	-0.56 ± 0.07	-0.54 (-0.76, -0.31)	<0.001
Placebo	63	8.03 ± 0.11	-0.02 ± 0.09		
Per Protocol population (LOCF)					
Alogliptin 25mg	124	7.94 ± 0.06	-0.62 ± 0.07	-0.60 (-0.83, -0.36)	<0.001
Alogliptin 12.5 mg	121	7.90 ± 0.07	-0.55 ± 0.07	-0.53 (-0.76, -0.30)	<0.001
Placebo	61	8.03 ± 0.12	-0.02 ± 0.10		
Completers[1]					
Alogliptin 25mg	107	7.81 ± 0.07	-0.71 ± 0.06	-0.36 (-0.58, -0.13)	0.002
Alogliptin 12.5 mg	105	7.76 ± 0.07	-0.65 ± 0.06	-0.30 (-0.53, -0.07)	0.010
Placebo	40	7.62 ± 0.11	-0.35 ± 0.10		
Rescued/Discontinued[1]					
Alogliptin 25mg	21	8.43 ± 0.20	-0.01 ± 0.19	-0.33 (-0.82, 0.15)	0.176
Alogliptin 12.5 mg	26	8.47 ± 0.18	-0.27 ± 0.18	-0.60 (-1.07, -0.13)	0.013
Placebo	23	8.74 ± 0.16	0.33 ± 0.8		

[1] Estimates of the net effect of alogliptin from the two subsets, subjects who completed and subjects who were rescued/discontinued are influenced by the differential rescue rate in the alogliptin arms compared to the placebo arm, and are challenging to interpret.

Sources: Study 010 Clinical Report, Table 11.a, Table 15.2.1.1.2, and additional analysis by this reviewer

FIGURE 4 Study 010; Change from baseline in LS Mean of HbA1c by visit; FAS/LOCF



Source: Study 011 Clinical Report, Figure 11.b
****P<0.001 compared to placebo arm*

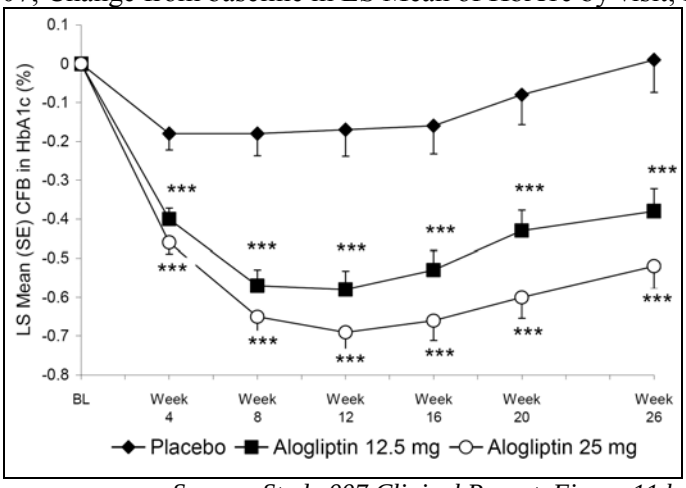
TABLE 9 Study 007; Results of primary and sensitivity analysis of HbA1c (change from baseline)

Study 007 (add-on to sulfonylurea) Treatment groups	**N**	**Baseline mean ± SE**	**Adjusted mean change from baseline at Week 26 endpoint ± SE[1]**	**Difference in adjusted mean change (95% CI) [1]**	**P-value vs. control**
Primary FAS population (LOCF)					
Alogliptin 25mg	197	8.09 ± 0.06	-0.52 ± 0.06	-0.53 (-0.73, -0.33)	<0.001
Alogliptin 12.5 mg	201	8.08 ± 0.06	-0.38 ± 0.06	-0.39 (-0.59, -0.19)	<0.001
Placebo	97	8.15 ± 0.09	0.01 ± 0.08		
Per Protocol population (LOCF)					
Alogliptin 25mg	187	8.09 ± 0.07	-0.53 ± 0.06	-0.55 (-0.76, -0.35)	<0.001
Alogliptin 12.5 mg	187	8.07 ± 0.06	-0.37 ± 0.06	-0.40 (-0.61, -0.19)	<0.001
Placebo	93	8.12 ± 0.09	0.03 ± 0.09		
Completers[1]					
Alogliptin 25mg	148	7.94 ± 0.07	-0.64 ± 0.07	-0.36 (-0.58, -0.14)	0.001
Alogliptin 12.5 mg	153	7.94 ± 0.06	-0.48 ± 0.07	-0.21 (-0.43, 0.01)	0.062
Placebo	62	7.91 ± 0.10	-0.28 ± 0.10		
Rescued/Discontinued[1]					
Alogliptin 25mg	49	8.52 ± 0.12	-0.06 ± 0.11	-0.48 (-0.80, -0.16)	0.003
Alogliptin 12.5 mg	48	8.53 ± 0.11	-0.04 ± 0.12	-0.45 (-0.77, -0.13)	0.006
Placebo	35	8.59 ± 0.13	0.42 ± 0.12		

[1] Estimates of the net effect of alogliptin from the two subsets, subjects who completed and subjects who were rescued/discontinued are influenced by the differential rescue rate in the alogliptin arms compared to the placebo arm, and are challenging to interpret.

Sources: Study 010 Clinical Report, Table 11.a, Table 15.2.1.1.2, and additional analysis by this reviewer

FIGURE 5 Study 007; Change from baseline in LS Mean of HbA1c by visit; FAS/LOCF



Source: Study 007 Clinical Report, Figure 11.b

**** P<0.001 compared to placebo arm*

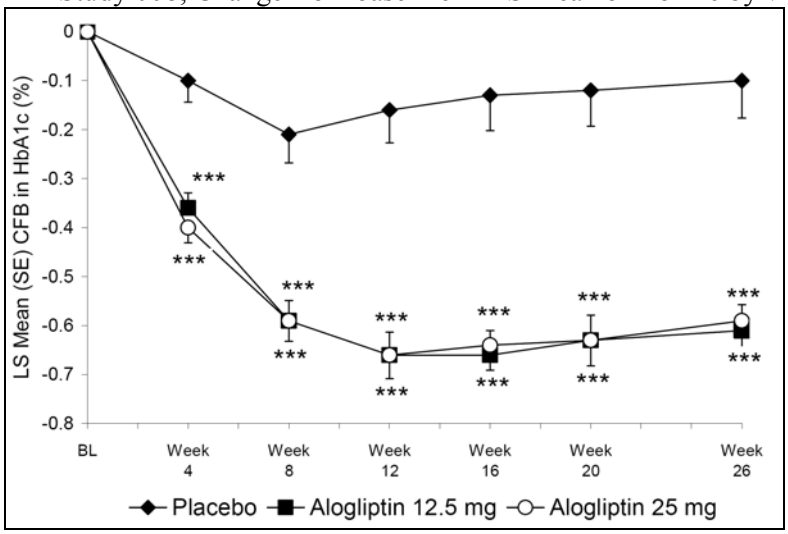
TABLE 10 Study 008; Results of primary and sensitivity analysis of HbA1c (change from baseline)

Study 008 (add-on to metformin) Treatment groups	N	Baseline mean ± SE	Adjusted mean change from baseline at Week 26 endpoint ± SE[1]	Difference in adjusted mean change (95% CI) [1]	P-value vs. control
Primary FAS population (LOCF)					
Alogliptin 25mg	203	7.93 ± 0.06	-0.59 ± 0.05	-0.48 (-0.67, -0.30)	<0.001
Alogliptin 12.5 mg	210	7.89 ± 0.05	-0.61 ± 0.05	-0.50 (-0.68, -0.32)	<0.001
Placebo	103	8.01 ± 0.09	-0.10 ± 0.08		
Per Protocol population (LOCF)					
Alogliptin 25mg	185	7.93 ± 0.06	-0.63 ± 0.06	-0.54 (-0.73, -0.35)	<0.001
Alogliptin 12.5 mg	193	7.85 ± 0.05	-0.63 ± 0.05	-0.54 (-0.73, -0.35)	<0.001
Placebo	94	8.04 ± 0.09	-0.09 ± 0.08		
Completers[1]					
Alogliptin 25mg	165	7.85 ± 0.06	-0.74 ± 0.05	-0.36 (-0.52, -0.18)	<0.001
Alogliptin 12.5 mg	176	7.73 ± 0.05	-0.73 ± 0.05	-0.35 (-0.52, -0.18)	<0.001
Placebo	72	7.73 ± 0.08	-0.38 ± 0.07		
Rescued/Discontinued[1]					
Alogliptin 25mg	38	8.28 ± 0.13	0.20 ± 0.13	-0.21 (-0.58, 0.17)	0.284
Alogliptin 12.5 mg	33	8.72 ± 0.15	-0.04 ± 0.14	-0.45 (-0.82, -0.07)	0.022
Placebo	31	8.65 ± 0.16	0.41 ± 0.14		

[1] Estimates of the net effect of alogliptin from the two subsets, subjects who completed and subjects who were rescued/discontinued are influenced by the differential rescue rate in the alogliptin arms compared to the placebo arm, and are challenging to interpret.

Sources: Study 010 Clinical Report, Table 11.a, Table 15.2.1.1.2, and additional analysis by this reviewer

FIGURE 6 Study 008; Change from baseline in LS Mean of HbA1c by visit; FAS/LOCF



Source: Study 008 Clinical Report, Figure 11.b
****P<0.001 compared to placebo arm*

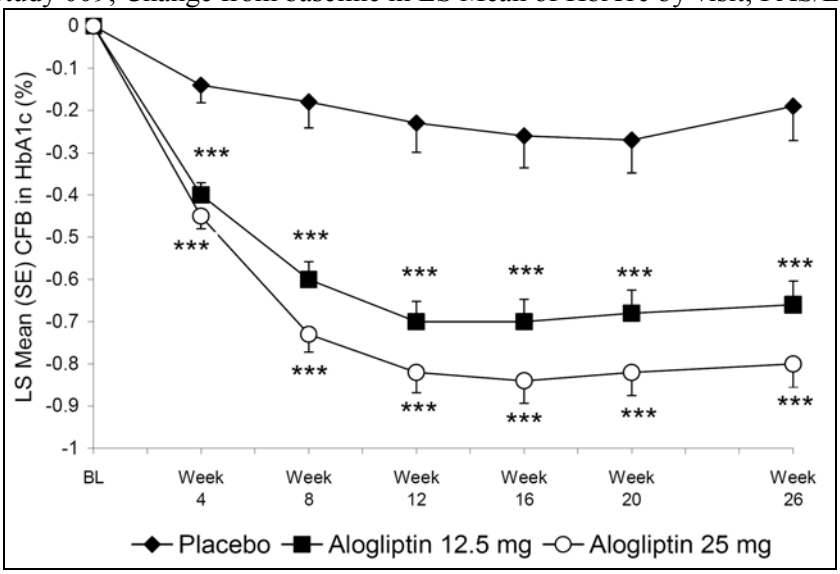
TABLE 11 Study 009; Results of primary and sensitivity analysis of HbA1c (change from baseline)

Study 009 (add-on to pioglitazone) Treatment groups	**N**	**Baseline mean ± SE**	**Adjusted mean change from baseline at Week 26 endpoint ± SE[1]**	**Difference in adjusted mean change (95% CI) [1]**	**P-value vs. control**
Primary FAS population (LOCF)					
Alogliptin 25mg	195	8.01 ± 0.06	-0.80 ± 0.06	-0.61 (-0.80, -0.41)	<0.001
Alogliptin 12.5 mg	196	8.08 ± 0.07	-0.66 ± 0.06	-0.47 (-0.67, -0.28)	<0.001
Placebo	95	7.97 ± 0.08	-0.19 ± 0.08		
Per Protocol population (LOCF)					
Alogliptin 25mg	178	7.96 ± 0.06	-0.78 ± 0.06	-0.54 (-0.74, -0.33)	<0.001
Alogliptin 12.5 mg	175	8.05 ± 0.06	-0.65 ± 0.06	-0.41 (-0.61, -0.20)	<0.001
Placebo	84	7.89 ± 0.08	-0.24 ± 0.09		
Completers[1]					
Alogliptin 25mg	160	7.85 ± 0.06	-0.93 ± 0.06	-0.48 (-0.65, -0.31)	<0.001
Alogliptin 12.5 mg	153	7.98 ± 0.07	-0.84 ± 0.06	-0.38 (-0.55, -0.21)	<0.001
Placebo	71	7.74 ± 0.09	-0.45 ± 0.08		
Rescued/Discontinued[1]					
Alogliptin 25mg	35	8.72 ± 0.14	-0.41 ± 0.17	-0.71 (-1.15, -0.26)	0.002
Alogliptin 12.5 mg	43	8.44 ± 0.17	-0.02 ± 0.15	-0.31 (-0.75, 0.12)	0.155
Placebo	24	8.66 ± 0.14	0.30 ± 0.20		

[1] Estimates of the net effect of alogliptin from the two subsets, subjects who completed and subjects who were rescued/discontinued are influenced by the differential rescue rate in the alogliptin arms compared to the placebo arm, and are challenging to interpret.

Sources: Study 010 Clinical Report, Table 11.a, Table 15.2.1.1.2, and additional analysis by this reviewer

FIGURE 7 Study 009; Change from baseline in LS Mean of HbA1c by visit; FAS/LOCF



Source: Study 009 Clinical Report, Figure 11.b
**** P<0.001 compared to placebo arm*

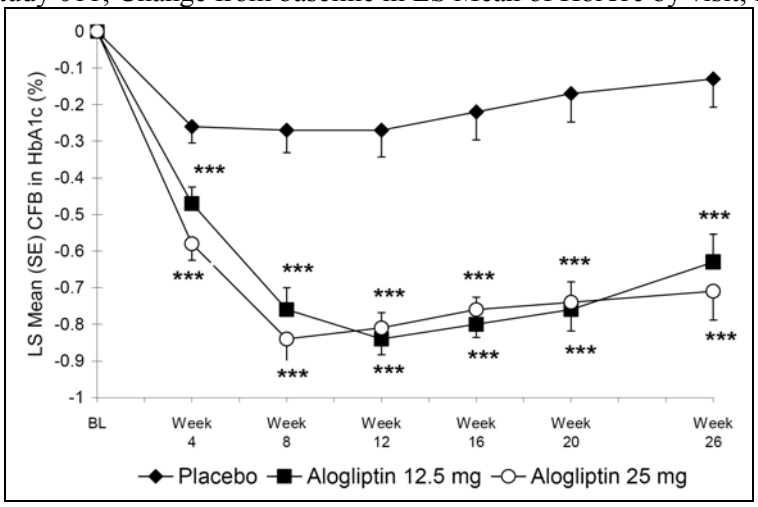
TABLE 12 Study 011; Results of primary and sensitivity analysis of HbA1c (change from baseline)

Study 011 (add-on to insulin) Treatment groups	**N**	**Baseline mean ± SE**	**Adjusted mean change from baseline at Week 26 endpoint ± SE[1]**	**Difference in adjusted mean change (95% CI) [1]**	**P-value vs. control**
Primary FAS population (LOCF)					
Alogliptin 25mg	126	9.27 ± 0.10	-0.71 ± 0.08	-0.59 (-0.80, -0.37)	<0.001
Alogliptin 12.5 mg	130	9.29 ± 0.09	-0.63 ± 0.08	-0.51 (-0.72, -0.30)	<0.001
Placebo	126	9.28 ± 0.10	-0.13 ± 0.08		
Per Protocol population (LOCF)					
Alogliptin 25mg	107	9.20 ± 0.10	-0.74 ± 0.08	-0.55 (-0.78, -0.33)	<0.001
Alogliptin 12.5 mg	115	9.25 ± 0.09	-0.58 ± 0.08	-0.39 (-0.61, -0.17)	<0.001
Placebo	103	9.16 ± 0.10	-0.18 ± 0.08		
Completers[1]					
Alogliptin 25mg	77	8.94 ± 0.10	-1.06 ± 0.09	-0.60 (-0.86, -0.35)	<0.001
Alogliptin 12.5 mg	83	9.12 ± 0.10	-0.79 ± 0.08	-0.33 (-0.58, -0.08)	0.011
Placebo	55	8.70 ± 0.10	-0.46 ± 0.10		
Rescued/Discontinued[1]					
Alogliptin 25mg	49	9.79 ± 0.18	-0.23 ± 0.12	-0.30 (-0.60, 0.00)	0.046
Alogliptin 12.5 mg	47	9.57 ± 0.18	-0.30 ± 0.12	-0.37 (-0.67, -0.06)	0.018
Placebo	71	9.73 ± 0.14	0.07 ± 0.10		

[1] Estimates of the net effect of alogliptin from the two subsets, subjects who completed and subjects who were rescued/discontinued are influenced by the differential rescue rate in the alogliptin arms compared to the placebo arm, and are challenging to interpret.

Sources: Study 011 Clinical Report, Table 11.a, Table 15.2.1.1.2, and additional analysis by this reviewer

FIGURE 8 Study 011; Change from baseline in LS Mean of HbA1c by visit; FAS/LOCF



Source: Study 011 Clinical Report, Figure 11.b
**** P<0.001 compared to placebo arm*

3.1.7. Other Efficacy Endpoints

Rescue/Discontinuation: The occurrence of rescue or discontinuation is an efficacy response, because the criteria for rescue involve HbA1c either directly or indirectly (see section 3.1.1). I combined the two outcomes together because I wanted to distinguish them from the outcome of completing a study without being rescued. Because the occurrence of discontinuation was relatively similar among and between studies, the differences among arms in the percentage of cases with the combined rescue/discontinuation outcome are mainly due to the rescue outcome.

The greater incidence of rescue/discontinuation in the placebo arm compared to the alogliptin arms in each study supports the efficacy of alogliptin. The odds of rescue/discontinuation were approximately twice as great in the placebo arm as in the alogliptin arms in four of the five studies (TABLE 13). The odds ratios ranged from 1.8 to 2.7, and the 95% confidence intervals did not include 1 in the monotherapy Study 010, the sulfonylurea add-on Study 007, the metformin add-on Study 008, and the insulin add-on Study 011. In the pioglitazone Study 009, the odds of rescue/discontinuation were 1.5 and 1.3 in the alogliptin arms compared to the placebo arm, and the 95% confidence intervals of these odds ratios did include 1 (TABLE 13).

TABLE 13 Incidence of rescue/discontinuation in the five key studies (Full Analysis Set)

Study Treatment groups	Number in Full Analysis Set	Number discontinued or rescued (%)	Odds ratio, Alogliptin vs. Placebo (95% CI) [1]
Study 010 (monotherapy)			
Alogliptin 25mg	131	24 (18.3%)	2.68 (1.37, 5.24)
Alogliptin 12.5 mg	133	28 (21.1%)	2.25 (1.17, 4.33)
Placebo	64	24 (37.5%)	
Study 007 (add-on to sulfonylurea)			
Alogliptin 25mg	198	50 (25.3%)	1.76 (1.05, 2.97)
Alogliptin 12.5 mg	203	50 (24.6%)	1.83 (1.09, 3.06)
Placebo	99	37 (37.4%)	
Study 008 (add-on to metformin)			
Alogliptin 25mg	207	42 (20.3%)	1.75 (1.02, 2.99)
Alogliptin 12.5 mg	212	36 (17.0%)	2.17 (1.25, 3.76)
Placebo	104	32 (30.8%)	
Study 009 (add-on to pioglitazone)			
Alogliptin 25mg	199	39 (19.6%)	1.50 (0.85, 2.66)
Alogliptin 12.5 mg	197	44 (22.3%)	1.27 (0.73, 2.23)
Placebo	97	26 (26.8%)	
Study 011 (add-on to insulin)			
Alogliptin 25mg	129	52 (40.3%)	1.99 (1.21, 3.27)
Alogliptin 12.5 mg	131	48 (36.6%)	2.33 (1.41, 3.83)
Placebo	129	74 (57.4%)	

[1] The odds ratio and confidence interval are based on an asymptotic estimate.
Sources: Analysis by this reviewer

Change from Baseline in Fasting Plasma Glucose: The efficacy of alogliptin was also demonstrated by a greater average change from baseline in fasting plasma glucose (FPG) compared to baseline. This change was statistically significant in three of the five key studies. In Study 011 (add-on to insulin) and Study 007 (add-on to pioglitazone), neither of the alogliptin dose arms were statistically significantly different from the placebo arm (TABLE 14).

TABLE 14 Change from baseline in mean Fasting Plasma Glucose (mg/dL) at week 26 in the five key studies (primary efficacy FAS population with LOCF)

Study **Treatment groups**	**N**	**Baseline mean FPG (mg/dL) ± SE**	**Adjusted mean change from baseline at Week 26 endpoint ± SE[1]**	**Difference in adjusted mean change (95% CI) [1]**	**P-value vs. control**
Study 010 (monotherapy)					
Alogliptin 25 mg	131	172.0 ± 3.7	-16.4 ± 3.7	-27.8 (-40.4, -15.1)	<0.001
Alogliptin 12.5 mg	133	173.5 ± 4.3	-10.3 ± 3.6	-21.6 (-34.1, -9.0)	<0.001
Placebo	64	173.4 ± 6.5	11.3 ± 5.2		
Study 007 (add-on to sulfonylurea)					
Alogliptin 25 mg	198	173.9 ± 3.5	-8.4 ± 3.4	-10.5 (-22.0, 0.9)	0.072
Alogliptin 12.5 mg	201	171.9 ± 3.5	-4.7 ± 3.3	-6.8 (-18.3, 4.6)	0.241
Placebo	99	177.3 ± 5.2	2.2 ± 4.8		
Study 008 (add-on to metformin)					
Alogliptin 25 mg	204	171.9 ± 3.2	-17.4 ± 2.5	-17.4 (-25.9, -8.8)	<0.001
Alogliptin 12.5 mg	211	168.3 ± 3.0	-18.7 ± 2.5	-18.7 (-27.3, -10.2)	<0.001
Placebo	104	179.5 ± 4.9	0.0 ± 3.6		
Study 009 (add-on to pioglitazone)					
Alogliptin 25 mg	197	169.5 ± 3.3	-19.9 ± 2.7	-14.1 (-23.3, -5.0)	0.003
Alogliptin 12.5 mg	196	173.4 ± 3.3	-19.7 ± 2.7	-13.9 (-23.1, -4.8)	0.003
Placebo	97	171.7 ± 5.2	-5.7 ± 3.8		
Study 011 (add-on to insulin)					
Alogliptin 25 mg	128	186.3 ± 6.2	-11.7 ± 5.7	-17.6 (-33.4, -1.7)	0.030
Alogliptin 12.5 mg	131	189.8 ± 5.4	2.3 ± 5.6	-3.5 (-19.2, 12.2)	0.662
Placebo	127	196.0 ± 6.9	5.8 ± 5.7		

Note:
[1] The adjusted mean change from baseline at week 26 and the difference in the adjusted mean change were estimated from the primary Analysis of Covariance model
Sources: Table 11.d in the clinical report of each study

Body weight: Although the large majority of subjects in each study, 84% to 94%, stayed within ± 5% of their baseline body weight at week 26 (FIGURE 9 to FIGURE 13), different studies had different patterns of weight change. Only one study showed an apparent effect of alogliptin on weight gain relative to placebo. In the add-on to sulfonylurea study 007, the alogliptin arms had a net average weight gain of 0.8 kg (12.5 mg arm) and 0.9 kg (25 mg arm) relative to placebo (TABLE 15). These placebo-adjusted weight gains had p-values < 0.05. Approximately two-thirds of the subjects in the alogliptin arms had a weight gain, compared to approximately half of the subjects in the placebo arm (FIGURE 10). The other four studies did not show a net weight change in the alogliptin arms compared to placebo. Patterns of weight change in these studies were similar among arms, but different between studies, as follows:

- In the monotherapy study 010, the placebo and the alogliptin arms had a similar distribution of weight at week 26, expressed as a percentage change from the baseline body weight. A somewhat greater percentage of subjects had a weight gain, ranging from 53% to 59% in the three arms, compared to a weight loss, ranging from 41% to 47% (FIGURE 9). The placebo adjusted average weight change was an average gain of 0.3 kg in the 12.5 mg arm and 0.4 kg in the 25 mg arm (TABLE 15). The p-values of 0.379 and 0.539, respectively, of these adjusted weight changes reflect the similarity in the pattern of weight change among the placebo and alogliptin arms.

- In the add-on to metformin study 008, the placebo and the alogliptin arms had a similar distribution of weight change at week 26, with a somewhat greater percentage of subjects with a weight loss, ranging from 53% to 56% in the three arms (FIGURE 11). The placebo adjusted average weight change of 0.0 kg in the 12.5 mg arm and a loss of 0.3 kg in the 25 mg arm, with p-values of 0.407 and 0.996, respectively, reflect the similarity in the pattern of weight change among the three arms (TABLE 15).

- In the add-on to pioglitazone study 009 and the add-on to insulin study 011, approximately twice as many subjects showed a weight gain than a weight loss in the placebo and the alogliptin arms (FIGURE 12 and FIGURE 13). The placebo adjusted weight changes were small, ranging from 0.0 kg in the alogliptin 25 mg arm of the insulin add-on study to 0.4 kg in the 12.5 mg arm of the pioglitazone add-on study (TABLE 15), and the p-values ranged from 0.294 to 0.948, reflecting the similarity in the pattern of weight change among the three arms.

In each study, the alogliptin arms and the placebo arms were relatively similar to each other in the percentage of subjects staying within ± 5% of their baseline body weight. These results support the conclusion that alogliptin does not have an important clinical effect on body weight.

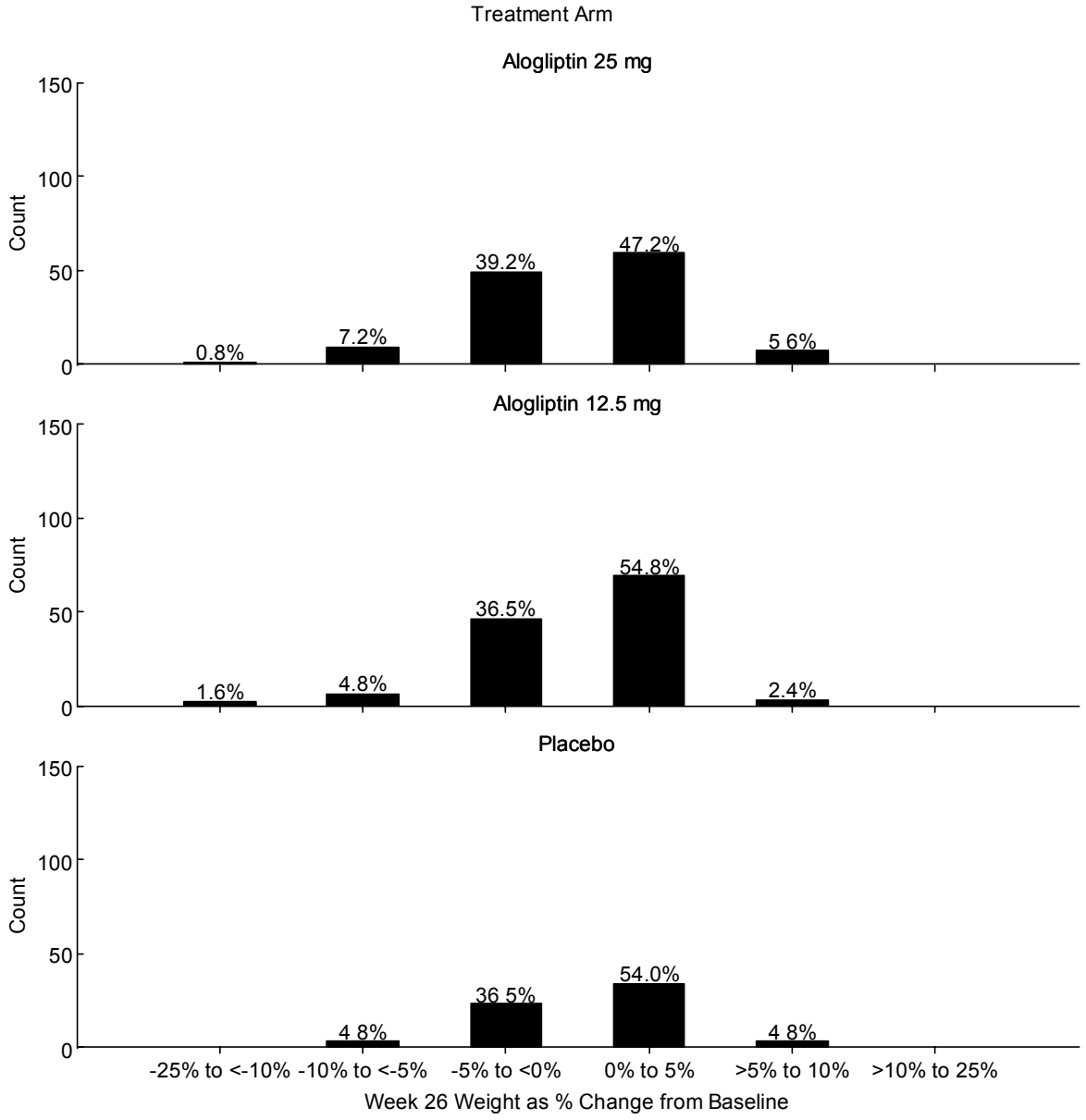
TABLE 15 Change from baseline in mean body weight (kg) at week 26 in the five key studies (primary efficacy FAS population with LOCF)

Study **Treatment groups**	**N**	**Baseline mean FPG (mg/dL) ± SE**	**Adjusted mean change from baseline at Week 26 endpoint ± SE[1]**	**Difference in adjusted mean change (95% CI) [1]**	**P-value vs. control**
Study 010 (monotherapy)					
Alogliptin 25 mg	125	88.8 ± 1.8	-0.2 ± 0.3	-0.4 (-1.3, 0.5)	0.379
Alogliptin 12.5 mg	126	88.2 ± 1.8	-0.1 ± 0.3	-0.3 (-1.2, 0.6)	0.539
Placebo	63	90.2 ± 2.8	0.2 ± 0.4		
Study 007 (add-on to sulfonylurea)					
Alogliptin 25 mg	195	80.4 ± 1.4	0.7 ± 0.2	0.9 (0.2, 1.5)	0.010
Alogliptin 12.5 mg	197	82.0 ± 1.2	0.6 ± 0.2	0.8 (0.1, 1.5)	0.018
Placebo	96	80.8 ± 2.1	-0.2 ± 0.3		
Study 008 (add-on to metformin)					
Alogliptin 25 mg	198	88.1 ± 1.4	-0.7 ± 0.2	-0.3 (-0.9, 0.4)	0.407
Alogliptin 12.5 mg	206	87.7 ± 1.3	-0.4 ± 0.2	0.0 (-0.7, 0.7)	0.996
Placebo	103	89.3 ± 2.0	-0.4 ± 0.3		
Study 009 (add-on to pioglitazone)					
Alogliptin 25 mg	189	94.8 ±1.5	1.1 ± 0.2	0.1 (-0.7, 0.8)	0.900
Alogliptin 12.5 mg	193	92.7 ± 1.5	1.5 ± 0.2	0.4 (-0.4, 1.2)	0.294
Placebo	94	95.7 ± 2.3	1.0 ± 0.3		
Study 011 (add-on to insulin)					
Alogliptin 25 mg	124	85.8 ± 1.7	0.6 ± 0.2	0.0 (-0.7, 0.7)	0.948
Alogliptin 12.5 mg	127	88.2 ± 1.8	0.7 ± 0.2	0.1 (-0.6, 0.7)	0.874
Placebo	121	91.2 ± 1.9	0.6 ± 0.2		

Note:
[1] The adjusted mean change from baseline at week 26 and the difference in the adjusted mean change were estimated from the primary Analysis of Covariance model

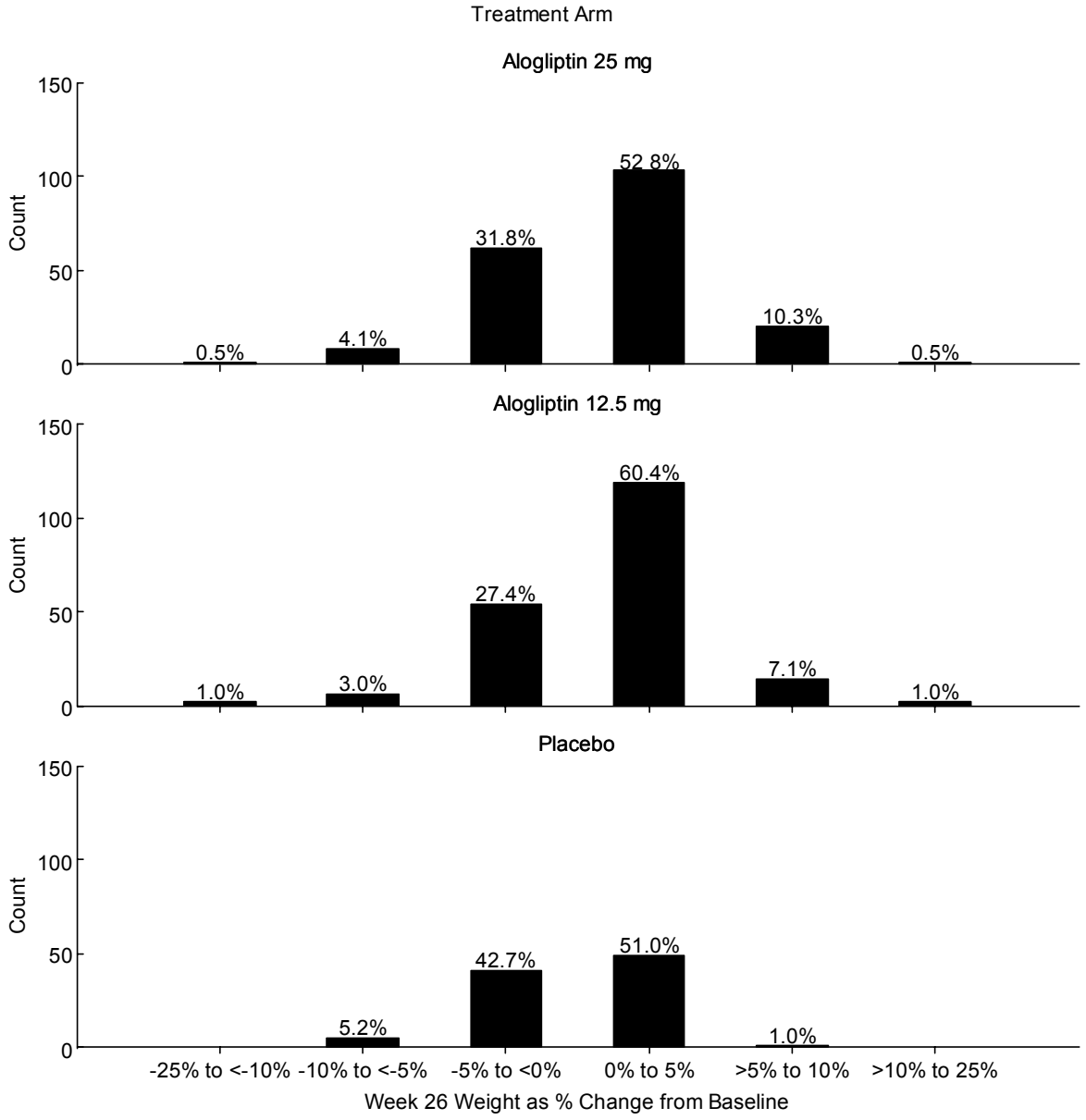
Sources: Table 15.2.7.1 in the clinical report of study 010, 007, 008 and 009, and Table 15.2.4.1 in the clinical report of study 011.

FIGURE 9 Study 010; Monotherapy study; Body weight at Week 26 as a % change from baseline (FAS population with LOCF)



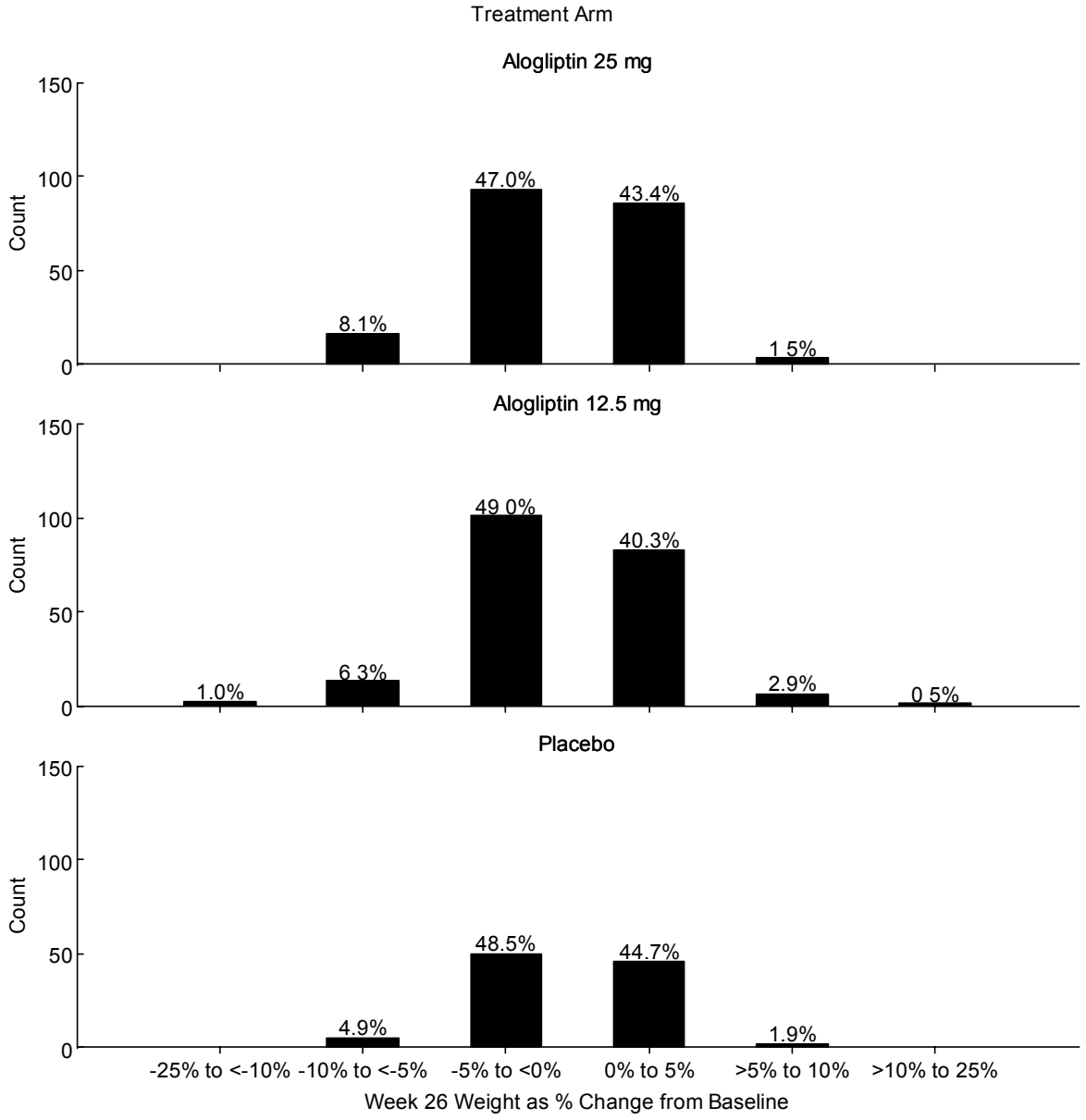
Source: Analysis by this reviewer

FIGURE 10 Study 007; Add-on to sulfonylurea; Body weight at Week 26 as % change from baseline (FAS population with LOCF)



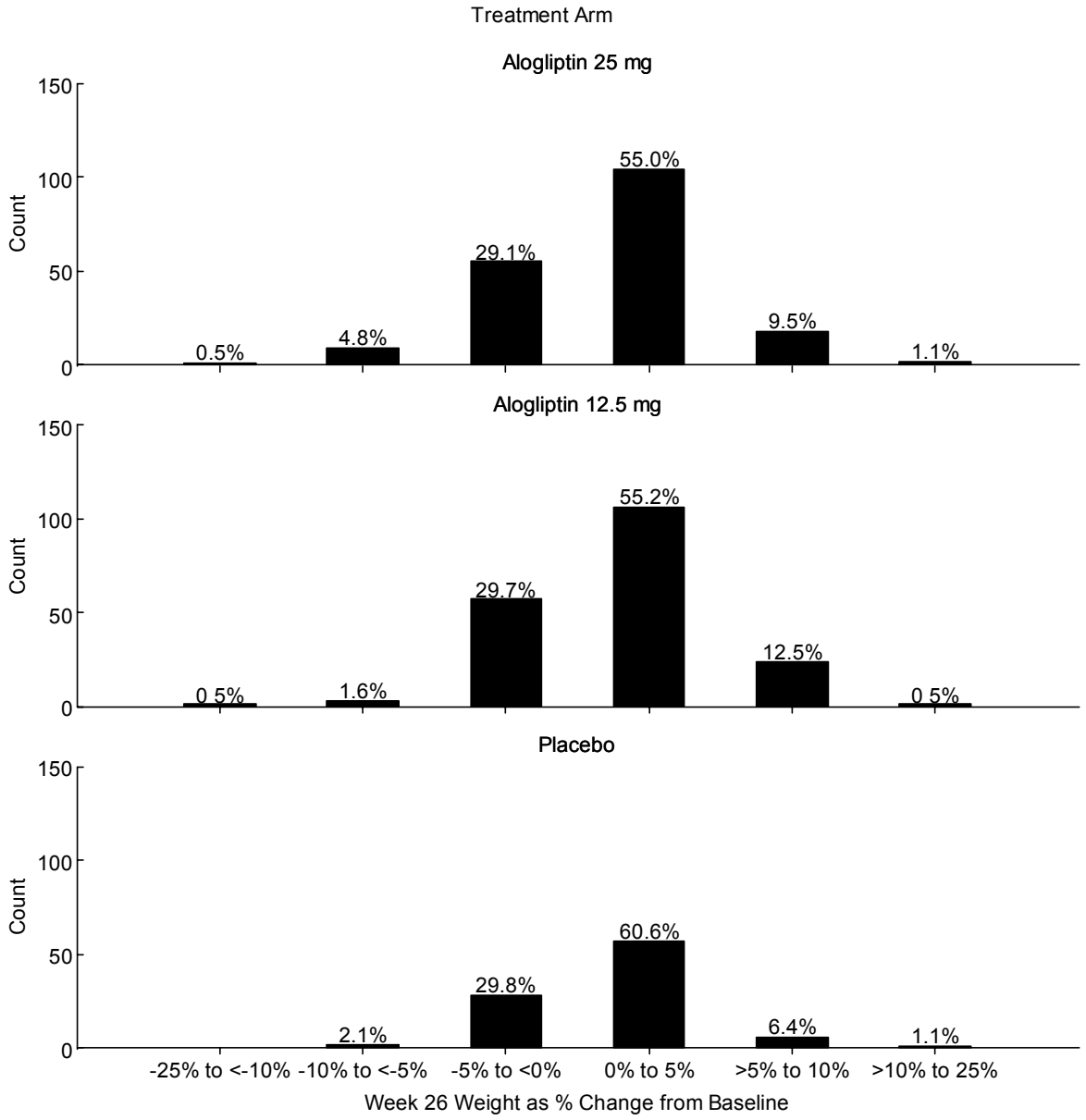
Source: Analysis by this reviewer

FIGURE 11 Study 008; Add-on to metformin; Body weight at Week 26 as % change from baseline; (FAS population with LOCF)



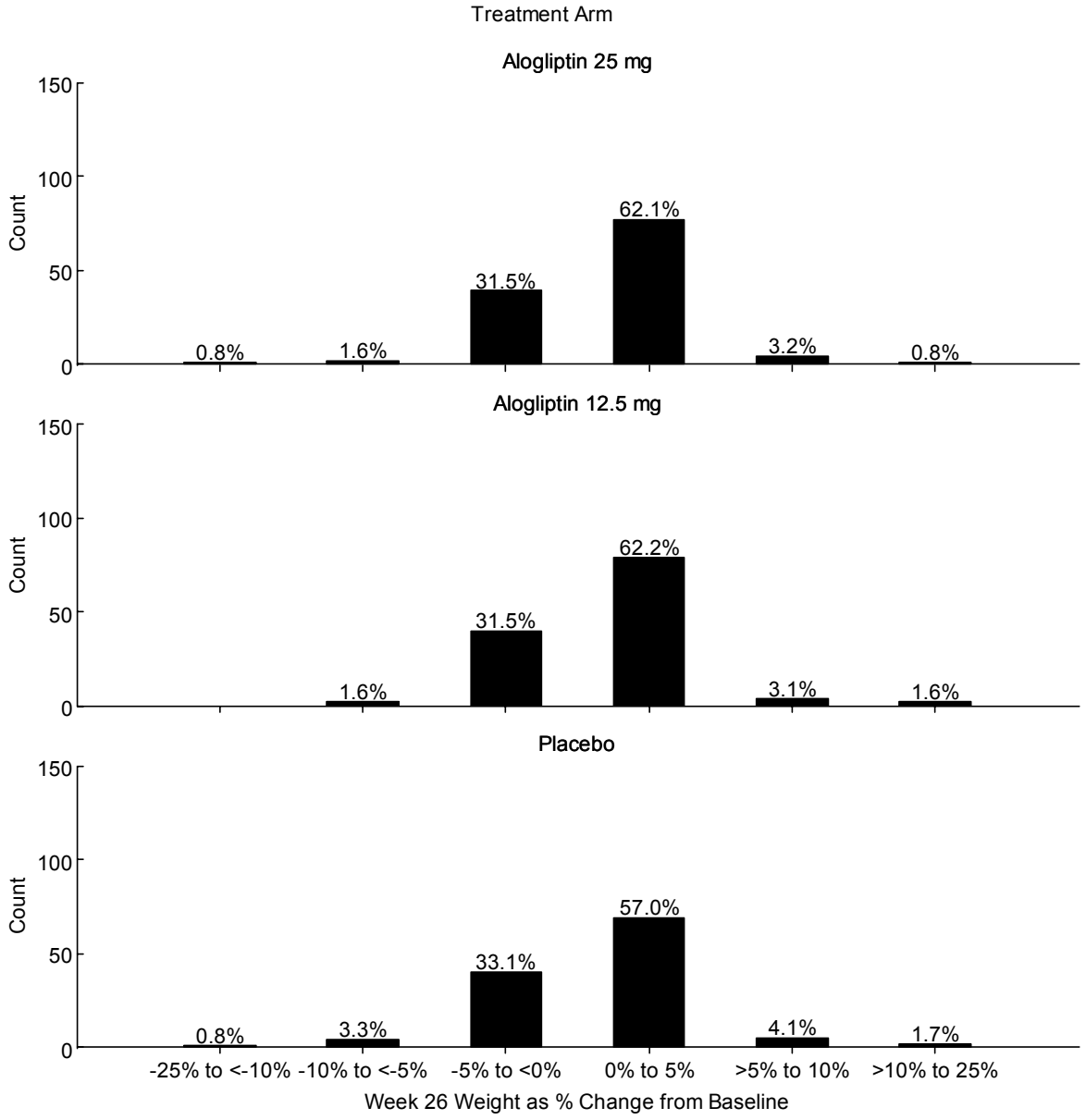
Source: Analysis by this reviewer

FIGURE 12 Study 009; Add-on to pioglitazone; Body weight at Week 26 as % change from baseline (FAS population with LOCF)



Source: Analysis by this reviewer

FIGURE 13 Study 011; Add-on to insulin; Body weight at Week 26 as % change from baseline (FAS population with LCOF)



Source: Analysis by this reviewer

3.2 Evaluation of Safety

An evaluation of safety is primarily covered in the FDA clinical review by Dr. Joanna Zawadski.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The average HbA_{1c} response in the younger and older age groups (< 65 and ≥ 65 years) were relatively similar (TABLE 16 through TABLE 21). The average HbA1c response for males appeared to be somewhat greater than in females. For this reason, I estimated the difference between males and females in the placebo-adjusted HbA1c change from baseline from the analysis of covariance model. The model-based comparisons did not show a strong or consistent trend among studies (TABLE 16 through TABLE 21; see end note 1 in each table). Most subjects were Caucasian in each of the five key studies. The numbers of subjects in the other identified race categories were small and did not support an evaluation of potential race-related difference in HbA_{1c} reduction. Two of the studies had sufficient number of subjects who were in the Hispanic/Latino ethnicity category to support an exploratory evaluation. In Studies 008 and 011, subjects in both ethnicity categories had about the same average reduction in HbA1c in the alogliptin arms compared to placebo (TABLE 18, TABLE 20).

TABLE 16 Study 010; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the FAS/LOCF population by age, gender, race and ethnicity

Study 010 (monotherapy)	**Placebo**			**Alogliptin 12.5 mg**			**Alogliptin 25 mg**		
	n	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**
Age (years)									
<65	52	8.1	0. 0 (0.9)	108	8.0	-0.5 (0.7)	110	8.0	-0.6 (0.8)
≥ 65	11	7.8	-0.1 (0.9)	23	7.7	-0.7 (0.5)	18	7.5	-0.8 (0.7)
Sex [1]									
Male	32	7.9	0.0 (0.9)	64	7.9	-0.7 (0.7)	75	7.9	-0.6 (0.8)
Female	31	8.1	-0.1 (0.9)	67	7.9	-0.5 (0.7)	53	7.9	-0.6 (0.8)
Race									
Caucasian	44	7.9	0.1 (1.0)	88	8.0	-0.5 (0.7)	85	7.9	-0.6 (0.7)
Black	5	7.6	-0.2 (0.3)	10	7.6	-0.3 (0.7)	10	7.9	-0.3 (1.3)
Asian	6	8.0	-0.2 (0.5)	16	8.0	-0.6 (0.7)	15	7.8	-0.8 (0.8)
Native American	0			1			0		
Pacific Islander	1			0			0		
Other	7	8.7	-0.4 (0.3)	16	7.9	0.7 (0.7)	18	7.9	-0.7 (0.8)
Ethnicity									
Hispanic/Latino	17	8.1	-0.5 (0.7)	36	7.9	-0.8 (0.8)	33	8.1	-0.7 (0.9)
not Hispanic/Latino	46	8.0	0.1 (0.9)	95	7.9	-0.5 (0.7)	95	7.9	-0.6 (0.8)

Note:
[1] Model-based LS Mean Change from Baseline (95%CI) for Male vs Female: -0.2 (-0.6, 0.3) for Alogliptin 12.5 mg – Placebo, 0.0 (-0.5, 0.4) for Alogliptin 25 mg - Placebo
Source: Study 010 Study Report, Table 15.2.1.6.1, Table 15.2.1.7.1, Table 15.2.1.8.1 and Table 15.2.1.9.1 and additional analysis by this reviewer

TABLE 17 Study 007; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the FAS/LOCF population by age, gender, race and ethnicity

Study 007 (add-on to sulfonylurea)	**Placebo**			**Alogliptin 12.5 mg**			**Alogliptin 25 mg**		
	n	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**
Age (years)									
<65	70	8.2	0.0 (1.0)	152	8.1	-0.3 (0.8)	145	8.1	-0.4 (0.9)
≥ 65	27	8.1	0.0 (0.7)	49	7.9	-0.6 (0.7)	52	8.0	-0.8 (0.8)
Sex[1]									
Male	49	8.1	0.0 (0.9)	109	8.0	-0.4 (0.7)	99	8.1	-0.6 (0.9)
Female	48	8.3	-0.1 (0.9)	92	8.2	-0.3 (0.8)	98	8.1	-0.4 (0.9)
Race									
Caucasian	70	8.1	-0.1 (0.9)	140	8.1	-0.4 (0.8)	140	8.0	-0.5 (0.9)
Black	3	7.6	0.0 (0.3)	8	8.0	-0.5 (0.6)	11	8.2	-0.7 (1.1)
Asian	13	8.5	0.4 (0.7)	20	8.0	-0.4 (1.0)	24	8.4	-0.3 (0.7)
Native American	0			0			0		
Pacific Islander	0			0			0		
Other	11	8.4	0.0 (1.2)	33	8.2	-0.4 (0.8)	22	8.2	-1.0 (0.7)
Ethnicity									
Hispanic/Latino	48	8.2	-0.2 (0.9)	97	8.1	-0.3 (0.8)	103	8.0	-0.6 (0.9)
not Hispanic/Latino	49	8.1	0.1 (0.7)	104	8.0	-0.5 (0.8)	94	8.2	-0.5 (0.8)

Note:
[1] Model-based LS Mean Change from Baseline (95%CI) for Male vs Female: -0.2 (-0.6, 0.2) for Alogliptin 12.5 mg – Placebo, -0.3 (-0.7, 0.1) for Alogliptin 25 mg - Placebo

Source: Study 007 Study Report, Table 15.2.1.6.1, Table 15.2.1.7.1, Table 15.2.1.8.1 and Table 15.2.1.9.1, and additional analysis by this reviewer

TABLE 18 Study 008; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the FAS/LOCF population by age, gender, race and ethnicity

Study 008 (add-on to metformin)	**Placebo**			**Alogliptin 12.5 mg**			**Alogliptin 25 mg**		
	n	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**
Age (years)									
<65	82	8.0	-0.1 (1.0)	170	7.9	-0.6 (0.7)	172	8.0	-0.6 (0.8)
≥ 65	21	7.9	-0.2 (1.3)	40	7.8	-0.5 (0.8)	31	7.7	-0.5 (0.9)
Sex[1]									
Male	50	7.9	-0.2 (0.9)	99	7.9	-0.7 (0.7)	108	8.0	-0.6 (0.8)
Female	53	8.1	-0.1 (0.7)	111	7.9	-0.5 (0.8)	95	7.9	-0.6 (0.8)
Race									
Caucasian	78	8.0	-0.1 (0.9)	169	7.9	-0.6 (0.8)	154	7.9	-0.5 (0.8)
Black	7	8.1	-0.6 (1.0)	5	7.7	-0.6 (0.7)	11	7.8	-0.8 (0.6)
Asian	6	7.6	0.2 (0.2)	16	7.9	-0.8 (0.8)	18	8.1	-1.0 (0.6)
Native American	1			1			1		
Pacific Islander	0			1			0		

Study 008 (add-on to metformin)	Placebo n	Placebo Base-line mean	Placebo Change from baseline (SD)	Alogliptin 12.5 mg n	Alogliptin 12.5 mg Base-line mean	Alogliptin 12.5 mg Change from baseline (SD)	Alogliptin 25 mg n	Alogliptin 25 mg Base-line mean	Alogliptin 25 mg Change from baseline (SD)
Other	11	8.3	0.0 (0.8)	18	7.9	-0.7 (0.6)	19	8.1	-0.9 (0.6)
Ethnicity									
Hispanic/Latino	25	8.2	-0.2 (0.8)	65	8.0	-0.7 (0.7)	67	8.0	-0.6 (0.9)
not Hispanic/Latino	78	8.0	-0.1 (0.8)	145	7.9	-0.6 (0.8)	136	7.9	-0.6 (0.7)

Note:
[1] Model-based LS Mean Change from Baseline (95%CI) for Male vs Female: 0.0 (-0.4, 0.3) for Alogliptin 12.5 mg – Placebo, 0.1 (-0.2, 0.5) for Alogliptin 25 mg - Placebo

Source: Study 008 Study Report, Table 15.2.1.6.1, Table 15.2.1.7.1, Table 15.2.1.8.1 and Table 15.2.1.9.1, and additional analysis by this reviewer

TABLE 19 Study 009; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the FAS/LOCF population by age, gender, race and ethnicity

Study 009 (add-on to pioglitazone)	Placebo n	Placebo Base-line mean	Placebo Change from baseline (SD)	Alogliptin 12.5 mg n	Alogliptin 12.5 mg Base-line mean	Alogliptin 12.5 mg Change from baseline (SD)	Alogliptin 25 mg n	Alogliptin 25 mg Base-line mean	Alogliptin 25 mg Change from baseline (SD)
Age (years)									
<65	81	8.0	-0.2 (0.8)	164	8.1	-0.7 (0.9)	156	8.0	-0.8 (0.8)
≥ 65	14	7.8	0.1 (0.6)	32	8.0	-0.7 (0.6)	39	7.9	-0.8 (0.8)
Sex[1]									
Male	53	7.8	-0.1 (0.7)	108	8.1	-0.6 (0.9)	123	8.0	-0.8 (0.8)
Female	42	8.2	-0.3 (1.0)	88	8.1	-0.7 (0.9)	72	8.1	-0.8 (0.9)
Race									
Caucasian	69	7.9	-0.1 (0.7)	142	8.0	-0.6 (0.7)	148	8.0	-0.8 (0.8)
Black	10	8.5	-0.1 (0.9)	22	8.4	-1.0 (1.2)	13	7.9	-1.1 (0.9)
Asian	11	8.1	-0.5 (0.9)	18	8.4	-1.0 (0.9)	24	8.0	-0.8 (0.9)
Native American	1			1			1		
Pacific Islander	0			1			0		
Other	4	7.7	-0.3 (0.8)	12	8.5	-0.7 (1.4)	8	7.9	-0.8 (0.4)
Ethnicity									
Hispanic/Latino	9	7.7	-0.1 (1.0)	37	8.3	-0.7 (1.0)	31	8.0	-0.9 (0.7)
not Hispanic/Latino	86	8.0	-0.3 (0.8)	159	8.0	-0.7 (0.8)	164	8.0	-0.8 (0.8)

Note:
[1] Model-based LS Mean Change from Baseline (95%CI) for Male vs Female: 0.0 (-0.4, 0.4) for Alogliptin 12.5 mg – Placebo, -0.1 (-0.5, 0.3) for Alogliptin 25 mg - Placebo

Source: Study 009 Study Report, Table 15.2.1.7.1, Table 15.2.1.8.1, Table 15.2.1.9.1 and Table 15.2.1.10.1, and additional analysis by this reviewer

TABLE 20 Study 011; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the FAS/LOCF population by age, gender, race and ethnicity

Study 011 (add-on to insulin)	**Placebo**			**Alogliptin 12.5 mg**			**Alogliptin 25 mg**		
	n	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**
Age (years)									
<65	106	9.4	-0.1 (0.8)	111	9.3	-0.6 (1.1)	103	9.4	-0.7 (0.9)
≥ 65	20	8.9	-0.4 (0.7)	19	9.1	-0.7 (0.8)	23	8.9	-0.7 (0.7)
Sex[1]									
Male	59	9.2	-0.1 (0.8)	54	9.3	-0.7 (1.1)	42	8.9	-0.7 (0.7)
Female	67	9.4	-0.1 (0.9)	76	9.3	-0.6 (1.0)	84	9.5	-0.8 (0.9)
Race									
Caucasian	86	9.1	-0.1 (0.7)	81	9.2	-0.7 (1.1)	83	9.2	-0.6 (0.8)
Black	16	9.9	0.1 (0.9)	18	9.6	-0.5 (1.2)	18	9.6	-0.8 (1.0)
Asian	14	9.4	-0.4 (0.5)	16	9.1	-0.4 (0.6)	15	9.2	-1.0 (1.1)
Native American	0			0			1		
Pacific Islander	1			1			0		
Other	9	9.3	0.0 (0.7)	14	9.6	-0.5 (0.8)	9	9.6	-0.9 (0.7)
Ethnicity									
Hispanic/Latino	41	9.5	-0.2 (0.8)	45	9.6	-0.9 (1.2)	42	9.7	-0.7 (0.9)
not Hispanic/Latino	85	9.2	-0.1 (0.8)	85	9.1	-0.5 (0.9)	84	9.1	-0.7 (0.9)

Note:
[1] Model-based LS Mean Change from Baseline (95%CI) for Male vs Female: -0.1 (-0.5, 0.3) for Alogliptin 12.5 mg – Placebo, 0.1 (-0.4, 0.5) for Alogliptin 25 mg - Placebo

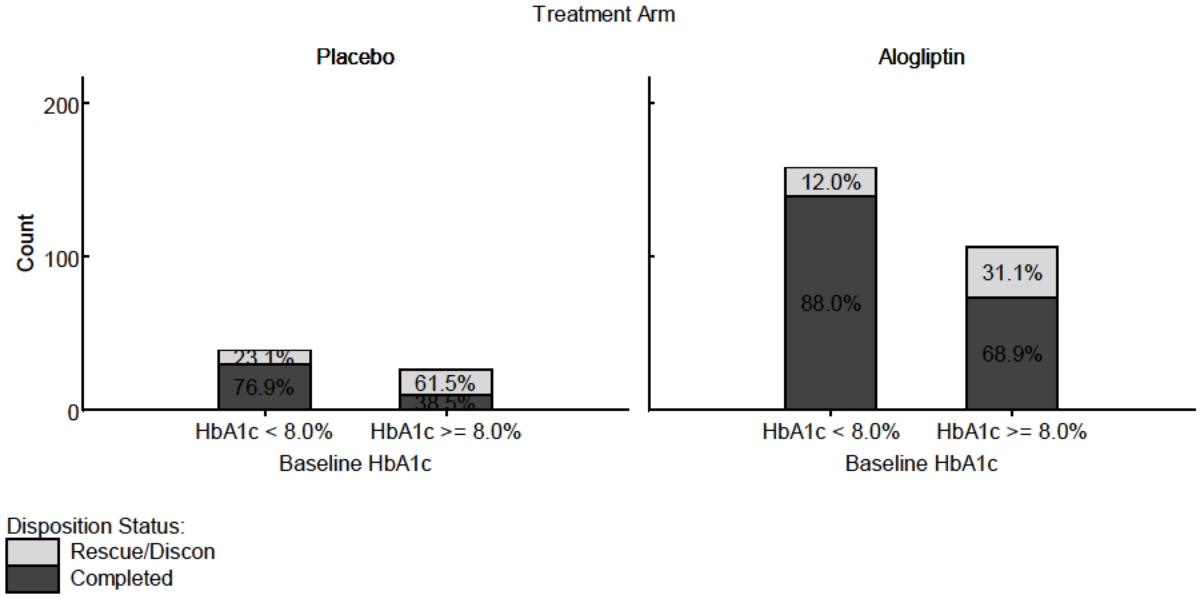
Source: Study 011 Study Report, Table 15.2.1.7.1, Table 15.2.1.8.1, Table 15.2.1.9.1 and Table 15.2.1.10.1, and additional analysis by this reviewer

4.2 Other Special/Subgroup Populations

Baseline HbA1c and the occurrence of rescue/discontinuation: Subjects who entered a study in the higher baseline HbA1c stratification level were more likely to meet the criteria for rescue, compared to subjects in the lower stratification level. This finding is consistent with the criteria for rescue. This pattern is illustrated in FIGURE 14 through FIGURE 18. The two alogliptin dose arms were combined in the figures for increased clarity, because the results for both arms were similar within each study. Similarly, the occurrence of rescue and discontinuation were combined in the figures to make the distinction between subjects who completed a study and those who did not. Because the occurrence of discontinuation was relatively similar among and between studies, the differences among arms in the percentage of cases with the combined rescue/discontinuation outcome are mainly due to the rescue outcome. More detailed results are summarized in TABLE 27 in the Technical Appendix. The baseline HbA1c cutpoint of 8.0 was

used to define the stratification levels for Studies 007, 008, 009 and 010, and the cutpoint of 9.0 was used for Study 011.

FIGURE 14 Study 010 (monotherapy); Percentage of rescued/discontinued by baseline HbA1c



Source: Analysis by this reviewer

FIGURE 15 Study 007 (add-on to sulfonylurea); Percentage of rescued/discontinued by baseline HbA1c

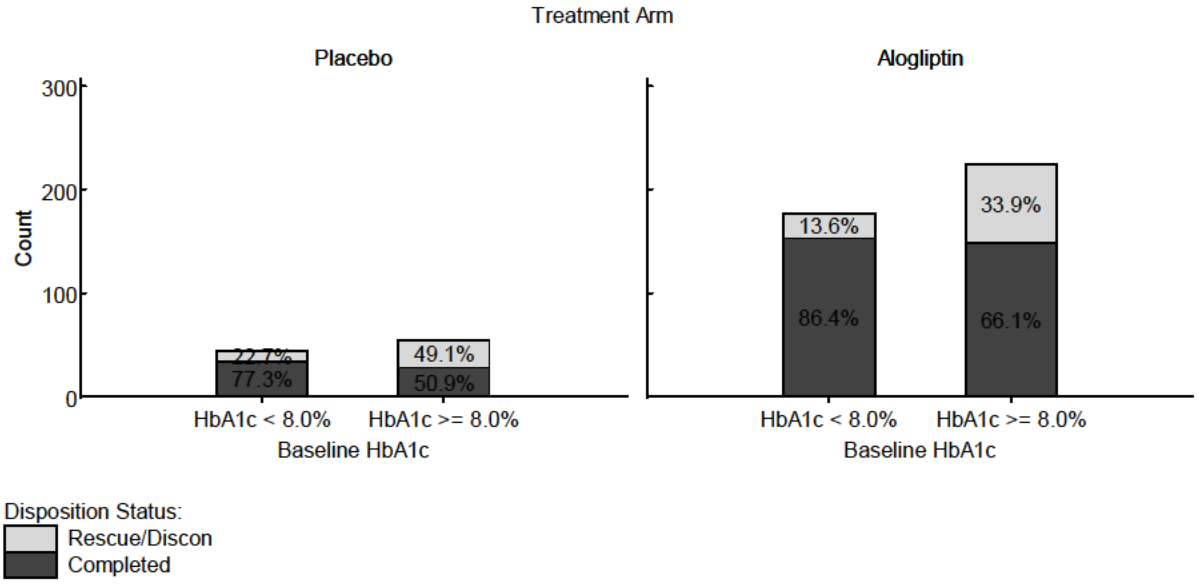


FIGURE 16 Study 008 (add-on to metformin); Percentage of rescued/discontinued by baseline HbA1c

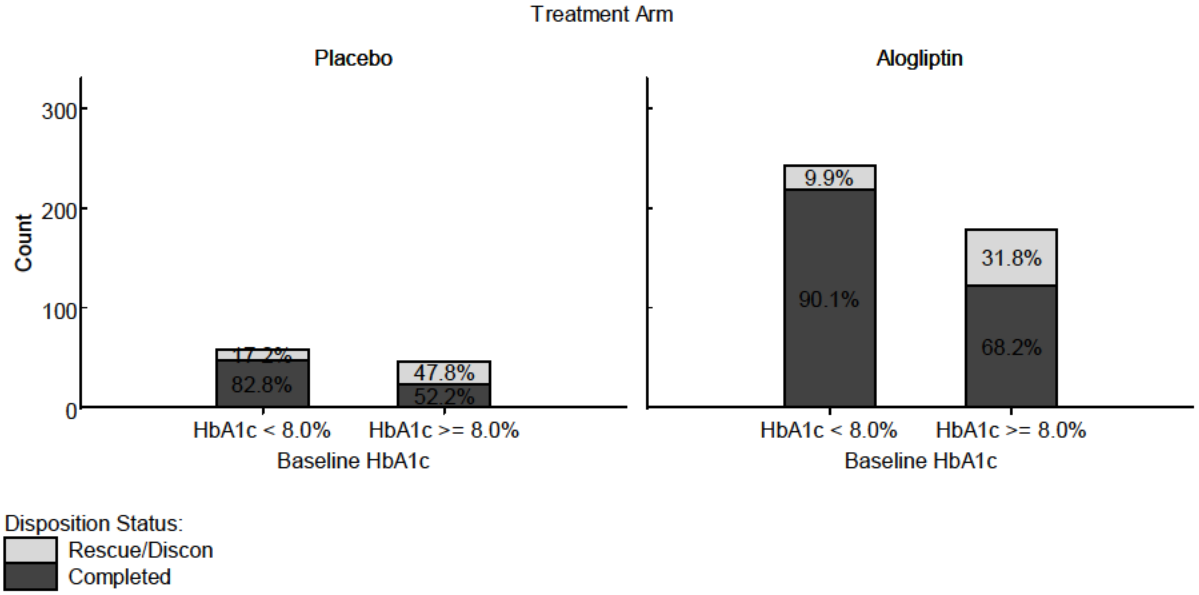


FIGURE 17 Study 009 (add-on to pioglitazone); Percentage of rescued/discontinued by baseline HbA1c

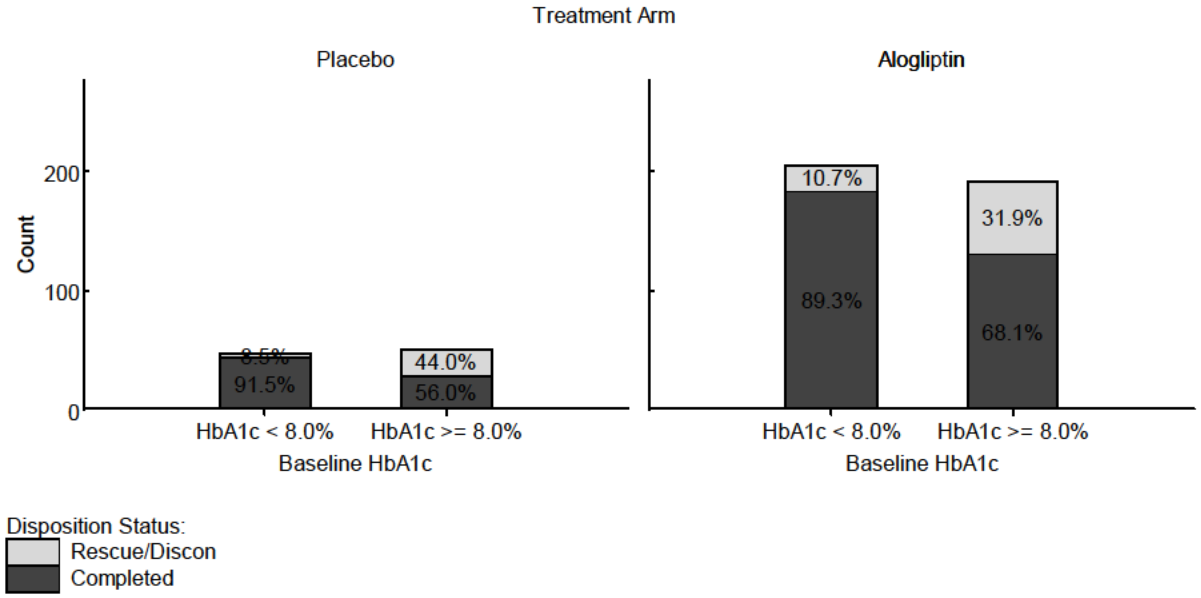
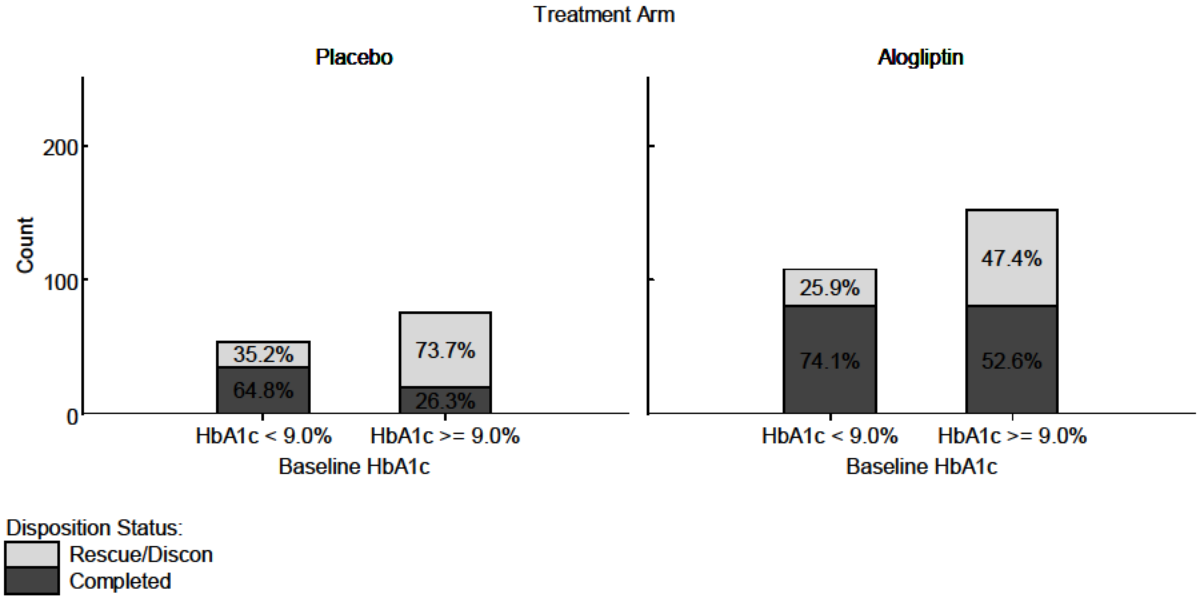


FIGURE 18 Study 011 (add-on to insulin); Percentage of rescued/discontinued by baseline HbA1c



Baseline HbA1c and change from baseline in HbA1c at week 26: Across the five key studies, subjects in subgroups with higher baseline HbA1c values generally had greater average reductions in HbA1c compared to subjects in subgroups with lower baseline HbA1c values in the alogliptin arms compared to placebo (TABLE 21 through TABLE 25). This relationship is illustrated not only in the alogliptin groups, but also in the placebo groups, and has also been demonstrated in clinical studies of other diabetes drugs. Several explanations are consistent with this finding: (1) The diabetic drugs may all promote a greater reduction in HbA1c in subjects with higher baseline values; (2) The regression to the mean effect will tend to cause a greater change from baseline in subjects who had higher than average HbA1c levels at baseline by chance; and (3) The general improvement in diabetes care and management in subjects who participate in these studies may have a greater impact on subjects with higher baseline HbA1c.

The sponsor proposes (b) (4) For this reason, I do not recommend (b) (4)

Baseline BMI: Differences in HbA1c response between categories of baseline BMI were not consistent across the five key studies. In Study 010, subjects in the lower BMI category (< 30 kg/m^2) had a smaller average reduction in HbA1c than subjects in the higher BMI category (≥ 30 kg/m^2; TABLE 21). In Studies 007 and 008, subjects in the lower BMI category had a greater average reduction in HbA1c than subjects in the higher BMI category (TABLE 22 and TABLE 23). In Studies 009 and 011, the average reduction in HbA1c was about the same in each BMI categories (TABLE 24 and TABLE 25).

TABLE 21 Study 010; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the FAS/LOCF population by age, gender, race and ethnicity

Study 010 (monotherapy)	**Placebo**			**Alogliptin 12.5 mg**			**Alogliptin 25 mg**		
	n	**BL avg**	**Diff (SD)**	**n**	**BL avg**	**Diff (SD)**	**n**	**BL avg**	**Diff (SD)**
Baseline HbA1c									
<7.5%	24	7.1	0.1 (0.7)	53	7.2	-0.4 (0.6)	51	7.2	-0.3 (0.6)
≥ 7.5%	41	8.5	-0.1 (0.9)	84	8.3	-0.7 (0.7)	84	8.3	-0.8 (0.9)
≥ 8.0%	29	8.9	-0.2 (0.9)	51	8.7	-0.7 (0.8)	52	8.7	-0.9 (0.9)
≥ 9.0%	13	9.4	-0.3 (1.0)	19	9.4	-0.8 (0.9)	15	9.4	-1.0 (1.0)
Baseline BMI									
< 30 kg/m^2	25	8.1	-0.5 (0.7)	53	8.0	-0.8 (0.7)	58	8.0	-0.7 (0.9)
≥ 30 kg/m^2	38	8.0	0.2 (0.9)	78	7.8	-0.4 (0.6)	70	7.9	-0.5 (0.8)

Source: Study 010 Study Report, Table 15.2.1.2 and Table 15.2.1.10.1

TABLE 22 Study 007; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the FAS/LOCF population by age, gender, race and ethnicity

Study 007 (add-on to sulfonylurea)	**Placebo**			**Alogliptin 12.5 mg**			**Alogliptin 25 mg**		
	n	**BL avg**	**Diff (SD)**	**n**	**BL avg**	**Diff (SD)**	**n**	**BL avg**	**Diff (SD)**
Baseline HbA1c									
<7.5%	32	7.3	0.2 (0.7)	64	7.2	-0.2 (0.6)	74	7.2	-0.3 (0.7)
≥ 7.5%	77	8.4	-0.1 (1.0)	150	8.4	-0.5 (0.8)	130	8.6	-0.6 (1.0)
≥ 8.0%	48	8.9	-0.1 (1.0)	100	8.8	-0.5 (0.9)	104	8.8	-0.7 (1.0)
≥ 9.0%	18	9.5	0.0 (1.1)	30	9.5	-0.8 (0.9)	40	9.5	-1.1 (1.0)
Baseline BMI									
< 30 kg/m^2	56	8.3	0.0 (0.8)	110	8.1	-0.4 (0.8)	108	8.2	-0.7 (0.8)
≥ 30 kg/m^2	41	7.9	0.0 (1.0)	91	8.1	-0.4 (0.8)	89	8.0	-0.3 (0.9)

Source: Study 007 Study Report, Table 15.2.1.2 and Table 15.2.1.10.1

TABLE 23 Study 008; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the FAS/LOCF population by age, gender, race and ethnicity

Study 008 (add-on to metformin)	**Placebo**			**Alogliptin 12.5 mg**			**Alogliptin 25 mg**		
	n	**BL avg**	**Diff (SD)**	**n**	**BL avg**	**Diff (SD)**	**n**	**BL avg**	**Diff (SD)**
Baseline HbA1c									
<7.5%	36	7.2	0.1 (0.5)	78	7.2	-0.5 (0.5)	80	7.2	-0.3 (0.6)
≥ 7.5%	72	8.4	-0.2 (0.9)	145	8.2	-0.7 (0.8)	133	8.3	-0.7 (0.9)
≥ 8.0%	42	8.9	-0.4 (1.1)	80	8.7	-0.7 (1.0)	83	8.7	-0.8 (1.0)
≥ 9.0%	18	9.5	-0.6 (1.3)	25	9.4	-0.5 (1.0)	27	9.4	-1.1 (1.1)
Baseline BMI									
< 30 kg/m^2	56	8.3	0.0 (0.8)	110	8.1	-0.4 (0.8)	108	8.2	-0.7 (0.8)
≥ 30 kg/m^2	41	7.9	0.0 (1.0)	91	8.1	-0.4 (0.8)	89	8.0	-0.3 (0.9)

Source: Study 008 Study Report, Table 15.2.1.2 and Table 15.2.1.10.1

TABLE 24 Study 009; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the FAS/LOCF population by age, gender, race and ethnicity

Study 009 (add-on to pioglitazone)	**Placebo**			**Alogliptin 12.5 mg**			**Alogliptin 25 mg**		
	n	**BL avg**	**Diff (SD)**	**n**	**BL avg**	**Diff (SD)**	**n**	**BL avg**	**Diff (SD)**
Baseline HbA1c									
<7.5%	35	7.2	-0.2 (0.3)	70	7.2	-0.4 (0.6)	75	7.2	-0.5 (0.6)
≥ 7.5%	63	8.4	-0.2 (1.0)	139	8.5	-0.8 (1.0)	130	8.4	-1.0 (0.9)
≥ 8.0%	97	8.6	-0.2 (1.0)	95	8.8	-0.9 (1.0)	87	8.8	-1.1 (0.9)
≥ 9.0%	13	9.5	-0.1 (1.4)	31	9.6	-1.3 (1.1)	31	9.5	-1.3 (1.1)
Baseline BMI									
< 30 kg/m^2	36	8.0	-0.1 (0.9)	75	8.2	-0.7 (1.1)	59	8.0	-0.9 (0.9)
≥ 30 kg/m^2	59	8.0	-0.2 (0.7)	121	8.0	-0.7 (0.7)	136	8.0	-0.8 (0.8)

Source: Study 009 Study Report, Table 15.2.1.2 and Table 15.2.1.11.1

TABLE 25 Study 011; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the FAS/LOCF population by age, gender, race and ethnicity

Study 011 (add-on to insulin)	**Placebo**			**Alogliptin 12.5 mg**			**Alogliptin 25 mg**		
	n	**BL avg**	**Diff (SD)**	**n**	**BL avg**	**Diff (SD)**	**n**	**BL avg**	**Diff (SD)**
Baseline HbA1c									
< 8.5%	37	8.2	0.1 (0.6)	37	8.2	-0.3 (0.7)	36	8.2	-0.6 (0.7)
≥ 8.5%	95	9.7	-0.2 (0.8)	99	9.6	-0.7 (1.1)	93	9.7	-0.7 (0.9)
≥ 9.0%	70	10.0	-0.3 (0.7)	74	10.0	-0.9 (1.1)	68	10.0	-0.8 (1.0)
Baseline BMI									
< 30 kg/m^2	48	9.3	-0.2 (0.7)	43	9.3	-0.7 (1.0)	51	9.2	-0.9 (0.9)
≥ 30 kg/m^2	78	9.3	-0.1 (0.8)	87	9.3	-0.6 (1.0)	75	9.3	-0.6 (0.8)

Source: Study 011 Study Report, Table 15.2.1.2 and Table 15.2.1.11.1

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

I evaluated the collective evidence in support of the efficacy of alogliptin from the results of five key Phase 3 studies. I confirmed a selection of the efficacy results for the primary endpoint, HbA1c at week 26, expressed as a change from baseline. I concurred with the pre-specified statistical methodology used in evaluating the primary endpoint. Results from the sensitivity analysis of the HbA1c endpoint supported the efficacy of alogliptin 12.5 mg and 25 mg. In my opinion, the collective evidence from the five key Phase 3 studies supports the efficacy of alogliptin in the clinical population of patients with diabetes resembling patients who participated in the monotherapy and add-on combination therapy studies. However, the insulin add-on study was different from the other four studies in the larger overall percentage of subjects in each arm who were rescued or discontinued (57.4% in the placebo add-on arm compared to 36.6% and 40.3% in the alogliptin add-on arms). In my opinion, the large percentage subjects who did not complete the study raises the issue of whether or not the effect of alogliptin as an add-on to insulin is adequately characterized from this study.

5.2 Conclusions

Alogliptin produced statistically significant net reductions in HbA1c when compared with placebo as a monotherapy, and when given as an add-on to sulfonylurea, metformin, pioglitazone or insulin. The net effect of alogliptin 12.5 mg ranged from an average improvement in HbA1c of 0.4 to 0.5 across the five studies. The net effect of alogliptin 25 mg ranged from an average improvement of 0.5 to 0.6 across the five studies. The net effect of the 12.5 mg dose and the 25 mg dose was very similar and would not be separable statistically (this was not an objective of the studies).

The average HbA_{1c} response in the younger and older age groups (< 65 and ≥ 65 years) and in males and females were relatively similar. Most subjects were Caucasian in each of the five key studies. The numbers of subjects in the other identified race categories were small and did not support an evaluation of potential race-related difference in HbA_{1c} reduction. In the two studies with reasonable representation in the Hispanic/Latino ethnicity category, results were relatively similar between the Hispanic/Latino subgroup and the non-Hispanic/Latino subgroup.

The large majority of subjects in each study, 84% to 94%, stayed within ± 5% of their baseline body weight at week 26. Four studies had no apparent difference among the alogliptin and placebo arms in the pattern of weight change. The add-on to sulfonylurea study showed a net average weight gain of 0.8 kg in the alogliptin 12.5 mg arm and 0.9 kg in the alogliptin 25 mg arm relative to placebo, with p-values < 0.05.

The effect of alogliptin appears to be established by week 12, after which time the placebo-adjusted effect of alogliptin remained relatively constant, even though the average change from baseline decreased from week 12 through week 26 in the alogliptin arms and in the placebo arm This decrease in average change from baseline in all arms may represent the progression of diabetes over the time course of the studies. However, the dynamics of disposition has also contributed to this apparent stabilization of response by week 12. In four of the five studies, a substantial proportion of rescues/discontinuations took place from weeks 12 through 16, following the change in criteria for hyperglycemic rescue from fasting plasma glucose to HbA1c at week 12. The proportion of cases with HbA1c levels carried forward from weeks 12 through 16 has contributed to the apparent stabilization of HbA1c response by week 12.

Across the five key studies, subjects in subgroups with higher baseline HbA1c values generally had a greater average reduction in HbA1c compared to subjects in subgroups with lower baseline HbA1c values in the alogliptin arms compared to placebo. This relationship is illustrated not only in the alogliptin groups, but also in the placebo groups, and has also been demonstrated in clinical studies of other diabetes drugs. However, I believe that these results are challenging to interpret in the alogliptin studies because of the relatively high overall incidence of discontinuations due to hyperglycemic rescue, and the disproportionate incidence of rescue in patients with higher baseline HbA1c compared to patients with lower baseline HbA1c. (b) (4)

5.3 Recommendations for Labeling

The sponsor used a similar format to describe the results from the monotherapy study (section 14.1) and the four combination therapy studies (section 14.2) in the Clinical Studies section of the package insert. General recommendations for reporting statistical results from each of these studies are summarized in TABLE 26.

TABLE 26 Recommendations for labeling text in the Clinical Studies section

14. Clinical Studies Topics that are covered for each study described in the Monotherapy and Combination Therapy sections (14.1 and 14.2)		
Topic	**Example of draft labeling text**	**Review comments / Proposed revisions**
Efficacy endpoint results	Treatment with NESINA 25 mg (b) (4) resulted in significant improvements from baseline in HbA1c and FPG compared to placebo at Week 26.	Review comment: Draft labeling text is acceptable.
Hyperglycemic rescue	(b) (4)	Review comment: Omit the term (b) (4) and report the percentage of patients in each arm who required rescue

14. Clinical Studies Topics that are covered for each study described in the Monotherapy and Combination Therapy sections (14.1 and 14.2)		
Topic	**Example of draft labeling text**	**Review comments / Proposed revisions**
	(b) (4)	therapy. Proposed revision: (b) (4)
Subgroups	(b) (4)	Review comment: Most patients were Caucasian in each of the five key studies. The numbers of patients in the other identified race categories were small and did not support an evaluation of potential race-related difference in HbA1c reduction. (b) (4) Differences in HbA1c response between categories of baseline BMI were not consistent across the five key studies. Proposed revision: (b) (4)
(b) (4)	(b) (4)	Review comment: Omit the discussion (b) (4)

14. Clinical Studies Topics that are covered for each study described in the Monotherapy and Combination Therapy sections (14.1 and 14.2)		
Topic	**Example of draft labeling text**	**Review comments / Proposed revisions**
		Proposed revision: (b) (4)
Body weight	(b) (4)	Review comment: Be consistent in describing results for body weight among studies, and do not use the term (b) (4) Proposed revision: • *For monotherapy, add-on to metformin, add-on to pioglitazone and add-on to insulin:* (b) (4) • *For add-on to sulfonurea (pending clinical input):* (b) (4)
Data Summaries Figure	(b) (4)	Review comment: This figure is a useful overall summary.
Tables 3 through 7: Summary of results for HbA1c and FPG for each study		Review comments: • The difference from placebo (adjusted mean) should also show the 95% Confidence Interval, for HbA1c and for FPG. • Omit the symbols related to statistical significance from results for % of patients achieving HbA1c ≤ 7%. • Consolidate the symbols pertaining to p-values by using a single criterion level such as p<0.001 for p-values < 0.001, and show specific p-values otherwise.

6. Technical Appendix

TABLE 27 Baseline HbA1c (by stratification category) and disposition status (completed, rescued and discontinued) in the five key studies, FAS population

	Placebo		Alogliptin 12.5 mg		Alogliptin 25 mg	
Study 010 (monotherapy)						
Baseline Hba1c:	**< 8.0%**	**≥ 8.0%**	**< 8.0%**	**≥ 8.0%**	**< 8.0%**	**≥ 8.0%**
Completed	30 (78.9%)	10 (38.5%)	71 (89.9%)	34 (63.0%)	68 (86.1%)	39 (75.0%)
Rescued	4 (10.5%)	15 (57.7%)	2 (2.5%)	11 (20.4%)	3 (3.8%)	7 (13.5%)
Discontinued[1]	4 (10.5%)	1 (3.8%)	6 (7.6%)	9 (16.7%)	8 (10.1%)	6 (11.5%)
Total	38	26	79	54	79	52
Study 007 (add-on to sulfonylurea)						
Baseline Hba1c:	**< 8.0%**	**≥ 8.0%**	**< 8.0%**	**≥ 8.0%**	**< 8.0%**	**≥ 8.0%**
Completed	34 (77.3%)	28 (50.9%)	77 (85.6%)	76 (67.3%)	76 (87.4%)	72 (64.9%)
Rescued	4 (9.1%)	24 (43.6%)	5 (2.5%)	25 (22.1%)	3 (3.4%)	28 (25.2%)
Discontinued	6 (6.1%)	3 (5.5%)	8 (8.9%)	12 (10.6%)	8 (9.2%)	11 (9.9%)
Total	44	55	90	113	87	111
Study 008 (add-on to metformin)						
Baseline Hba1c	**< 8.0%**	**≥ 8.0%**	**< 8.0%**	**≥ 8.0%**	**< 8.0%**	**≥ 8.0%**
Completed	48 (82.8%)	24 (52.2%)	115 (94.3%)	61 (67.8%)	104 (86.0%)	61 (70.9%)
Rescued	5 (8.6%)	20 (43.5%)	4 (3.3%)	15 (16.7%)	4 (3.3%)	13 (15.1%)
Discontinued	5 (8.6%)	2 (4.3%)	3 (3.3%)	14 (15.6%)	13 (10.7%)	12 (14.0%)
Total	58	46	122	90	121	86
Study 009 (add-on to pioglitazone)						
Baseline Hba1c	**< 8.0%**	**≥ 8.0%**	**< 8.0%**	**≥ 8.0%**	**< 8.0%**	**≥ 8.0%**
Completed	43 (91.5%)	28 (56.0%)	85 (85.0%)	68 (70.1%)	98 (93.3%)	62 (66.0%)
Rescued	3 (6.4%)	9 (18.0%)	3 (3.0%)	15 (16.5%)	2 (1.9%)	16 (17.0%)
Discontinued	1 (2.1%)	13 (26.0%)	12 (12.0%)	13 (13.4%)	5 (4.8%)	16 (17.0%)
Total	47	50	100	97	105	94
Study 011 (add-on to insulin)						
Baseline Hba1c	**< 9.0%**	**≥ 9.0%**	**< 9.0%**	**≥ 9.0%**	**< 9.0%**	**≥ 9.0%**
Completed	35 (27.1%)	20 (26.7%)	38 (29.0%)	45 (58.4%)	42 (77.8%)	35 (46.7%)
Rescued	12 (22.2%)	40 (53.3%)	8 (14.8%)	19 (24.7%)	5 (9.3%)	20 (26.7%)
Discontinued	7 (13.0%)	15 (20.2%)	8 (14.8%)	13 (16.9%)	7 (13.0%)	20 (26.7%)
Total	54	75	54	77	54	75

Source: Analysis by this reviewer
Note:
[1] The category of "discontinued" is separate from the category of "rescued"

SIGNATURES/DISTRIBUTION LIST

Janice Derr, Ph.D.
Mathematical Statistician

Concur:

J. Todd Sahlroot, Ph.D.:
Statistics Team Leader and Deputy Division Director, DB2

Thomas Permutt, Ph.D.
Division Director, DB2

cc:
NDA 022271/0
DMEP/JMarchick, JZawadski, HJoffe, MParks
OB DBII/JDerr, JTSahlroot, TPermutt
OB/RTiwari, ENevius

c:\NDA\NDA 022271_0 statistical review.doc

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

/s/

Janice Derr
9/2/2008 10:41:03 AM
BIOMETRICS

Todd Sahlroot
9/2/2008 10:45:18 AM
BIOMETRICS

Thomas Permutt
9/3/2008 02:28:25 PM
BIOMETRICS
concur

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI (HFD-705)

Carcinogenicity Studies
(An Addendum)

NDA NO.:	22-271
SERIAL NO.:	S_000
DATE RECEIVED BY THE CENTER:	Dec. 27, 2007
DRUG NAME:	SYR-322 (Nesina/alogliptin)
DOSAGE FORM:	Oral
INDICATION:	Type 2 diabetest
SPONSOR:	Takeda Pharmaceutical Company Limited.
DOCUMENTS REVIEWED:	Electronic Copy Dated Dec. 27, 2007
NAME OF STATISTICAL REVIEWER:	Meiyu Shen, Ph.D. (HFD-705)
NAME OF PHARM TOX REVIEWER:	David Carlson, Ph.D.

_____

Meiyu Shen, Mathematical Statistician

Concur: _____

Karl K Lin, Ph.D.
Team Leader, DBVI

Distribution: NDA 22-271
HFD-705/Karl K Lin, Ph.D.
OND/ODEII/DMEP, David Carlson, Ph.D.

Background

The statistical review of the carcinogenicity studies of this submission was done by Dr. Meiyu Shen, and the statistical review and evaluation report by her was put into DFS May 27, 2008. The final results of this submission was disscuded at the ECAC meeting 8/5/2008. Dr. Abigail C. Jacobs, a member of the ECAC, read the statistical review and evaluation report before the ECAC meeting and made some comments about the FDA statistical review of this submission. This addendum to the original statistical review and evaluation report conains some additional statistical analyses including pairwise comparisons of some tumor types, and the checking of the difference in p-values of trend test in incidence in C-cell adenoma/carcinoma of thyroid gland between the sponsor's and FDA testing results in response to Dr. Jacobs' comments.

1. C-cell thyroid tumor analysis for male rates

The tumor analysis of hyperplasis is not conducted by this reviewer because there is no data of hyperplasis in this submission. In male rates, tumor HAS (hemangiosarcoma, malignan) appeared in one rat, no tumor HAO (hemangioma, benign) appeared in any rat. The combination of HAO and HAS could not be done.

Table 1 Comparison of FDA Peto analyses with the sponsor's Peto analyses for neoplastic and non-neoplastic lesion, male

Dose level, mg free base/kg/day			0 (Vehicle)	75	400	800
Thyroid Gland						
Adenoma, C-cell, benign	Overall rate	Sponsor	3/60	8/60	10/60	11/60
		FDA	3/60	8/60	10/60	11/60
	p-value	Sponsor	0.0151	0.0651	0.0071	0.020
		FDA	0.0333	0.0622	0.0054	0.0189
Carcinoma, C-cell, malignant	Overall rate	Sponsor	0/60	0/60	1/60	3/60
		FDA	0/60	0/60	1/60	3/60
	p-value	Sponsor	0.0283	1.0	0.4688	0.1577
		FDA	0.0291	NA	0.4857	0.1559
Adenoma, C-cell, benign/ Carcinoma, C-cell, malignant	Overall rate	Sponsor	3/60	8/60	11/60	13/60
		FDA	3/60	8/60	11/60	13/60
	p-value	Sponsor	0.0042	0.0651	0.0036	0.0073
		FDA	0.0100	0.0622	0.0028	0.0068

2. C-cell thyroid tumor analysis for female rates

The tumor analysis of hyperplasis is not conducted by this reviewer because there is no data of hyperplasis in this submission.

Table 2 Comparison of FDA Peto analyses with the sponsor's Peto analyses for neoplastic and non-neoplastic lesion, female

Dose level, mg free base/kg/day			0 (Vehicle)	75	400	800
Thyroid Gland						
Adenoma, C-cell, benign	Overall rate	Sponsor	3/60	10/60	10/59	7/60
		FDA	3/60	10/60	10/60	7/60
	p-value	Sponsor	0.0423	0.020	0.0163	0.0370
		FDA	0.1546	0.0222	0.0180	0.0473
Carcinoma, C-cell, malignant	Overall rate	Sponsor	0/60	2/60	0/59	1/60
		FDA	0/60	2/60	0/60	1/60
	p-value	Sponsor	0.4406	0.2529	1	0.5717
		FDA	0.3825	0.2674	NA	0.3913
Adenoma, C-cell, benign/ Carcinoma, C-cell, malignant	Overall rate	Sponsor	3/60	11/60	10/59	8/60
		FDA	3/60	11/60	10/60	8/60
	p-value	Sponsor	0.0329	0.0117	0.0163	0.0244
		FDA	0.1162	0.0130	0.0180	0.0229

3. The p-value for tumor PCT (pheochromocytoma, benign) pair-wise comparison of the medium dose group with the control group is 0.0015 although the p-value of the trend test for tumor PCT is 0.0378.

Dose level, mg free base/kg/day		0 (Vehicle)	75	400	800
PCT (pheochromocytoma, benign)	Overall rate	1/60	3/60	11/60	4/60
	p-value	0.0378	0.3144	0.0015	0.1358

4. The tumor analysis of hemangiomas at all sites was conducted for males and females in the review and the tumor analysis of hemangiosarcomas at all sites was conducted for males in the review because tumor hemangiosarcomas did not appear in females. The combined tumor analysis of hemangiomas/ hemangiosarcomas for males was conducted here.

Male rats

Dose level, mg free base/kg/day		0 (Vehicle)	75	400	800
HAS (hemangiosar	Overall rate	0/60	1/60	0/60	0/60

comas)	p-value	0.7568	0.4857	NA	NA

Female rats

Dose level, mg free base/kg/day		0 (Vehicle)	75	400	800
HAS (hemangiosarcomas)	Overall rate	0/60	0/60	1/60	1/60
	p-value	0.1874	NA	0.5333	0.5312
HAO (hemangioma, benign)	Overall rate	0/60	1/60	0/60	0/60
	p-value	0.7558	0.5227	NA	NA
HAS (hemangiosarcomas)/HAO (hemangioma, benign)	Overall rate	0/60	1/60	1/60	1/60
	p-value	0.2864	0.5227	0.5333	0.5312

5. Rats' body weight graphs

Figure 2 Mean Body Weight Values – MALE

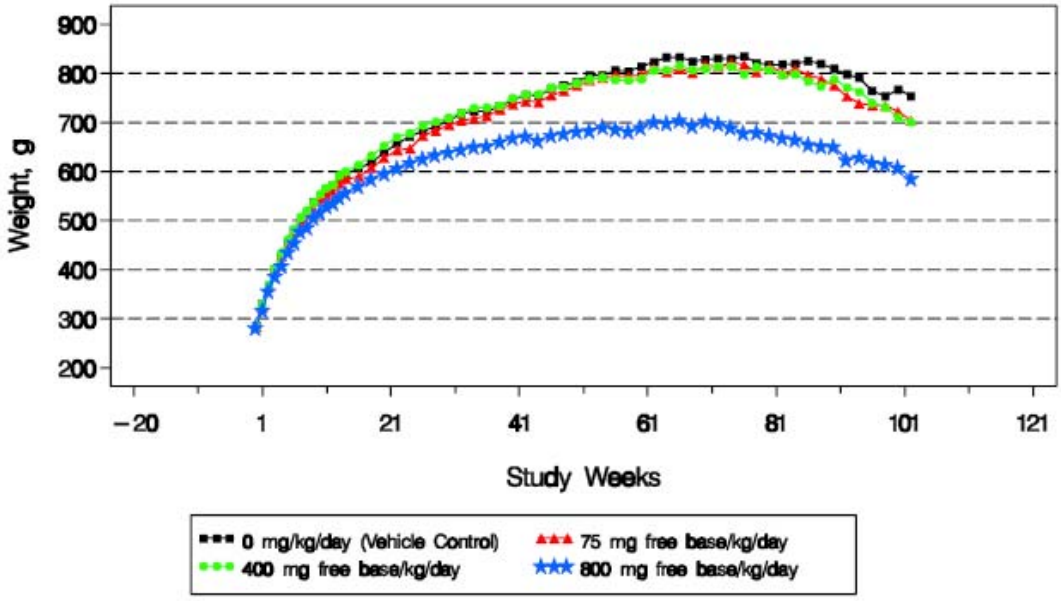
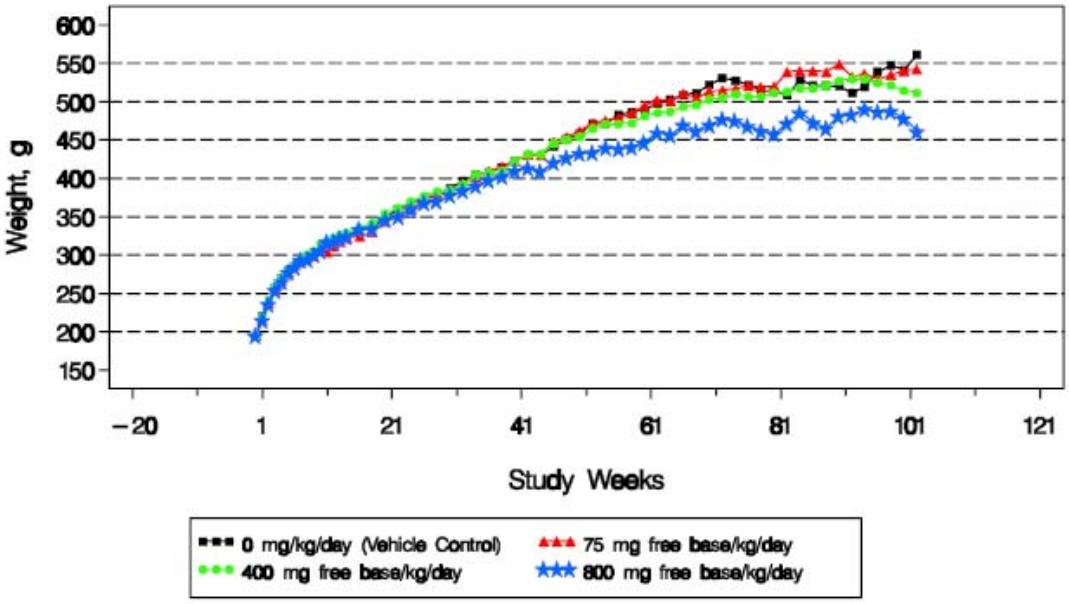


Figure 2A Mean Body Weight Values – FEMALE



Appendix

Dr. Abigail Jacob's Comments and Statistical Reviewers' Responses

From: Shen, Meiyu
Sent: Friday, July 25, 2008 3:23 PM
To: Lin, Karl K; Jacobs, Abigail (Abby) C; Carlson, David; Seifried, Adele S; Jacobson-Kram, David; Bourcier, Todd; Laniyonu, Adebayo A
Cc: Machado, Stella G; ONeill, Robert T
Subject: RE: N22271 carc results

In the previous email, I reported the exact p-value for female pairwise comparisons. Because the total tumor number in female pairwise comparisons is larger than 10 , the sponsor reported the asymptotic p-value whenever the total tumor is larger than 10. To make my analysis more comparable with the sponsor's p-values, today I doubly checked my tables where I should put asymptotic p-value and where I should put exact p-value. I found I should put asymptotic p-value in female pairwise comparisons, however I reported the exact p-value in my document email-reply.doc on Wednesday. I did a lot of calculations in ONE single day. Now I correct these discrepancies found by Dr. Jacobs.

Females: *asymptotic p-value

Sponsor	0.0329	0.0117	0.0163	0.0244
FDA	0.1162	0.013*	0.018*	0.0229*

Female: **exact p-value

Sponsor	0.0329	0.0117	0.0163	0.0244
FDA	0.1162	0.0238**	0.0340**	0.046**

Thanks!

Meiyu

From: Shen, Meiyu
Sent: Friday, July 25, 2008 10:04 AM
To: Lin, Karl K; Jacobs, Abigail (Abby) C; Carlson, David; Seifried, Adele S; Jacobson-Kram, David; Bourcier, Todd; Laniyonu, Adebayo A
Cc: Machado, Stella G; ONeill, Robert T
Subject: RE: N22271 carc results

Sorry. There is a typo. The p-value for pairwise comparison of the highest dose vs. control (8/60 vs. 3/60) is 0.046. See attached output from the SAS program.
<< File: email_reply.doc >> << File: Pairwise_comparison.doc >>

I went back to my file email-reply.doc, I did not find denominator 70 in any table. Could you point out where you see the number 70? Thanks!

Meiyu

From: Lin, Karl K
Sent: Thursday, July 24, 2008 4:00 PM
To: Jacobs, Abigail (Abby) C; Shen, Meiyu; Carlson, David; Seifried, Adele S; Jacobson-Kram, David; Bourcier, Todd; Laniyonu, Adebayo A
Cc: Machado, Stella G; ONeill, Robert T
Subject: RE: N22271 carc results

I will double check with Dr. Shen on this too. I also feet that it is a typo. It should be 0.04 instead of 0.004

Thanks

Karl

From: Jacobs, Abigail (Abby) C
Sent: Thursday, July 24, 2008 3:49 PM
To: Lin, Karl K; Shen, Meiyu; Carlson, David; Seifried, Adele S; Jacobson-Kram, David; Bourcier, Todd; Laniyonu, Adebayo A
Cc: Machado, Stella G; ONeill, Robert T
Subject: RE: N22271 carc results

I still think there is something "wrong" with the high dose female rat comparison P value from the FDA. Why is a smaller incidence in the high dose group giving such a much smaller P value than the mid dose group? You'd expect the P value to be larger. You wouldn't expect 8/60 vs 3/60 to be P=0.004?

Abby

From: Lin, Karl K
Sent: Thursday, July 24, 2008 3:44 PM
To: Jacobs, Abigail (Abby) C; Shen, Meiyu; Carlson, David; Seifried, Adele S; Jacobson-Kram, David; Bourcier, Todd; Laniyonu, Adebayo A
Cc: Machado, Stella G; ONeill, Robert T
Subject: RE: N22271 carc results

For less complicated statistical analyses, the results from different computer software systems should be identical up to certain decimal places. However, the Peto survival-adjusted test for dose response trend in tumor incidence rate adjusts the differences in mortality by partitioning the study duration into different time intervals. Different partitions of the study duration will result in different results. Of course, the results should be totally different. Also we usually use the actual doses as weights in the Peto test. Some people simply use 0, 1, 2, 3 as the weights for the treatment groups. Also the Peto test handles (in adjusting mortality differences) fatal tumors and incidental tumors differently. Sponsors usually do not give us that much detailed information about how they performed the Peto Test.

We can work with the sponsor to find out why there are big differences in few p-values between sponsor's and FDA's analyses. Because I will be on leave for about a week starting this Friday, Dr. Shen and I can continue to work on this issue after I come back August 4.

Dr. Shen included hyperplasia with tumors in her additional analyses simply for the purpose of comparing her p-values with those of the sponsor since sponsor had done that in their reports.

Karl

From: Jacobs, Abigail (Abby) C
Sent: Thursday, July 24, 2008 8:26 AM
To: Jacobs, Abigail (Abby) C; Shen, Meiyu; Carlson, David; Lin, Karl K; Seifried, Adele S; Jacobson-Kram, David; Bourcier, Todd; Laniyonu, Adebayo A
Cc: Machado, Stella G; ONeill, Robert T
Subject: RE: N22271 carc results

OK, so there is agreement that the pairwise comparisons for males are statistically significant, which coupled with exceeding any historical incidences seen, would seem to be a clear effect.

The effect in females seems equivocal. However, Note that the pairwise comparison for high dose females seems to have a large discrepancy-- see below table. Highly Stat signif for FDA and not for the sponsor in pairwise??? Since the incidences are 3/60, 11/60, 10/59 and 8/60, are you sure there isn't an extra zero in the pairwise comparison for the high dose group? Is it perhaps 0.046? The sponsor p value for the high dose group is larger than the mid dose group?? Why would the P value for FDA be so much lower than both the sponsor P value for the high dose group and the FDA mid dose P value?

females

Sponsor	0.0329	0.0117	0.0163	0.0244
FDA	0.1162	0.0238	0.0340	0.0046

Note that hyperplasia is not a tumor and we do not analyze hyperplasia together with tumors.

I think it is very important to understand the discrepancies, but it is OK for our purposes if don't have all the answers before next week. (i.e., no need to work overtime).

Thank you for you rapid response, and I hope you will be good detectives.

Thanks,

Abby

From: Jacobs, Abigail (Abby) C
Sent: Thursday, July 24, 2008 7:54 AM
To: Shen, Meiyu; Carlson, David; Lin, Karl K; Seifried, Adele S; Jacobson-Kram, David; Bourcier, Todd; Laniyonu, Adebayo A
Cc: Machado, Stella G; ONeill, Robert T
Subject: RE: N22271 carc results

Strangely, I did not get the 4:56 pm email with any attached file from Karl Lin yesterday on my work computer email. It's only on my blackberry and the attachment doesn't open. Could someone please forward it to me.

FYI, We are interested in the combination of C-cell adenomas and carcinomas (combined) not C-cell adenomas only: those numbers are 3/60, 11/60, 10/59, and 8/60 for females. You can get a plateau for effects. Note that I don't think that the trend or pairwise for females will be statistically significant-- Nevertheless the incidences are substantially above historicals. I call the effect equivocal for females. For males I think there is a clear effect (3/60; 8/60; 11/60; 13/60) and the incidences are substantially above historicals.

I noted that you gave a denominator of 70 for the high dose group instead of 60. I assume that that is a typo. Although there was not dose -related mortality (trend), when I look at the curves, there were groups, strangely, that appeared to have markedly lower survival that other groups (for example, mid dose male rats)

Thanks,

Abby

From: Shen, Meiyu
Sent: Thursday, July 24, 2008 7:22 AM
To: Carlson, David; Lin, Karl K; Jacobs, Abigail (Abby) C; Seifried, Adele S; Jacobson-Kram, David; Bourcier, Todd; Laniyonu, Adebayo A
Cc: Machado, Stella G; ONeill, Robert T
Subject: RE: N22271 carc results

David,

You are most welcome. If you need more analysis, please ask me. Doing science right is our utilmate goal.

Meiyu

From: Carlson, David
Sent: Wednesday, July 23, 2008 5:09 PM
To: Lin, Karl K; Jacobs, Abigail (Abby) C; Seifried, Adele S; Jacobson-Kram, David; Bourcier, Todd; Laniyonu, Adebayo A
Cc: Shen, Meiyu; Machado, Stella G; ONeill, Robert T
Subject: RE: N22271 carc results

Thank you Karl and Meiyu for your rapid and thorough responses to Abby's questions and concerns. As Abby noted, we are not very concerned about the human risk based on the high doses tested, but your comments and comparative analyses are very helpful to understand the different statistical outcomes.

David

David Carlson
301-796-2174
<David.Carlson@fda.hhs.gov>

From: Lin, Karl K
Sent: Wednesday, July 23, 2008 4:56 PM
To: Jacobs, Abigail (Abby) C; Carlson, David; Seifried, Adele S; Jacobson-Kram, David; Bourcier, Todd; Laniyonu, Adebayo A
Cc: Shen, Meiyu; Machado, Stella G; ONeill, Robert T
Subject: RE: N22271 carc results

Thank Dr. Shen again for her great efforts to provide you with the desired additional analysis results. Dr. Shen's additional analysis results are in the attached file.

As you can see from results of Dr. Shen's additional analyses, the p-values of the pairwise comparisons for C-cell thyroid adenoma , and adenoma/carcinoma in both male and female rats from the sponsor's and the FDA's analyses are extremely close. But the p-values of the trend tests are quite different. Based on the computer runs using the well established software StatXact, we really have questions about the sponsor's p-values.

The survival-unadjusted p-values for C-cell thyroid adenomas are 0.03021 (versus sponsor's value 0.0151, and Dr. Shen's value 0.0362) for males and 0.3168 (versus sponsor's value 0.0423 and Dr. Shen's value 0.1595). Since the dose-mortality trend is not statistically significant at all, the right p-value should be close to the p-value from the StatXact. For females, the dose-mortality trend is also not statistically significant at 0.05 significance level, but it is close to be significant in the Kruskal Wallis test that places more weight on early death. With the tumor incidence rates 3/60, 10/60, 10/60, and 7/70, the sponsor's survival-adjusted p-value is unreasonably low.

In a statistical test to compare the means of two populations for example, it considers not only the difference of the two sample means, it also considers the variability of the populations. If the units in the populations are very homogeneous, then a small difference in sample means can show a statistically significant result. The opposite is true. So one has to look both the magnitude of differences the sample data of things being compared and the variability of the populations being compared. That is the essential element of the science of statistics: considering observed difference and observed variability together.

Karl

<< File: email_reply.doc >>

From: Jacobs, Abigail (Abby) C
Sent: Wednesday, July 23, 2008 3:46 PM
To: Lin, Karl K; Carlson, David; Seifried, Adele S; Jacobson-Kram, David; Bourcier, Todd; Laniyonu, Adebayo A
Cc: Shen, Meiyu; Machado, Stella G; ONeill, Robert T
Subject: RE: N22271 carc results

Lower body weight in a high dose group may indeed result in lower tumor incidences for hormonally related neoplasms. Perhaps I could have worded it more clearly. The opposite is not true.

Different stat analyses can give different values. I think it is important to understand why. Regardless of the stat values, the incidences are well outside of the historical range for c-cell tumors. Can you independently calculate the Peto values? Are you both using the same data set? Is there any reason not to accept the Peto results? IN other case, we have used sponsor's Peto results.

Although survival was not dose-related, there were very big differences in survival among groups. This is peculiar. How survival differences were treated is a potential source of different results.

When the NTP went to new stat analysis procedures, they would also conduct stat analyses with the old procedures. It was not uncommon to get differences in stat significance.

We always consider historical rates when considering whether a tumor is "rare" or not:

Fortunately in this case, the results have no relevance to risk to humans at the dose that they are exposed, but for the future, it is important to understand what is going on with the stat analyses.

Abby

From: Lin, Karl K
Sent: Wednesday, July 23, 2008 3:21 PM
To: Jacobs, Abigail (Abby) C; Carlson, David; Seifried, Adele S; Jacobson-Kram, David; Bourcier, Todd; Laniyonu, Adebayo A
Cc: Shen, Meiyu; Machado, Stella G; ONeill, Robert T
Subject: RE: N22271 carc results

Dr. Shen and I have discussed Abby's comments on the FDA statistical review of the carcinogenicity studies of this submission. The following are our responses to the comments. For clarity, the responses are inserted directly under each comment in the original e-mail.

The additional information (results of pairwise comparisons of the two tumor types in question, group mean body weight graphs) will be provided when the additional analyses are done.

I would like to express my sincere thanks to Dr, Shen for her willingness to help the OB Pharm/Tox Statistics Team to reduce the heavy workload of the team by doing the statistical review and evaluation of the carcinogenicity studies of this and several other submissions. She has done an excellent job.

Karl

From: Jacobs, Abigail (Abby) C
Sent: Wednesday, July 23, 2008 8:20 AM
To: Carlson, David; Seifried, Adele S; Jacobson-Kram, David; Bourcier, Todd; Laniyonu, Adebayo A
Cc: Lin, Karl K; Shen, Meiyu
Subject: N22271 carc results

David,

I won't be at the meeting, but I have a few comments.

It is most peculiar that the FDA Peto analyses gave such different results from the sponsor Peto analysis for C-cell thyroid neoplasms in rats.

The p-values of the sponsor's test and the FDA statistical reviewer's test for trend in incidence of C-cell thyroid adenoma in both male and female rats are indeed quite different. We have used a well established commercial software package (Statxact) and run a survival-unadjusted analysis for the tumor type to check the sponsor and FDA p-values. Our preliminary conclusion is that the sponsor's trend test p-values are unreasonably low, and that FDA p-values are more reasonable. We will provide you more information on this when we do more computer runs to check the differences further.

Evaluation of hyperplasis in the c-cell of the thyroid is unreliable in that when there are neoplasms, hyperplasia is not necessarily diagnosed. There have been clear findings in the C-cell htyroid without seeing hyperplasia reported as increased either at 13-weeks or at 2 years.

The FDA stat reviewer did not give us the pairwise comparison results, but I think the difference may be related to how survival was handled.

Dr. Shen has agreed to perform the pairwise comparisons of C-cell thyroid adenoma in both male and female rats.

Although there may not have been a dose-related trend in survival, survival differences were taken into account in the sponsor's analysis.

If the name Peto method is mentioned, then the tumor data analysis is survival-adjusted. Both the sponsor's and the FDA's analyses are survival-adjusted. So the differences are not due to survival-adjusted or survival-unadjusted reason.

For male rats, in the sponsor's analysis, 11/60 for the mid dose gives a lower P value than the 13/50 in the high dose; that is because the mid dose had lower survival than the high dose and neoplasms were seen earlier.

It is correct.

I was wondering if the male rat withthe C- Cell carcinoma seen in the lung is an animal for which a primary c-cell neoplasms was diagnosed. If not then that animal should be included in the high group for stat analysis. I donit understand why the FDA stat review is calculating numbers for nonprimary neoplasms.

The FDA computer software system performs tests for all individual combinations of organ codes and tumor codes included in the electronic tumor datasets submitted by the sponsor.

I don't see any pairwise comparison values for most neoplams, but it would seem that the incidence of pheochromocytoms in mid dose female rats is significantly higher than

than that in controls (11/60 vs 1/60). The high dose incidences could be affected by the lower body weight.

Dr, Shen has also agreed to perform the pairwise comparisons for this tumor type.

High dose incidences in the high dose males and females could be affected by the lower body weight (22% for males and 17% for female). I don't see any body weight curves to know how bw was during the study.

In general the opposite is true. There are studies showing positive correlations between incidence rate and body weight for tumors. Dr. Shen has agreed to provide graphs of group mean body weights from sponsor's hardcopy reports.

I don't see a problem with the sponsor's stat analysis.

As mentioned above, the sponsor's p-values for trend tests for C-cell thyroid adenomas may not be right. It will be checked further. I hope the above statement does not imply problems with FDA statistical analyses.

The results in females for the c-cell neoplasms are also outside historical values, but are not statistically signif by our criteria. Effects can level off and metabolism pathways can be saturated (800 mg/kg is a whopping dose compared to 75 mg/kg)

Without reliable historical control data from the sponsor or directions from pharm/tox reviewers, FDA statistical reviewers classify rare and common tumors totally based on the incidence rates of the concurrent control group(s).

Several DPP inhibitor resulted in drug related hemangiosarcomas in female rats or mice; one did not. I didn't see any stat analysis of hemangiomas/hemangiosarcomas at all sites.

Statistical reviewers combine tumor types in their analyses based on suggestions from the pharm/tox reviewers. She should have done that if the pharm/tox reviewer had made the request. However, Dr. Shen will be able to perform the analysis of the above two tumors combined.

The liver adenomas are NOT rare tumors in female mice; historical values need to be considered. I do not consider them drug-related.

Without reliable historical control data from the sponsor or directions from pharm/tox reviewers, FDA statistical reviewers classify rare and common tumors totally based on the incidence rates of the concurrent control group(s).

***I think the results in male rats are clear for thyroid C-cell neoplasms and the incidences in the mid and high dose group are well outside historical values (with or without stat). I think the results in females are equivocal for C-cell thyoid neoplasms and adrenal pheochomocytomas. Effects on the thyroid C-cell and adrenal are biologically plausible. Because of the high multiple of human exposure at the doses for which there are potential findings, there is no apparent risk to humans under conditions of use.

This was a hard one to write up.

David,
Thanks for giving us time to review and pointing out some of the problems. I greatly appreciate the effort that went into this review.

Abby

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

/s/

Karl Lin
8/11/2008 09:39:50 AM
BIOMETRICS
This an addendum to the original statistical review and evaluation report that was put into DFS May 27, 2008 in response to comments from a member of the ECAC (Abigail Jacobs).

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI (HFD-705)

NDA NO.:	22-271
SERIAL NO.:	S_000
DATE RECEIVED BY THE CENTER:	Dec. 27, 2007
DRUG NAME:	SYR-322 (Nesina/alogliptin)
DOSAGE FORM:	Oral
INDICATION:	Type 2 diabetest
SPONSOR:	Takeda Pharmaceutical Company Limited.
DOCUMENTS REVIEWED:	Electronic Copy Dated Dec. 27, 2007
NAME OF STATISTICAL REVIEWER:	Meiyu Shen, Ph.D. (HFD-705)
NAME OF PHARM TOX REVIEWER:	David Carlson, Ph.D.

_____

Meiyu Shen, Mathematical Statistician

Concur: _____

Karl K Lin, Ph.D.
Team Leader, DBVI

Distribution: NDA 22-271
HFD-705/Karl K Lin, Ph.D.
OND/ODEII/DMEP, David Carlson, Ph.D.

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1. BACKGROUND

SYR-322 (Nesina/alogliptin) is for treatment of type 2 diabetes. In this submission (NDA 22271), the sponsor submitted one 2-year oral carcinogenicity study of SYR-322 in CD-1 mice (Study syr-322-00356) and one 2-year oral carcinogenicity study of SYR-322 in sprague dawley rats (Study syr-322-00357).

2. MOUSE STUDY (STUDY SYR-322-00356)

2.1 Introduction

The objective of this study was to evaluate the carcinogenic potential of SYR-322 following daily oral administration in mice for 104 consecutive weeks at a dose volume of 10 mL/kg. Three treatment groups of 60 male and 60 female mice/group were administered the test article at respective dose levels of 50, 150, and 300 mg free base/kg/day. One additional group of 60 animals/sex served as the control and received the vehicle, 0.5% methylcellulose in deionized water. Additionally, four groups of 32 or 82 animals/sex/group served as toxicokinetic (TK) animals and received the vehicle or test article in the same manner and dose levels as the main study groups.

A total of 941 male and 791 female Crl:CD1®(Icr) mice (approximately 6 weeks of age at arrival) were received from [redacted] (b) (4) on March 10, 2005.

The animals considered suitable for study were weighed. Using a standard, by weight, block randomization procedure, 518 male and 518 female animals (weighing 27.9 to 32.6 g and 21.9 to 26.0 g, respectively, at randomization) were assigned to the control and treatment groups identified in the following table. Animals assigned to study had body weights within ±20% of the mean body weight for each sex. Extra animals obtained for the study, but not placed on study, were found dead or euthanized via carbon dioxide inhalation and the carcasses were discarded.

Group Assignments			
Group Number	Dose Level	Number of Animals	
		Male	Female
1[a]	0 mg/kg/day (Vehicle Control)	60	60
2[a]	50 mg free base/kg/day	60	60
3[a]	150 mg free base/kg/day	60	60
4[a]	300 mg free base/kg/day	60	60
5[b]	0 mg/kg/day (Vehicle Control)	32	32
6[b]	50 mg free base/kg/day	82	82
7[b]	150 mg free base/kg/day	82	82
8[b]	300 mg free base/kg/day	82	82

[a]Main study animals
[b]Toxicokinetic animals

The surviving control and treated males were terminated in Week 105 of the study. Females in the control and all treatment groups were terminated during Week 98 (Day 686) because the number of surviving animals reached 15 to 20 (25 to 33.3%) in either the control or low dose groups in Week 97.

2.2 Sponsor's analysis

The sponsor presented the mean survival estimate in Figure 1 of the sponsor's study report and the summary of survival estimates in Table 1 of the sponsor's study report. However, the sponsor did not present any statistical analysis for the mice mortality data.

The sponsor analyzed the mice tumor trend data using Peto's method. The statistical analysis was presented in Table 11 of the sponsor's study report. The p-values under the control group were from trend tests. The p-values under each dosed group were from pair-wise comparisons between that dosed group and the control group. The sponsor used 0.005 and 0.025 significance levels for positive trend tests of common and rare tumors, respectively. Also, the sponsor used 0.01 and 0.05 significance levels for pair-wise comparisons of common and rare tumors with the control, respectively. In Table 11, the p-value for the trend test of adenoma, hepatocellular tumor in liver for females was 0.0163 (Peto Exact Test), which is smaller than 0.025 for rare tumor. There is a statistically significantly positive trend for hepatocellular adenoma tumor in liver for females.

2.3 Data Analyzed and Sources

The sponsor submitted the data in electronic format on December 27, 2007. The data are located in the EDR at the following link: \\cdsesub1\n22271\S_00.

2.4 Reviewer's analysis

This reviewer independently analyzed the survival data for males and females, separately. This reviewer also independently analyzed the mice tumor data for males and females, separately using Peto's method.

2.4.1 Survival analysis

The summaries of the mortality data are given in Table 1 for males. The time intervals 0-52, 53-78, 79-91 and 92-104 weeks were chosen for males. The Kaplan-Meier curves for males are shown in Figure 1. Analysis of Dose-Mortality Trend for Male Mice is presented in Table 2. From Figure 1, we can see that the survival probability in control group is little higher than that in the dosed group before Week 32. The highest dose group in males has the highest mortality rate before Week 60. The analysis of Dose-Mortality trend for males in Table 2 does not show a statistically significant dose-related trend among the control and the dosed groups because the p-value is 0.5937 (Cox method) and 0.9469 (Kruskal-Wallis tests), respectively, which is much larger than 0.05.

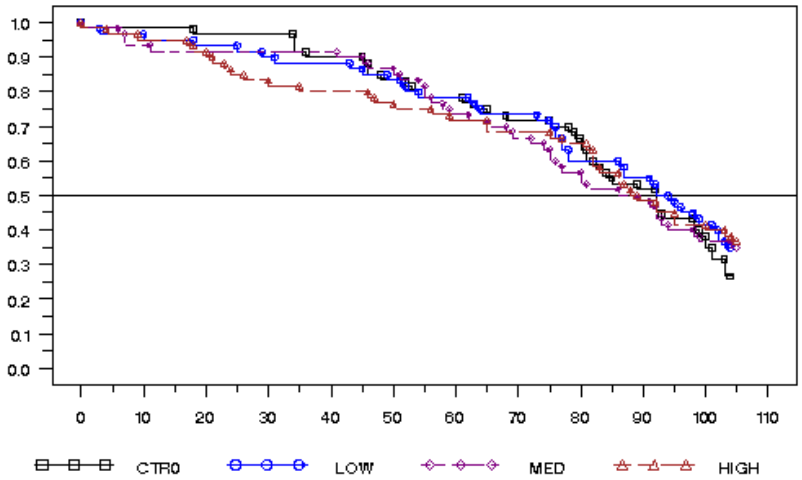

Figure 1 Kaplan-Meier Survival functions for Male Mice

Table 1 Analysis of mortality data for male mice

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR0 control	**0-52**	60	10	50	83.3	16.7
	53-78	50	8	42	70.0	30.0
	79-91	42	10	32	53.3	46.7
	92-104	32	16	16	26.7	73.3
	FINALKILL105-105	16	16	0		
LOW 50 mg/kg/day	**0-52**	60	11	49	81.7	18.3
	53-78	49	11	38	63.3	36.7
	79-91	38	5	33	55.0	45.0
	92-104	33	12	21	35.0	65.0
	FINALKILL105-105	21	21	0		
MED 150 mg/kg/day	**0-52**	60	9	51	85.0	15.0
	53-78	51	16	35	58.3	41.7
	79-91	35	6	29	48.3	51.7
	92-104	29	7	22	36.7	63.3
	FINALKILL105-105	22	22	0		
HIGH 300 mg/kg/day	**0-52**	60	14	46	76.7	23.3
	53-78	46	6	40	66.7	33.3
	79-91	40	10	30	50.0	50.0
	92-104	30	7	23	38.3	61.7
	FINALKILL105-105	23	23	0		

Table 2 Analysis of Dose-Mortality Trend for Male Mice

	Method			
	Cox		**Kruskal-Wallis**	
	Statistics	**P-Value**	**Statistics**	**P-Value**
Time-Adjusted Trend Test	0.3379	0.8445	0.2030	0.9035
Depart from Trend				
Dose-Mortality Trend	0.2847	0.5937	0.0044	0.9469
Homogeneity	0.6226	0.8912	0.2074	0.9764

Note: This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

The summaries of the mortality data are given in Table 3 for females. The time intervals 0-52, 53-78, 79-91 and 92-97 weeks were chosen for females because the study for females was terminated in Week 98. The Kaplan-Meier curves for females are shown in Figure 2. Analysis of Dose-Mortality Trend for Female Mice is presented in Table 4. From Figure 2, we can see that the survival probability in control group is much higher than that in the dosed groups before Week 70. There is not much difference in mortality rate seen among the dosed groups. The analysis of Dose-Mortality trend for females in Table 4 does not show a statistically significant dose-related trend among the control and the dosed groups because the p-value is 0.5772 (Cox method) and 0.4976 (Kruskal-Wallis tests), respectively, which is much larger than 0.05.

From Tables 1 and 3, it is seen that the females' mortality rate was much higher than the males' mortality rate because the females' mortality rates by Week 91 were 50%, 51.7%, 56.7%, and 60% for the control, the low dose group (50 mg/kg/day), the medium dose group (150 mg/kg/day), and high dose group (300 mg/kg/day), respectively; the males' mortality rates by Week 91 were 46.7%, 45%, 51.7%, and 50% for the control, the low dose group, the medium dose group, and high dose group, respectively. In other words, in the highest dose group, the death rate of females is 10% more than that of the corresponding group in males.

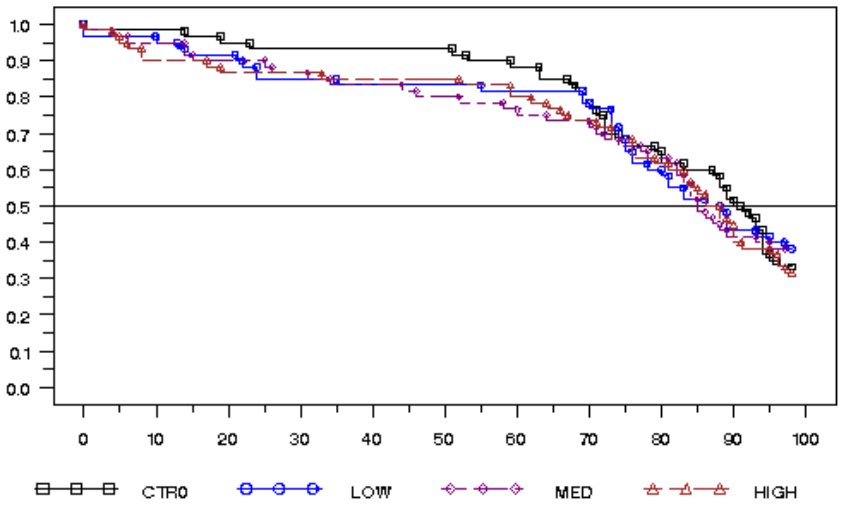

Figure 2 Kaplan-Meier Survival functions for Female Mice

Table 3 Analysis of mortality data for female mice

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR0 control	**0-52**	60	4	56	93.3	6.7
	53-78	56	15	41	68.3	31.7
	79-91	41	11	30	50.0	50.0
	92-97	30	9	21	35.0	65.0
	FINALKILL 98-98	21	21	0		
LOW 50 mg/kg/day	**0-52**	60	9	51	85.0	15.0
	53-78	51	14	37	61.7	38.3
	79-91	37	8	29	48.3	51.7
	92-97	29	5	24	40.0	60.0
	FINALKILL 98-98	24	24	0		
MED 150 mg/kg/day	**0-52**	60	12	48	80.0	20.0
	53-78	48	9	39	65.0	35.0
	79-91	39	13	26	43.3	56.7
	92-97	26	3	23	38.3	61.7
	FINALKILL 98-98	23	23	0		
HIGH 300 mg/kg/day	**0-52**	60	9	51	85.0	15.0
	53-78	51	10	41	68.3	31.7
	79-91	41	17	24	40.0	60.0
	92-97	24	4	20	33.3	66.7
	FINALKILL 98-98	20	20	0		

Table 4 Analysis of Dose-Mortality Trend for Female Mice

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	0.0463	0.9771	0.0957	0.9533
Depart from Trend				
Dose-Mortality Trend	0.3107	0.5772	0.4601	0.4976
Homogeneity	0.3570	0.9490	0.5557	0.9065

2.4.2 Tumor data analysis

The dose response analyses in incidental tumors and fatal tumors were performed using the Peto prevalence method and the Peto death-rate method, respectively. The actual dose levels of treatment groups were used as the weights for the trend analysis. The number of tumor bearing animals of each tumor type and its p-values for many organs were presented in Tables 5 and 6 for males and females, respectively. Multiplicity for the trend testing was adjusted using a significance level of 0.025 for rare tumors, and 0.005 for common tumors because two species were studied. A tumor type with a background rate of 1 percent or less is classified as rare by Haseman; more frequent tumors are classified as common.

It is also well known that the approximation results may not be stable and reliable, and tend to underestimate the exact p-values when the total numbers of tumor occurrence across treatment groups are small. In this situation, the exact permutation trend test should be used to test for the positive trend. The exact permutation trend test is a generalization of the Fisher's exact test.

From Table 5, it is seen that there is no statistically significantly positive trend in both incidental tumors and fatal tumors for males. From Table 6, it is seen that the p-value of the trend test for the rare tumor HEA (adenoma, hepatocellular benign) in liver for females is 0.0172 (<0.025).

2.4.3 Conclusion

Survival probability in control group is much higher than that in the dosed groups before Week 70. There is not much difference in mortality rate seen among the dosed groups. The analysis of Dose-Mortality trend for males and females does not show a statistically significant dose-related trends among the control and the dosed groups in both genders. There is no statistically significantly positive trend in both incidental tumors and fatal tumors for males. From Table 6, it is seen that the p-value of the trend test for the rare tumor HEA (adenoma, hepatocellular benign) in liver for females is 0.0172 (<0.025).

Table 5 Report on Test for Positive Linear Dose-Tumor Trends in Male Mice

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
109	liver	HEA	adenoma, hepatocellular, benig	2	7	2	4	0.5839	0.5680
109	liver	HER	carcinoma, hepatocellular, mal	2	1	2	0	0.9032	0.8830
113	lung	AAB	adenoma, bronchiolar alveolar,	10	10	11	7	0.6926	0.6821
113	lung	CAB	carcinoma, bronchiolar alveola	2	4	3	1	0.8207	0.8069
113	lung	CMC	carcinoma, basal cell, maligna	0	1	0	0	0.6190	0.6447
113	lung	HER	carcinoma, hepatocellular, mal	0	0	1	0	0.3333	0.2872
116	lymph node, cervical	CMC	carcinoma, basal cell, maligna	0	1	0	0	0.6190	0.6447
123	lymph node, mandibular	SAR	sarcoma, undifferentiated, mal	1	0	0	0	1.0000	0.7919
124	lymph node, mediastinal	CAB	carcinoma, bronchiolar alveola	0	1	1	0	0.5645	0.5683
124	lymph node, mediastinal	CMC	carcinoma, basal cell, maligna	0	1	0	0	0.6190	0.6447
137	mesentery/peritoneum	OSR	osteosarcoma, malignant	0	1	0	0	0.7442	0.7382
171	pituitary gland	AMD	adenoma, pars distalis, benign	0	0	1	0	0.4872	0.4016
171	pituitary gland	MEL	meningioma, malignant	1	0	0	0	1.0000	0.8597
184	seminal vesicles	ADE	adenoma, benign	0	0	1	0	0.5488	0.4572
201	skin	SQC	carcinoma, squamous cell, mali	0	0	1	0	0.4837	0.4026
201	skin	SQP	papilloma, squamous cell, beni	0	1	0	0	0.8049	0.7782
201	skin	TPS	trichofolliculoma, benign	0	0	0	1	0.2805	0.0781
202	skin, subcutis	CMC	carcinoma, basal cell, maligna	0	1	0	0	0.6190	0.6447
202	skin, subcutis	SAR	sarcoma, undifferentiated, mal	2	0	1	0	0.8576	0.8499
223	testes	ACE	adenoma, interstitial cell, benign	0	2	2	2	0.1370	0.1181
226	thyroid gland	FLA	adenoma, follicular cell, beni	0	1	0	0	0.6190	0.6447
226	thyroid gland	SAR	sarcoma, undifferentiated, mal	0	0	0	1	0.2805	0.0781
30	brain	MEL	meningioma, malignant	1	0	1	0	0.7356	0.7260
308	adrenal glands	ACD	adenoma, cortical, benign	0	0	0	1	0.2716	0.0742
308	adrenal glands	ADP	adenoma, subcapsular cell, ben	0	0	2	0	0.5432	0.4277
61	epididymides	LMS	leiomyosarcoma, malignant	0	0	0	1	0.2805	0.0781
69	gallbladder	ADE	adenoma, benign	0	0	1	0	0.5488	0.4572
79	harderian glands	ACC	adenocarcinoma, malignant	0	0	0	1	0.3226	0.0943
79	harderian glands	ADE	adenoma, benign	5	4	6	5	0.4451	0.4305
91	kidneys	ADT	adenoma, tubular cell, benign	0	0	1	0	0.5488	0.4572
91	kidneys	CAB	carcinoma, bronchiolar alveola	0	1	0	0	0.6190	0.6447
999	multicentric neoplasm	HAO	hemangioma, benign	0	1	0	1	0.2610	0.2164
999	multicentric neoplasm	HAS	hemangiosarcoma, malignant	2	6	2	4	0.4878	0.4730
999	multicentric neoplasm	HSS	sarcoma, histiocytic, malignan	1	0	1	0	0.7297	0.7234
999	multicentric neoplasm	LYM	lymphoma, malignant	3	1	2	2	0.5767	0.5595

Table 6 Report on Test for Positive Linear Dose-Tumor Trends in Female Mice

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
102	large intestine, colon	ACC	adenocarcinoma, malignant	0	1	0	0	0.6875	0.6900
109	liver	ACC	adenocarcinoma, malignant	0	1	0	0	0.6875	0.6900
6109	liver	HEA	adenoma, hepatocellular, benig	0	0	0	3	0.0172 !	0.0052
109	liver	HER	carcinoma, hepatocellular, mal	0	0	1	0	0.4886	0.3990
113	lung	AAB	adenoma, bronchiolar alveolar,	7	10	5	6	0.7216	0.7108
113	lung	ACC	adenocarcinoma, malignant	0	3	0	0	0.8736	0.8589
113	lung	CAB	carcinoma, bronchiolar alveola	2	3	4	2	0.4948	0.4789
113	lung	LMS	leiomyosarcoma, malignant	1	0	0	0	1.0000	0.7896
113	lung	SAR	sarcoma, undifferentiated, mal	0	1	0	0	0.7755	0.8029
125	lymph node, mesenteric	LMS	leiomyosarcoma, malignant	0	1	1	0	0.5718	0.5726
133	mammary gland	ACC	adenocarcinoma, malignant	1	2	0	0	0.9579	0.9471
160	ovaries	ACC	adenocarcinoma, malignant	0	1	1	0	0.6407	0.6371
160	ovaries	CTS	carcinoma, tubulostromal cell,	1	0	0	0	1.0000	0.8627
160	ovaries	CYA	cystadenoma, benign	1	0	0	1	0.4373	0.3215
160	ovaries	LMS	leiomyosarcoma, malignant	0	0	1	0	0.4886	0.3990
160	ovaries	SSB	sex-cord/stromal tumor, benign	1	1	0	0	0.9464	0.9137
162	pancreas	ACC	adenocarcinoma, malignant	0	1	0	0	0.6875	0.6900
162	pancreas	AIC	adenoma, islet cell, benign	1	0	0	0	1.0000	0.7896
162	pancreas	LMS	leiomyosarcoma, malignant	0	1	0	0	0.6875	0.6900
171	pituitary gland	AMD	adenoma, pars distalis, benign	0	2	6	1	0.3578	0.3344
171	pituitary gland	CRO	craniopharyngioma, benign	0	1	0	0	0.7380	0.7330
201	skin	TPS	trichofolliculoma, benign	0	1	0	0	0.7755	0.8029
202	skin, subcutis	LMS	leiomyosarcoma, malignant	0	1	0	0	0.6875	0.6900
202	skin, subcutis	SAR	sarcoma, undifferentiated, mal	1	0	2	0	0.7802	0.7331
213	spleen	ACC	adenocarcinoma, malignant	0	1	0	0	0.6875	0.6900
225	thymus gland	ACC	adenocarcinoma, malignant	0	1	0	0	0.7750	0.7300
225	thymus gland	THO	thymoma, benign	0	1	0	0	0.5556	0.6315
233	urinary bladder	ACC	adenocarcinoma, malignant	0	0	1	0	0.6122	0.5084
233	urinary bladder	LMS	leiomyosarcoma, malignant	1	0	0	0	1.0000	0.7896
234	uterus with cervix	ACC	adenocarcinoma, malignant	0	2	2	1	0.4130	0.3973
234	uterus with cervix	FIO	fibroma, benign	0	0	1	1	0.1698	0.0923
234	uterus with cervix	LMO	leiomyoma, benign	3	1	0	2	0.6780	0.6544
234	uterus with cervix	LMS	leiomyosarcoma, malignant	1	2	1	0	0.8649	0.8529
234	uterus with cervix	POD	polyp, stromal, benign	5	5	5	5	0.4338	0.4187
234	uterus with cervix	SCS	sarcoma, stromal, malignant	1	0	1	2	0.1817	0.1383
234	uterus with cervix	TSG	granular cell tumor, malignant	2	0	0	4	0.2432	0.1561
235	vagina	LMS	leiomyosarcoma, malignant	1	0	0	0	1.0000	0.7898
308	adrenal glands	ADP	adenoma, subcapsular cell, ben	0	1	0	0	0.7614	0.7399
308	adrenal glands	LMS	leiomyosarcoma, malignant	1	0	0	0	1.0000	0.7896
313	aorta	LMS	leiomyosarcoma, malignant	1	0	0	0	1.0000	0.7896
44	cavity, abdominal	SAR	sarcoma, undifferentiated, mal	0	1	0	0	0.7403	0.7423
47	cavity, thoracic	OSR	osteosarcoma, malignant	0	0	1	0	0.4928	0.4083
79	harderian glands	ADE	adenoma, benign	1	4	0	2	0.5871	0.5647
91	kidneys	ADT	adenoma, tubular cell, benign	0	0	1	0	0.6122	0.5084
91	kidneys	LMS	leiomyosarcoma, malignant	1	0	1	0	0.6591	0.6521
999	multicentric neoplasm	HAO	hemangioma, benign	1	1	0	0	0.9451	0.8909
999	multicentric neoplasm	HAS	hemangiosarcoma, malignant	3	2	0	1	0.9057	0.8875
999	multicentric neoplasm	HSS	sarcoma, histiocytic, malignan	3	3	1	3	0.5300	0.5156
999	multicentric neoplasm	LYM	lymphoma, malignant	3	5	11	8	0.0601	0.0527

3. RAT STUDY (STUDY SYR-322-00357)

3.1 Introduction

The objective of this study was to evaluate the carcinogenic potential of SYR-322 following daily oral administration in mice for 104 consecutive weeks at a dose volume of 10 mL/kg. Three treatment groups of 60 male and 60 female rats/group were administered the test article at respective dose levels of 75, 400, and 800 mg free base/kg/day. One additional group of 60 animals/sex served as the control and received the vehicle, 0.5% methylcellulose in deionized water at a dose volume of 10 mL/kg. Additionally, four groups of 12 or 28 animals/sex/group served as toxicokinetic (TK) animals and received the vehicle or test article in the same manner and dose levels as the main study groups.

A total of 370 male and 369 female CD® [Crl:CD®(SD)] rats (approximately 6 weeks of age at arrival) were received from [redacted] (b) (4) on March 3, 2005.

The animals considered suitable for study were weighed. Using a standard, by weight, block randomization procedure, 336 male and 336 female animals (weighing 247 to 294 g and 166 to 212 g, respectively, at randomization) were assigned to the control and treatment groups identified in the following table.

Group Assignments			
Group Number	Dose Level	Number of Animals	
		Male	Female
1[a]	0 mg/kg/day (Vehicle Control)	60	60
2[a]	75 mg free base/kg/day	60	60
3[a]	400 mg free base/kg/day	60	60
4[a]	800 mg free base/kg/day	60	60
5[b]	0 mg/kg/day (Vehicle Control)	12	12
6[b]	75 mg free base/kg/day	28	28
7[b]	400 mg free base/kg/day	28	28
8[b]	800 mg free base/kg/day	28	28

[a]Main study animals
[b]Toxicokinetic animals

All control and treatment groups were terminated during Week 104 as originally planned or when the number of surviving animals reached 15 to 20 (25 to 33.3%) in either the control or low dose groups.

3.2 Sponsor's analysis

The sponsor presented the mean survival estimate in Figure 1 of the sponsor's study report and the summary of survival estimates in Table 1 of the sponsor's study report. However, the sponsor did not present any statistical analysis for the rate mortality data.

The sponsor analyzed the rat tumor trend data using Peto's method. The statistical analysis was presented in Table 12 of the sponsor's study report. The p-values under the control group were from trend tests. The p-values under each dosed group were from pair-wise comparisons between that dosed group and the control group. The sponsor used 0.005 and 0.025 significance levels for

positive trend tests of common and rare tumors, respectively. Also, the sponsor used 0.01 and 0.05 significance levels for pair-wise comparisons between the control and individual dosed group of common and rare tumors with the control, respectively. Table 7 listed the statistical analysis for thyroid gland in males (excerpt from the sponsor's Table 12). Table 8 listed the statistical analysis for thyroid gland in females (excerpt from the sponsor's Table 12). The increase in incidence of C-cell adenoma (a common tumor in context of concurrent and historical control groups) in males was statistically significant by pair wise comparison with the control at 400 mg free base/day but not at 800 mg free base/kg/day. When the incidences of C-cell adenoma and carcinoma were combined (a combination considered common) in males, the combined incidence was statistically significant by trend test and significant by pair wise comparison with the controlat 400 and 800 mg free base/kg/day.

The sponsor concluded that SYR-322 was not considered to be carcinogenic in rat thyroids at the dose levels administered in this study.

Table 7 Statistical Analysis of Thyroid Gland tumor in Males

Statistical Analysis of Neoplastic and Non-Neoplastic Lesions Terminal Male				
Dose level: mg free base/kg/day	**0 (Vehicle)**	**75**	**400**	**800**
Thyroid Gland				
Adenoma, C-cell, benign				
Overall Rates (a)	3/60 (5.00%)	8/60 (13.33%)	10/60 (16.67%)	11/60 (18.33%)
Peto Test; P-value	0.0151	0.0651	0.0071	0.0200
Adenoma, C-cell, benign / carcinoma, C-cell, malignant				
Overall Rates (a)	3/60 (5.00%)	8/60 (13.33%)	11/60 (18.33%)	13/60 (21.67%)
Peto Test; P-value	0.0042	0.0651	0.0036	0.0073
Adenoma, C-cell, benign / carcinoma, C-cell, malignant hyperplasia, C-cell, focal				
Overall Rates (a)	9/60 (15.00%)	14/60 (23.33%)	17/60 (28.33%)	19/60 (31.67%)
Peto Test; P-value	0.0163	0.1315	0.0109	0.0321
Adenoma, C-cell, benign / hyperplasia, C-cell, focal				
Overall Rates (a)	9/60 (15.00%)	14/60 (23.33%)	17/60 (28.33%)	17/60 (28.33%)
Peto Test; P-value	0.0396	0.1315	0.0109	0.0701
Carcinoma, C-cell, malignant				
Overall Rates (a)	0/60 (0.00%)	0/60 (0.00%)	1/60 (1.67%)	3/60 (5.00%)
Peto Test; P-value	0.0183	1.0000	0.1435	0.0545
Peto Exact Test; P-value	0.0283	1.0000	0.4688	0.1577
Hyperplasia, C-cell, focal				
Overall Rates (a)	6/60 (10.00%)	7/60 (11.67%)	7/60 (11.67%)	10/60 (16.67%)
Peto Test; P-value	0.1744	0.4107	0.2951	0.2030

(a) – Number of tumor-bearing animals/number of animals examined at site
Notes: The p-values under the control group are from trend tests.
The p-values under each dosed group are from pair-wise comparisons between that dosed group and the control group.
Peto Exact Test was applied for the tumors less than 10 of total incidence in all groups.

Table 8 Statistical Analysis of Thyroid Gland tumor in Females

Statistical Analysis of Neoplastic and Non-Neoplastic Lesions Terminal Female				
Dose level: mg free base/kg/day	**0 (Vehicle)**	**75**	**400**	**800**
Thyroid Gland				
Adenoma, C-cell, benign				
Overall Rates (a)	3/60 (5.00%)	10/60 (16.67%)	10/59 (16.95%)	7/60 (11.67%)
Peto Test; P-value	0.0423	0.0200	0.0163	0.0370
Adenoma, C-cell, benign / carcinoma, C-cell, malignant				
Overall Rates (a)	3/60 (5.00%)	11/60 (18.33%)	10/59 (16.95%)	8/60 (13.33%)
Peto Test; P-value	0.0329	0.0117	0.0163	0.0244
Adenoma, C-cell, benign / carcinoma, C-cell, malignant / hyperplasia, C-cell, focal				
Overall Rates (a)	8/60 (13.33%)	21/60 (35.00%)	12/59 (20.34%)	12/60 (20.00%)
Peto Test; P-value	0.2141	0.0022	0.1306	0.0559
Adenoma, C-cell, benign / hyperplasia, C-cell, focal				
Overall Rates (a)	8/60 (13.33%)	21/60 (35.00%)	12/59 (20.34%)	11/60 (18.33%)
Peto Test; P-value	0.2767	0.0022	0.1306	0.0786
Carcinoma, C-cell, malignant				
Overall Rates (a)	0/60 (0.00%)	2/60 (3.33%)	0/59 (0.00%)	1/60 (1.67%)
Peto Test; P-value	0.3420	0.0798	1.0000	0.1932
Peto Exact Test; P-value	0.4406	0.2529	1.0000	0.5714
Hyperplasia, C-cell, focal				
Overall Rates (a)	5/60 (8.33%)	12/60 (20.00%)	4/59 (6.78%)	7/60 (11.67%)
Peto Test; P-value	0.4431	0.0286	0.5268	0.1263

(a) – Number of tumor-bearing animals/number of animals examined at site
Notes: The p-values under the control group are from trend tests.
The p-values under each dosed group are from pair-wise comparisons between that dosed group and the control group.

3.3 Data Analyzed and Sources

The sponsor submitted the data in electronic format on December 27, 2007. The data are located in the EDR at the following link: \\cdsesub1\n22271\S_00.

3.4 Reviewer's analysis

This reviewer independently analyzed the survival data for males and females, separately. This reviewer also independently analyzed the tumor data of the rat study for males and females, separately using Peto's method.

3.4.1 Survival analysis

The summaries of the mortality data are given in Table 9 for males. The time intervals 0-52, 53-78, 79-91 and 92-104 weeks were chosen for males. The Kaplan-Meier curves for males are shown in Figure 3. Analysis of Dose-Mortality Trend for Male Mice is presented in Table 10. From Figure 3, we can see that the survival probability in control group is lower than that in lowest and highest dosed groups overall. The highest dose group in males has the highest survival rate overall. For

example, the survival rate for the highest dose group is 80% from Week 53 to 78, while the survival rate for the control is 70%. It is unusual that highest dose group had 10% more survival rate than the control from Week 53 to 78. The analysis of Dose-Mortality trend for males in Table 10 does not show a statistically significant dose-related trend among the control and the dosed groups because the p-value is 0.5587 (Cox method) and 0.6224 (Kruskal-Wallis tests), respectively, which is much larger than 0.05.

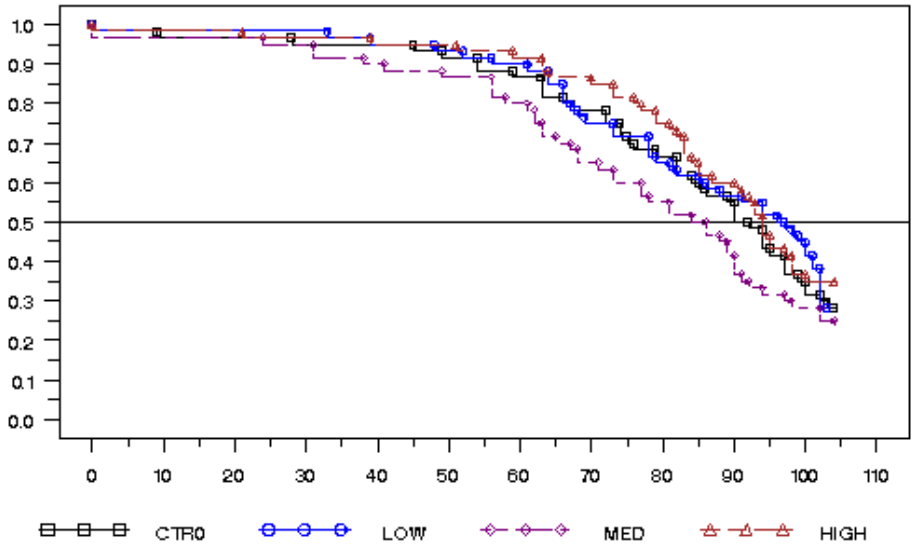

Figure 3 Kaplan-Meier Survival Functions for Male Rats

Table 9 Analysis of Mortality Data for Male Rats by Treatment and Time

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR0	**0-52**	60	4	56	93.3	6.7
	53-78	56	14	42	70.0	30.0
	79-91	42	9	33	55.0	45.0
	92-103	33	15	18	30.0	70.0
	FINALKILL104-104	18	18	0		
LOW	**0-52**	60	4	56	93.3	6.7
	53-78	56	13	43	71.7	28.3
	79-91	43	9	34	56.7	43.3
	92-103	34	17	17	28.3	71.7
	FINALKILL104-104	17	17	0		
MED	**0-52**	60	7	53	88.3	11.7
	53-78	53	19	34	56.7	43.3
	79-91	34	12	22	36.7	63.3
	92-103	22	5	17	28.3	71.7
	FINALKILL104-104	17	17	0		
HIGH	**0-52**	60	3	57	95.0	5.0
	53-78	57	9	48	80.0	20.0
	79-91	48	13	35	58.3	41.7
	92-103	35	13	22	36.7	63.3

	FINALKILL104-104	22	22	0		

Table 10 Analysis of Dose-Mortality Trend for Male Rats

	Method			
	Cox		**Kruskal-Wallis**	
	Statistics	**P-Value**	**Statistics**	**P-Value**
Time-Adjusted Trend Test	2.6600	0.2645	5.2384	0.0729
Depart from Trend				
Dose-Mortality Trend	0.3597	0.5487	0.2426	0.6224
Homogeneity	3.0196	0.3886	5.4810	0.1398

Note: This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

The summaries of the mortality data are given in Table 11 for females. The time intervals 0-52, 53-78, 79-91 and 92-104 weeks were chosen for females. The Kaplan-Meier curves for females are shown in Figure 4. Analysis of Dose-Mortality Trend for Female Mice is presented in Table 12. From Figure 4, we can see that the survival probability in control group is little lower than that in lowest dosed group overall. The analysis of Dose-Mortality trend for females in Table 12 does not show a statistically significant dose-related trend among the control and the dosed groups at the 0.05 significance level because the p-value is 0.1843 (Cox method) and 0.0701 (Kruskal-Wallis tests), respectively. However, the p-value from Kruskal-Wallis test of the trend is just a little bit larger than 0.05.

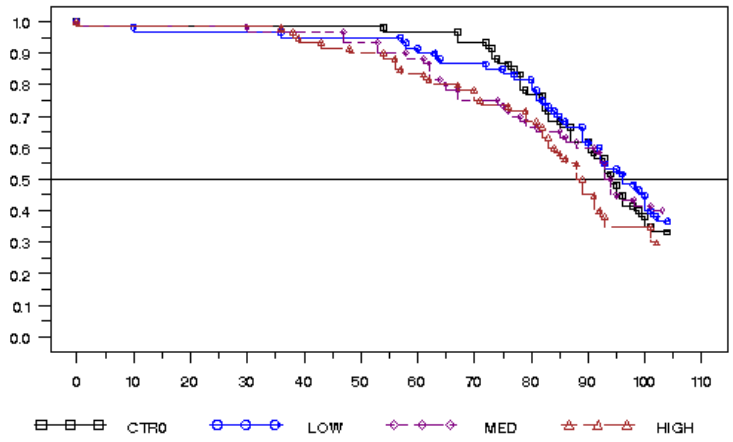

Figure 4 Kaplan-Meier Survival Functions for Female Rats

Table 11 Analysis of Mortality Data for Female Rats by Treatment and Time

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR0	**53-78**	60	10	50	83.3	16.7
	79-91	50	15	35	58.3	41.7
	92-103	35	14	21	35.0	65.0
	FINALKILL104-104	21	21	0		
LOW	**0-52**	60	2	58	96.7	3.3
	53-78	58	8	50	83.3	16.7
	79-91	50	13	37	61.7	38.3
	92-103	37	14	23	38.3	61.7
	FINALKILL104-104	23	23	0		
MED	**0-52**	60	2	58	96.7	3.3
	53-78	58	16	42	70.0	30.0
	79-91	42	6	36	60.0	40.0
	92-103	36	12	24	40.0	60.0
	FINALKILL104-104	24	24	0		
HIGH	**0-52**	60	5	55	91.7	8.3
	53-78	55	11	44	73.3	26.7
	79-91	44	17	27	45.0	55.0
	92-103	27	9	18	30.0	70.0
	FINALKILL104-104	18	18	0		

Table 12 Analysis of Dose-Mortality Trend for Female Rats

	Method			
	Cox		**Kruskal-Wallis**	
	Statistics	**P-Value**	**Statistics**	**P-Value**
Time-Adjusted Trend Test	0.6150	0.7353	0.1873	0.9106
Depart from Trend				
Dose-Mortality Trend	1.7627	0.1843	3.2804	0.0701
Homogeneity	2.3777	0.4978	3.4678	0.3250

Note: This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

3.4.2 Tumor data analysis

The dose response analyses in incidental tumors and fatal tumors were performed using the Peto prevalence method and the Peto death-rate method, respectively. The actual dose levels of treatment groups were used as the weights for the trend analysis. The number of tumor bearing animals of each tumor type and its p-values for many organs were presented in Tables 13 and 14 for males and females, respectively. Multiplicity for the trend testing was adjusted using a significance level of 0.025 for rare tumors, and 0.005 for common tumors because two species were studied. A tumor type with a background rate of 1 percent or less is classified as rare by Haseman; more frequent tumors are classified as common.

It is also well known that the approximation results may not be stable and reliable, and tend to underestimate the exact p-values when the total numbers of tumor occurrence across treatment groups are small. In this situation, the exact permutation trend test should be used to test for the positive trend. The exact permutation trend test is a generalization of the Fisher's exact test. From Tables 13 and 14, it is seen that there is no statistically significantly positive trend in both incidental tumors and fatal tumors for males and females. The combined tumor analysis of adenoma, c-cell benign and carcinoma, c-cell, malignant was also done for thyroid gland in males. The p-value for the combined tumor analysis for thyroid gland in males is 0.01 (>0.005).

Table 13 Report on Test for Positive Linear Dose-Tumor for Male

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
109	liver	HEA	adenoma, hepatocellular, benig	3	0	3	1	0.5862	0.5776
109	liver	HER	carcinoma, hepatocellular, mal	1	0	0	0	1.0000	0.7962
113	lung	CRT	carcinoma, cortical, malignant	1	0	1	0	0.5951	0.6249
113	lung	PCC	carcinoma, c-cell, malignant	0	0	0	1	0.2973	0.0842
113	lung	ZGC	carcinoma, zymbals gland, mali	0	0	1	0	0.5091	0.3443
121	lymph node, iliac	CRT	carcinoma, cortical, malignant	0	0	1	0	0.3600	0.3517
133	mammary gland	ACC	adenocarcinoma, malignant	0	1	0	0	0.7455	0.7749
133	mammary gland	FIA	f broadenoma, benign	1	1	1	0	0.7739	0.7699
137	mesentery/peritoneum	FPR	f brous histiocytoma, malignan	1	0	0	0	1.0000	0.8466
162	pancreas	AIC	adenoma, islet cell, benign	4	8	6	6	0.5113	0.5109
162	pancreas	ICC	carcinoma, islet cell, maligna	0	0	0	1	0.2973	0.0842
171	pituitary gland	AMD	adenoma, pars distalis, benign	38	36	38	45	0.0467	0.0454
171	pituitary gland	MEL	meningioma, malignant	0	1	0	0	0.7455	0.7749
171	pituitary gland	PAB	carcinoma, pars distalis, mali	0	0	1	0	0.5270	0.4365
171	pituitary gland	PIA	adenoma, pars intermedia, beni	0	0	0	2	0.0486	0.0128
171	pituitary gland	SWB	schwannoma, malignant	1	0	0	0	1.0000	0.8549
177	prostate gland	ACC	adenocarcinoma, malignant	0	1	0	0	0.7568	0.7965
177	prostate gland	ADE	adenoma, benign	1	0	0	0	1.0000	0.8549
184	seminal vesicles	FPR	f brous histiocytoma, malignan	1	0	0	0	1.0000	0.8466
200	skeletal muscle, thoracic	FPR	f brous histiocytoma, malignan	1	0	0	0	1.0000	0.8466
201	skin	ADL	adenoma, basal cell, benign	0	0	0	1	0.2973	0.0842
201	skin	CMC	carcinoma, basal cell, maligna	1	1	0	0	0.9270	0.8792
201	skin	FIO	f broma, benign	1	0	0	0	1.0000	0.8549
201	skin	KAO	keratoacanthoma, benign	3	1	4	1	0.6917	0.6738
201	skin	SQC	carcinoma, squamous cell, mali	1	0	0	0	1.0000	0.8549
201	skin	SQP	papilloma, squamous cell, beni	0	0	1	0	0.5270	0.4365
202	skin, subcutis	FIO	f broma, benign	3	0	1	1	0.8065	0.7789

202	skin, subcutis	FPR	f brous histiocytoma, malignan	1	0	0	0	1.0000	0.8466
202	skin, subcutis	FSA	f brosarcoma, malignant	2	0	1	1	0.5991	0.5337
202	skin, subcutis	LIO	lipoma, benign	2	1	0	1	0.8002	0.7649
202	skin, subcutis	SWB	schwannoma, malignant	0	1	3	0	0.5194	0.4872
218	stomach, nonglandular	SQC	carcinoma, squamous cell, mali	0	0	0	1	0.2973	0.0842
223	testes	ACE	adenoma, interstitial cell, be	0	2	1	2	0.2500	0.2606
223	testes	MED	mesothelioma, malignant	0	0	1	0	0.5091	0.3443
226	thyroid gland	FLA	adenoma, follicular cell, beni	2	0	1	1	0.6638	0.6092
226	thyroid gland	FLC	carcinoma, follicular cell, ma	0	1	0	0	0.7000	0.7262
226	thyroid gland	PCA	adenoma, c-cell, benign	3	8	10	11	0.0362	0.0333
226	thyroid gland	PCC	carcinoma, c-cell, malignant	0	0	1	3	0.0291	0.0141
247	zymbal`s gland	ZGC	carcinoma, zymbals gland, mali	1	1	1	0	0.7889	0.7655
30	brain	AST	astrocytoma, malignant	1	2	3	1	0.5235	0.5097
30	brain	MEL	meningioma, malignant	0	1	0	0	0.7500	0.7791
30	brain	PAB	carcinoma, pars distalis, mali	0	0	1	0	0.5270	0.4365
30	brain	TSG	granular cell tumor, benign	0	2	0	0	0.7754	0.8437
308	adrenal glands	ACD	adenoma, cortical, benign	1	1	0	1	0.5734	0.5137
308	adrenal glands	CRT	carcinoma, cortical, malignant	1	0	1	0	0.6507	0.6527
308	adrenal glands	PCT	pheochromocytoma, malignant	22	20	22	6	0.9829	0.9803
317	bone	CRT	carcinoma, cortical, malignant	0	0	1	0	0.3600	0.3517
44	cavity, abdominal	CRT	carcinoma, cortical, malignant	0	0	1	0	0.3600	0.3517
44	cavity, abdominal	FPR	f brous histiocytoma, malignan	1	0	0	0	1.0000	0.8466
44	cavity, abdominal	SWB	schwannoma, malignant	0	1	0	0	0.7568	0.7965
47	cavity, thoracic	FPR	f brous histiocytoma, malignan	1	0	0	0	1.0000	0.8466
61	epididymides	MED	mesothelioma, malignant	0	0	1	0	0.5091	0.3443
65	eyes	SWB	schwannoma, malignant	1	0	1	1	0.4676	0.3887
80	heart	SWB	schwannoma, malignant	1	1	0	0	0.9250	0.8705
91	kidneys	CTM	carcinoma, tubular cell, malig	0	0	1	0	0.5270	0.4365
91	kidneys	SAR	sarcoma, undifferentiated, mal	1	0	0	0	1.0000	0.8416
999	multicentric neoplasm	HAS	hemangiosarcoma, malignant	0	1	0	0	0.7568	0.7965
999	multicentric neoplasm	HSS	sarcoma, histiocytic, malignan	0	4	0	1	0.7114	0.7385
999	multicentric neoplasm	LYM	lymphoma, malignant	1	2	1	0	0.8796	0.8792

Table 14 Report on Test for Positive Linear Dose-Tumor for Females

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
109	liver	HEA	adenoma, hepatocellular, benig	0	0	2	0	0.4229	0.2896
109	liver	SQC	carcinoma, squamous cell, mali	0	0	0	1	0.2304	0.0551
113	lung	CRT	carcinoma, cortical, malignant	0	1	0	0	0.7558	0.7722
113	lung	CSU	carcinoma (primary site unknow	0	0	1	0	0.4884	0.3694
113	lung	OSR	osteosarcoma, malignant	1	0	0	0	1.0000	0.8293
113	lung	SQC	carcinoma, squamous cell, mali	0	0	0	2	0.0449	0.0100
115	lymph node, axillary	FPR	fibrous histiocytoma, malignan	0	0	0	1	0.1875	0.0374
119	lymph node, hepatic	SQC	carcinoma, squamous cell, mali	0	0	0	1	0.2444	0.0686
121	lymph node, iliac	ACC	adenocarcinoma, malignant	0	0	0	1	0.2093	0.0482
122	lymph node, inguinal	FPR	fibrous histiocytoma, malignan	0	0	0	1	0.1957	0.0400
124	lymph node, mediastinal	SQC	carcinoma, squamous cell, mali	0	0	0	1	0.2444	0.0686
133	mammary gland	ACC	adenocarcinoma, malignant	15	15	16	12	0.6813	0.6786
133	mammary gland	ADE	adenoma, benign	7	4	7	1	0.9337	0.9278
133	mammary gland	FIA	fibroadenoma, benign	25	17	18	15	0.8487	0.8492
162	pancreas	AIC	adenoma, islet cell, benign	5	3	1	0	0.9967	0.9904
162	pancreas	SQC	carcinoma, squamous cell, mali	0	0	0	1	0.2444	0.0686
171	pituitary gland	AMD	adenoma, pars distalis, benign	51	53	49	51	0.3039	0.3031
201	skin	KAO	keratoacanthoma, benign	0	1	0	0	0.7558	0.7722
201	skin	SQC	carcinoma, squamous cell, mali	1	0	0	0	1.0000	0.8166
202	skin, subcutis	FIO	fibroma, benign	0	1	0	0	0.7143	0.7418
202	skin, subcutis	FPR	fibrous histiocytoma, malignan	0	0	0	1	0.1837	0.0357
202	skin, subcutis	FSA	fibrosarcoma, malignant	0	0	1	0	0.4286	0.3262
202	skin, subcutis	LIO	lipoma, benign	1	0	1	0	0.7412	0.6807
226	thyroid gland	FLA	adenoma, follicular cell, beni	0	0	0	2	0.0706	0.0182
226	thyroid gland	PCA	adenoma, c-cell, benign	3	10	10	7	0.1595	0.1546
226	thyroid gland	PCC	carcinoma, c-cell, malignant	0	2	0	1	0.3825	0.4331
234	uterus with cervix	ACC	adenocarcinoma, malignant	1	1	0	0	0.9343	0.8829
234	uterus with cervix	POD	polyp, stromal, benign	1	1	5	2	0.1717	0.1440
234	uterus with cervix	TSG	granular cell tumor, benign	1	4	3	1	0.7051	0.7171
247	zymbal`s gland	ZGC	carcinoma, zymbals gland, mali	0	2	0	0	0.7591	0.8366
30	brain	AST	astrocytoma, malignant	1	0	0	0	1.0000	0.8402
30	brain	TSG	granular cell tumor, benign	1	1	0	0	0.9160	0.8738
308	adrenal glands	ACD	adenoma, cortical, benign	1	0	0	2	0.2488	0.1558
308	adrenal glands	CRT	carcinoma, cortical, malignant	0	1	0	0	0.7558	0.7722
308	adrenal glands	PCT	pheochromocytoma,	1	3	11	4	0.0458	0.0378

			benign						
44	cavity, abdominal	ACC	adenocarcinoma, malignant	0	1	0	0	0.7143	0.7418
44	cavity, abdominal	LIS	liposarcoma, malignant	1	0	0	0	1.0000	0.8340
44	cavity, abdominal	OSR	osteosarcoma, malignant	1	0	0	0	1.0000	0.8293
55	clitoral glands	SEI	carcinoma, sebaceous cell, mal	0	0	1	0	0.4884	0.3694
55	clitoral glands	SQC	carcinoma, squamous cell, mali	1	0	0	1	0.4703	0.3332
91	kidneys	ADT	adenoma, tubular cell, benign	1	0	0	0	1.0000	0.8402
91	kidneys	LIO	lipoma, benign	0	0	1	0	0.4286	0.3262
91	kidneys	LIS	liposarcoma, malignant	0	0	1	0	0.6000	0.4363
999	multicentric neoplasm	HAO	hemangioma, benign	0	1	0	0	0.7558	0.7722
999	multicentric neoplasm	HAS	hemangiosarcoma, malignant	0	0	1	1	0.1874	0.1096
999	multicentric neoplasm	HSS	sarcoma, histiocytic, malignan	1	1	0	0	0.9298	0.8822
999	multicentric neoplasm	LYM	lymphoma, malignant	0	2	1	0	0.7219	0.7610

3.4.3 Conclusion

The survival probability in control group is lower than that in lowest and highest dosed groups overall. The highest dose group in males has the highest survival rate overall. For example, the survival rate for the highest dose group is 80% from Week 53 to 78, while the survival rate for the control is 70%. It is unusual to see that highest dose group has 10% more survival rate than the control from Week 53 to 78. The analysis of Dose-Mortality trend for males in Table 10 does not show a statistically significant dose-related trend difference among the control and the dosed groups because the p-value is 0.5587 (Cox method) and 0.6224 (Kruskal-Wallis tests), respectively, which is much larger than 0.05.

The survival probability in control group is little lower than that in lowest dosed group overall for females. The analysis of Dose-Mortality trend for females in Table 12 does not show a statistically significant dose-related trend among the control and the dosed groups at the 0.05 significance level because the p-value is 0.1843 (Cox method) and 0.0701 (Kruskal-Wallis tests), respectively. However, the p-value from Kruskal-Wallis test of the trend is just a little bit larger than 0.05.

There is no statistically significantly positive trend in both incidental tumors and fatal tumors for males and females. The combined tumor analysis of adenoma, c-cell benign and carcinoma, c-cell, malignant was also done for thyroid gland in males. The p-value for the combined tumor analysis for thyroid gland in males is 0.01 (>0.005).

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