CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022426Orig1s000

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

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.
Concurring Reviewers:	J. Todd Sahlroot, Ph.D., Team Leader and Deputy Division Director
Medical Division:	Division of Metabolic and Endocrinology Products
Clinical Team:	Valerie Pratt, M.D., Clinical Reviewer Hylton Joffe, M.D., Team Leader
Project Manager:	Mehreen Hai, Ph.D.

Keywords: NDA review, clinical studies

Table of Contents

List of Tables

List of Figures

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

Study 004: 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).

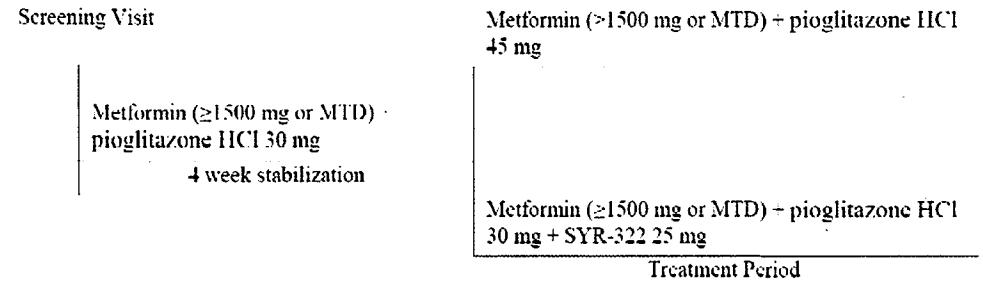
Schedule B: Subjects with a screening HbA1c > 8.0% and a treatment regimen of metformin and another oral antidiabetic agent (i.e., sulfonylureas, rosiglitazone, or pioglitazone 15 mg) entered a pre-screening period of up to two weeks. These subjects were then instructed to discontinue their previous 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

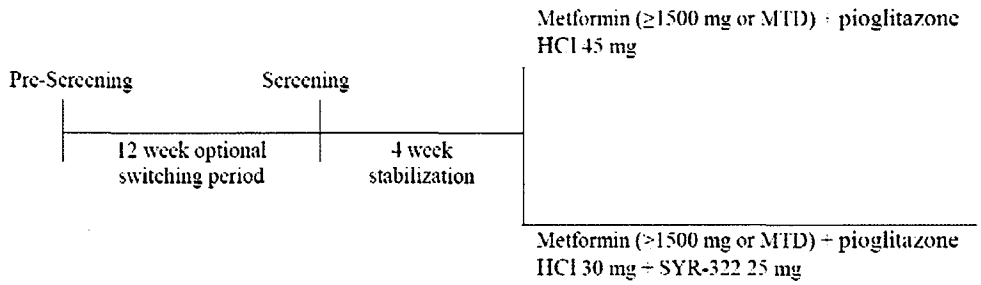
Study Schedule A

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		-1.0	-1.6
(95% CI)		(-1.6, -0.4)	(-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		-1.5	-1.5
(95% CI)		(-2.0, -1.0)	(-2.0, -1.0)
Difference from pioglitazone 30 mg (approx 95% CI)			-0.1 (-0.6, 0.5)

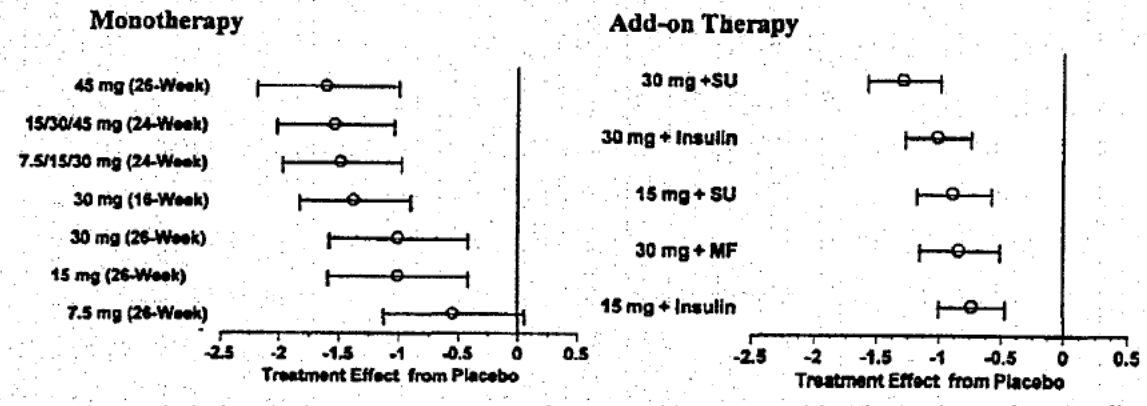
[1] HbA1c expressed as a change from baseline

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

[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 $\geq$ 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 $\geq$ 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.

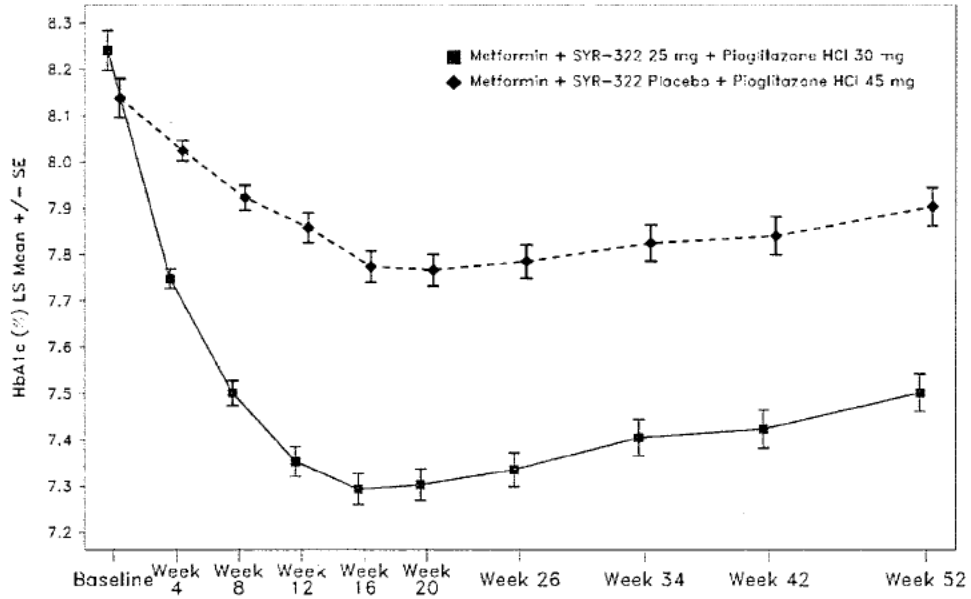
[2] The p-values and corresponding odds ratio and 95% confidence interval were from a logistic regression model with effects for treatment, study schedule, geographic region, baseline metformin dose and baseline HbA1c.

[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.

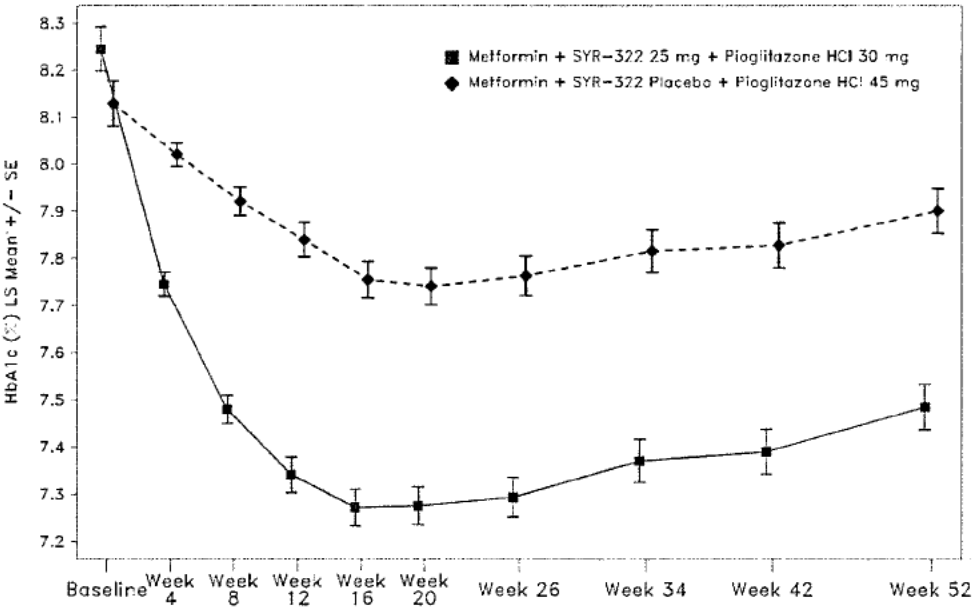
Source: Study 004 clinical report:
1A, B and C: Table 15.2.26, and additional analysis by this reviewer.
2A and B: Table 15.2.2.1
3A and B: Table 15.2.7.1

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

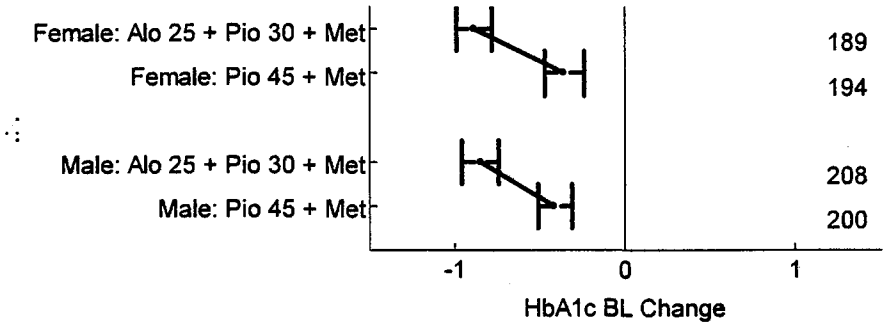
An evaluation of the safety of alogliptin and the alogliptin + pioglitazone combination product is included in the clinical review by Dr. Valerie Pratt. Dr. Eugenio Andraca-Carrera of the Division of Biometrics 7 is conducting a statistical review of cardiovascular safety of alogliptin.

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

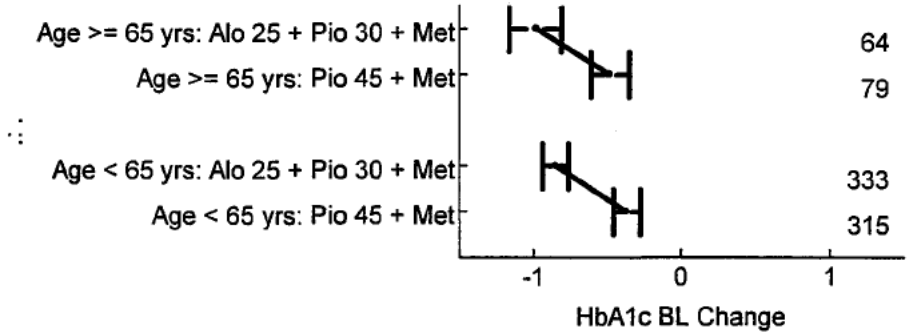
The comparison between the alogliptin and pioglitazone arms did not appear to be appreciably affected by sex, age group (< 65 and ≥ 65 years of age), race (4 subgroups: white, black, Asian and all others), ethnicity (Hispanic / Latino or not Hispanic / Latino), or region (U.S. or outside the U.S.), at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

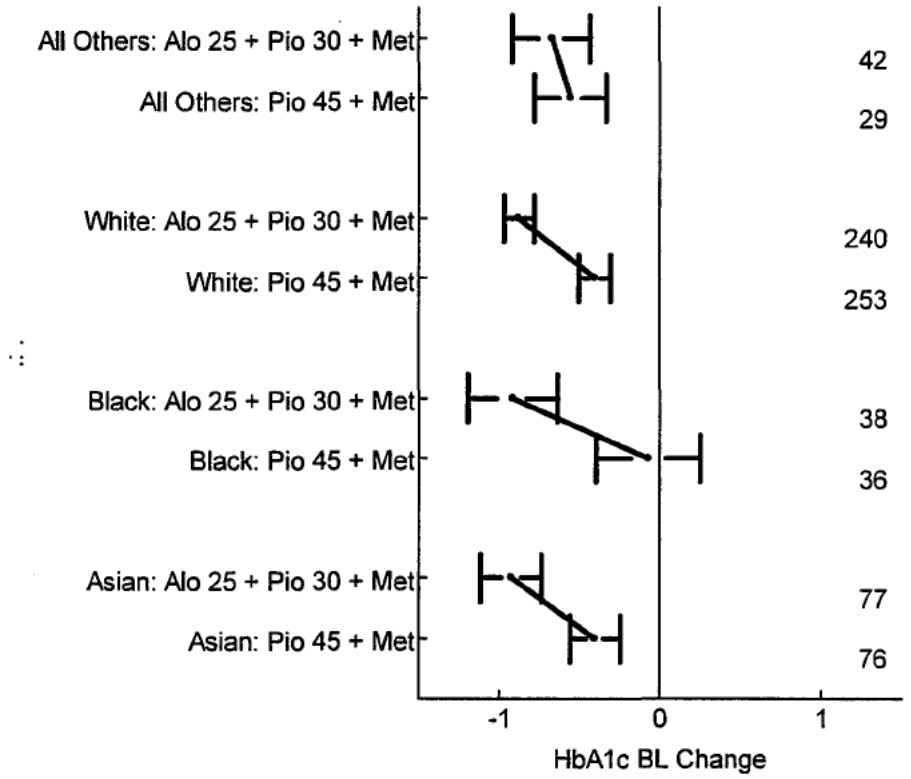
A. Sex; p-value of sex by treatment arm interaction is 0.2205



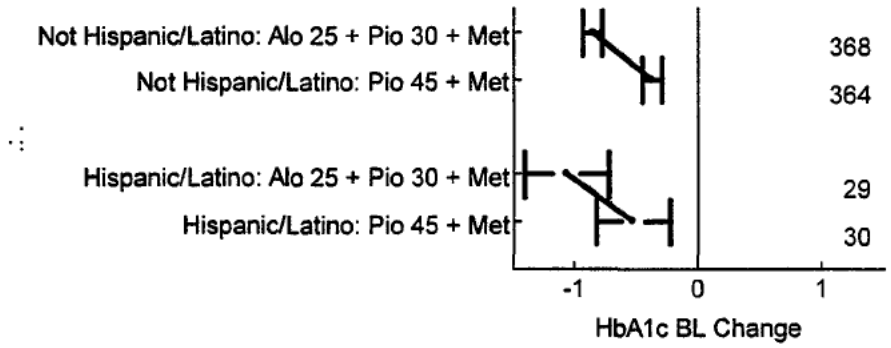
B. Age group; p-value of age group by treatment arm interaction is 0.7062



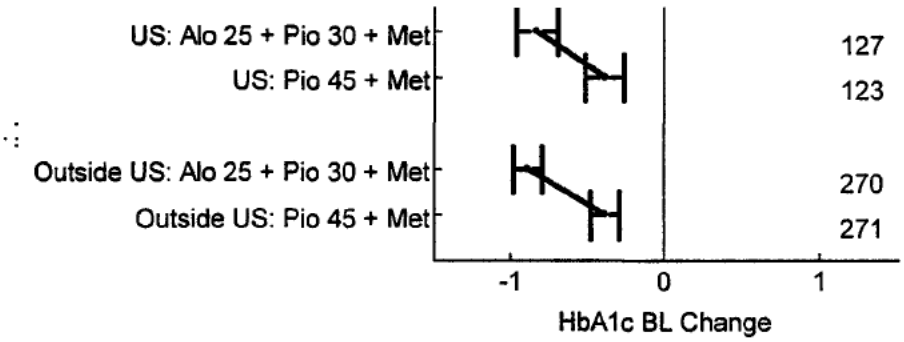
C. Race; p-value of race by treatment arm interaction is 0.1900



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

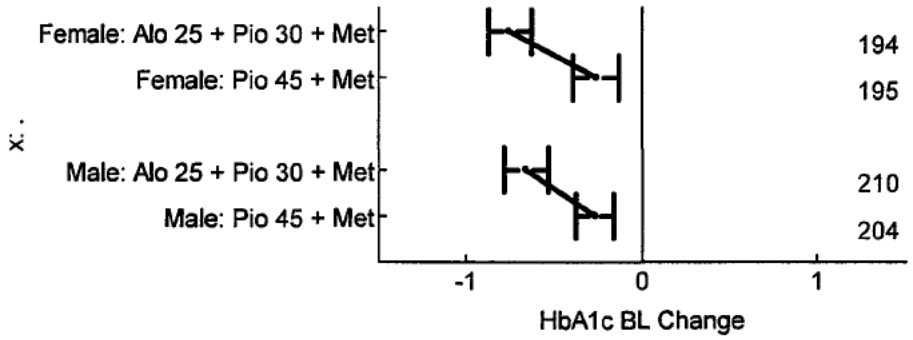


Notes: A separate analysis of covariance model was evaluated for each subgroup. The FAS/LOCF analysis population was used for the analysis. The analysis model was based on the primary analysis model, with fixed effect terms added for the subgroup and the interaction of the subgroup with the treatment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

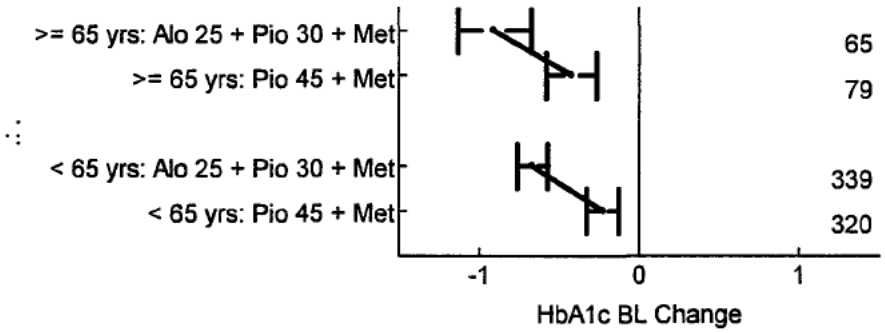
Source: Analysis by this reviewer

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

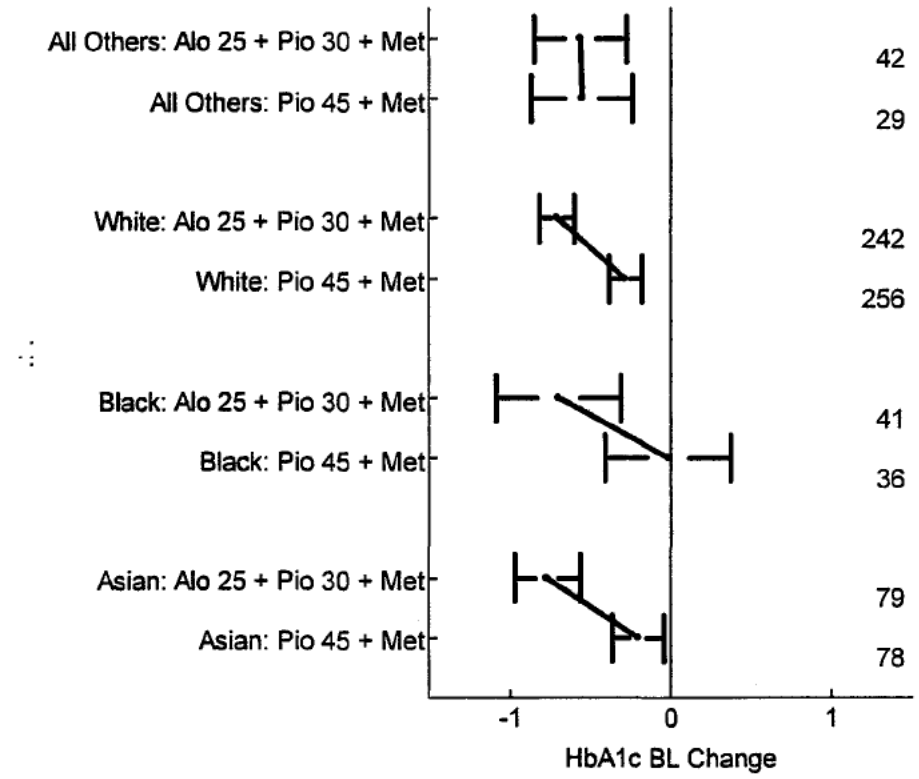
A. Sex; p-value of sex by treatment arm interaction is 0.2555



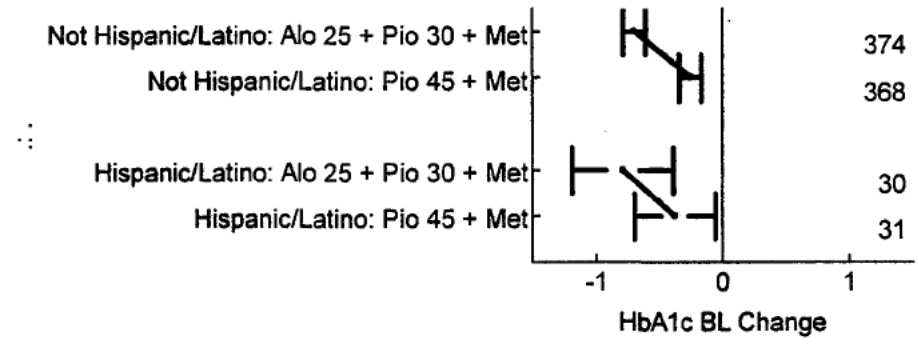
B. Age group; p-value of age group by treatment arm interaction is 0.5579



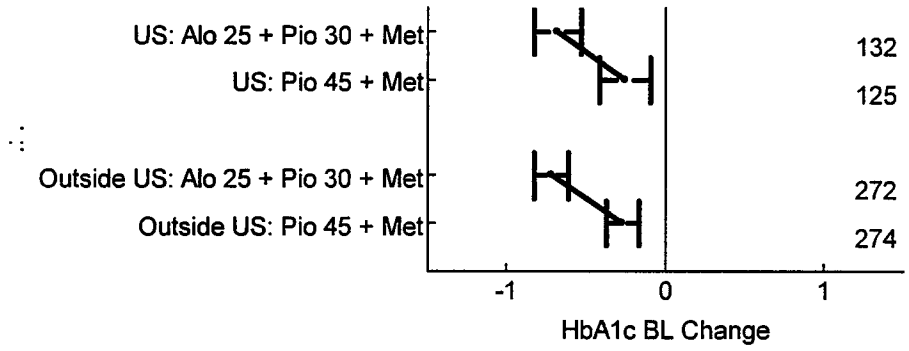
C. Race; p-value of race by treatment arm interaction is 0.7419



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.

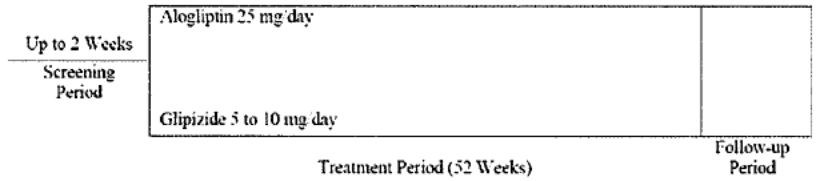
Subjects following Schedule A had a screening period of up to two weeks, a treatment period of 52 weeks, followed by a week 52 visit (or early termination visit) and a follow-up visit two weeks after the week 52 visit (FIGURE 6).

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

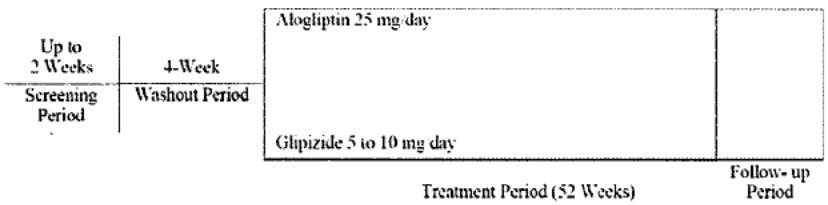
Schedule A subjects

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 $\geq$ 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 $\geq$ 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 $\leq$ 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, $\geq$ 0.0 and $\leq$ 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:

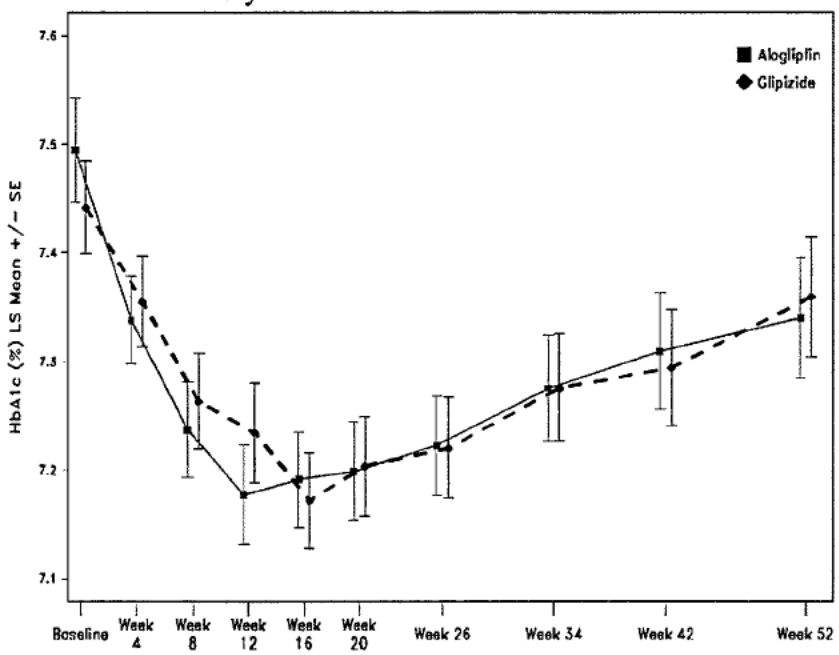
[1] The adjusted mean change from baseline at week 26 and the difference in the adjusted mean change were estimated from the primary analysis of covariance model, with treatment, study schedule and geographic region as class variables, and baseline HbA1c as a covariate.

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

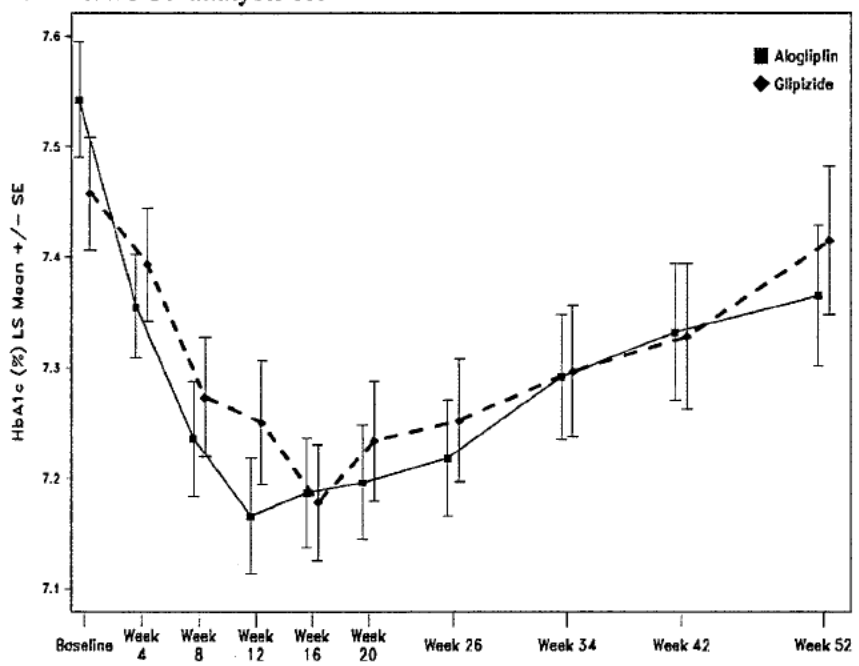
Sources: Study 303 clinical report; Table 11.b, Table 11.hand additional analysis by this reviewer

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)	First sentence: No changes Second and third sentence: Replace with (b) (4) First sentence: Replace with (b) (4) Second sentence: No changes

Proposed Label Summary	Statistical Review Comments
(b) (4)	

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)

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

/s/

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

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

/s/

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:	022426/0
Drug Name:	Alogliptin / Pioglitazone fixed-dose combination tablets (SYR-322-4833)
Indication(s):	Treatment of type 2 diabetes mellitus
Applicant:	Takeda Global Research & Development Center, Inc.
Date(s):	Letter date September 19, 2008
	PDUFA Goal Date July 22, 2009
	Statistical review completed 7/31/09
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:	Valerie Pratt, 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

Table of Contents

LIST OF TABLES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Efficacy Conclusions: Based on an evaluation of the two Phase 3 studies, I conclude that the combination product of alogliptin + pioglitazone had superior efficacy compared to either alogliptin alone or pioglitazone alone, at the dose levels tested (alogliptin 12.5 mg and 25 mg; pioglitazone 15, 30 and 45 mg). In the two combination studies, alogliptin + pioglitazone had a statistically significantly greater effect on the average reduction in HbA1c at week 26 from baseline, compared to either alogliptin alone or pioglitazone alone. The contribution of alogliptin in the combination product was an additional average reduction of HbA1c of approximately 0.5 percent units compared to pioglitazone alone. The contribution of the two doses of alogliptin, 12.5 and 25 mg, was fairly similar. The combination studies were not powered or intended to quantify the difference between doses.

The effect of alogliptin from the combination studies was similar to the effect estimated from five Phase 3 studies reviewed under NDA 022271/0. The applicant submitted results from these studies to NDA 022271/0 to support an indication for alogliptin as monotherapy or as add-on therapy. One study, conducted with pioglitazone as background therapy, was submitted to both NDA 022271/0 and NDA 022426/0. At the time of this review, the action on NDA 022271/0 was a complete response from the Division in a letter dated June 26, 2009.

In the combination studies, the alogliptin component was not associated with a statistically significant average change in body weight at week 26 compared to baseline. In contrast, the pioglitazone component was associated with a statistically significant average weight gain at week 26, ranging from 1.3 kg to 3.4 kg between the two studies and across the dose arms. The findings for body weight in the combination studies are consistent with the results from the Phase 3 studies reviewed in NDA 022271/0. In these studies, the large majority of patients treated with alogliptin, 84% to 94%, stayed within ± 5% of their baseline body weight at week 26.

Results for fasting plasma glucose at week 26 also supported the efficacy of the combination product in comparison to either alogliptin alone or pioglitazone alone. Subgroups defined by gender, race, ethnicity and age (< 65 and ≥ 65 years) were fairly similar with respect to the effect of alogliptin in the combination product.

Safety Conclusions: The evaluation of cardiovascular risk associated with alogliptin is the focus of ongoing review by the Division. The evaluation of safety is included in the clinical review by Dr. Valerie Pratt.

Recommendations: There are no additional recommendations.

1.2 Brief Overview of Clinical Studies

The clinical development of alogliptin includes efficacy studies of alogliptin monotherapy, add-on therapy with other common oral anti-diabetic drugs (sulfonylurea, metformin or pioglitazone) or insulin, and combination studies of alogliptin + pioglitazone. The applicant conducted studies in two general populations of patients with type 2 diabetes mellitus:

(1) Patients who had never received pharmacologic therapy or had received only minimal therapy. Alogliptin was evaluated as a monotherapy in a study that was reviewed under NDA 022271/0. The combination of alogliption + pioglitazone was evaluated in Study PI-002 and is reviewed in this NDA.

(2) Patients whose diabetes was no longer adequately controlled with one or more anti-diabetic drugs. Alogliptin was evaluated as add-on therapy to different background anti-diabetic therapies in four studies, reviewed under NDA 022271/0. Study 009, which used pioglitazone as background therapy, is included in both NDAs. The combination of alogliptin + pioglitazone was evaluated with metformin as background therapy in Study PI-001, which is reviewed in this NDA.

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 and change in body weight were key secondary efficacy endpoints.

1.3 Statistical Issues and Findings

The evaluation of a combination product: At the development stage of the two combination studies, the biometrics review team recommended features of the design and analysis that emphasized the comparison of the alogliptin + pioglitazone combination product to each component on its own (i.e., to alogliptin alone and to pioglitazone alone). In my opinion, this approach accurately reflects the regulatory requirements for evaluating a combination product[1]. The applicant followed this recommendation in part, by designing each study to include both the combination product and its monotherapy components in the relevant doses. However, as a primary analysis, the applicant followed a mixed strategy. In Study PI-001, the applicant compared the alogliptin + pioglitazone combination product to pioglitazone alone. This analysis focuses on the contribution of the alogliptin component to the combination product. Although pioglitazone is an already approved drug, the biometrics team noted that the contribution of each component to the efficacy of the alogliptin + pioglitazone combination should still be evaluated.

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

The applicant did provide additional results from each study showing the comparisons of the combination to alogliptin alone. This information enabled me to complete the evaluation of the combination product. In Study PI-002, the applicant compared the alogliptin + pioglitazone combination to each component on its own at the 25 mg level of alogliptin.

Another statistical issue concerned the primary approach to analyzing data from Study PI-001, which had 12 arms, designed as a factorial combination of alogliptin (0, 12.5 mg and 25 mg) crossed with pioglitazone (0, 15, 30 and 45 mg). The applicant evaluated the alogliptin + pioglitazone combinations in a sequence of two comparisons. First, all combinations with the 25 mg dose of alogliptin were averaged and compared to an average of the pioglitazone only arms. Second, contingent on the statistical significance of the first, all combinations with the 12.5 mg dose of alogliptin were averaged and compared to the average of the pioglitazone only arms. The biometrics review team preferred a sequence twelve comparisons, structured as six sets of two pair-wise comparisons. Each set consisted of one of the alogliptin + pioglitazone arms compared to the alogliptin arm and to the pioglitazone arm at the pertinent doses. All comparisons would be evaluated at the nominal level of 0.05. If not all comparisons were significant at this nominal level, statistical and clinical judgment would guide the overall conclusion about the contribution of each component to the efficacy of the combination product.

In my opinion, both approaches have advantages and disadvantages. For the applicant's approach to be fully interpretable as an estimate of the contribution of the alogliptin 25 mg component to the combination product, we need to assume that the contribution of alogliptin 25 mg is not influenced by the dose of piogligazone with which it is combined, through the dose range of 15 through 45 mg of pioglitazone. A similar assumption is necessary to interpret the contribution of alogliptin 12.5 mg to the combination product. The approach used by the biometrics team has the advantage of being able to identify potential differences in the contribution of alogliptin at different levels of pioglitazone, but it also has the disadvantage of having less statistical power to do so, because each pairwise comparison is based on two arms, whereas the applicant's approach involves a linear combination of six arms. The advice from the biometrics review team at the protocol stage reflects these considerations.

I developed a post-hoc approach to conducting the 12 pair-wise comparisons that were needed to evaluate each of the six alogliptin/pioglitazone combinations. I chose an approach that I believed would reflect the spirit of the gate-keeping approach used by the applicant, the focus on pairwise comparisons of each combination recommended by the biometrics review team at the protocol stage, and the post-hoc nature of the evaluation. The study results from my post-hoc approach and the applicant's approach were the same.

2. INTRODUCTION

2.1 Overview

SYR-322-4833 is a fixed-dose combination product that the applicant is developing under IND 73193 for the treatment of type 2 diabetes mellitus (T2DM). The active components of SYR-322-4833 (which will be referred to as "Alo/Pio" in this review) are alogliptin and pioglitazone. Alogliptin and pioglitazone have different mechanisms of action as anti-diabetic drugs. Alogliptin acts by selectively inhibiting the enzymatic activity of dipeptidyl peptidase IV (DPP-4), an enzyme that rapidly degrades incretin hormones. Inhibition of DPP-IV activity augments glucose-stimulated insulin secretion, resulting in reductions in glycemia. At the time of this review, one DPP-4 inhibitor, sitagliptin (Januvia™) has been approved by the Agency. Pioglitazone is characterized as a "PPARγ agonist" that is a member of the thiazolidinedione (TZD) 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[2]. Because of the different mechanisms of action, the applicant believes that the combination of Alo/Pio could act in a complementary way and potentially improve glycemic control compared with the administration of either agent alone. Pioglitazone (ACTOS®) has been commercially available since 1999.

The applicant submitted NDA 022271 in December 2007 in support of the safety and efficacy of alogliptin as monotherapy and as add-on therapy to several anti-diabetic background therapies. At the time of this review, alogliptin has not been approved. The Division sent a "Complete Response" letter, dated June 26, 2009, to the applicant in response to the NDA 022271/0 submission.

The applicant developed an orally available, immediate-release formulation of Alo/Pio in six dosage strengths:

- Alo 12.5 mg + Pio 15 mg (A12.5/P15)
- Alo 12.5 mg + Pio 30 mg (A12.5/P30)
- Alo 12.5 mg + Pio 45 mg (A12.5/P45)
- Alo 25 mg + Pio 15 mg (A25/P15)
- Alo 25 mg + Pio 30 mg (A25/P30)
- Alo 25 mg + Pio 45 mg (A25/P45)

Bioequivalence between the combination product and the individual components was established using the highest and lowest dosage strengths (A12.5/P15 and A25/P45). A food effect study using the highest dose (A25/P45) determined that Alo/Pio may be given with or without food.

Scope of Statistical Review: Pivotal Efficacy and Safety Studies

This statistical review covers three Phase 3 studies that were designed to assess the efficacy and safety of alogliptin and pioglitazone. One of these studies, Study 009, was originally reviewed in the NDA 022271/0 submission for alogliptin. Study 009 evaluated alogliptin as an add-on

[2] The source of this paragraph is Section 2.2 Introduction (paraphrased).

therapy to a background therapy of pioglitazone, either alone or in combination with metformin or a sulfonylurea. Information from Study 009 will be included in this review, where doing so would facilitate the overall assessment of efficacy and safety of the combination of alogliptin + pioglitazone. The reader is also referred to the statistical review of NDA 022271/0 dated 9/2/2008. Study PI-001 evaluated Alo/Pio as an add-on to maximized metformin therapy, and Study PI-002 evaluated Alo/Pio as an adjunct to diet and exercise. All studies were randomized, double-blind studies of 26 weeks duration. The primary efficacy endpoint was the change from baseline in HbA1c at week 26.

Study PI-001: Study PI-001 was conducted in 1168 randomized patients who were inadequately controlled on a regimen of metformin alone, of whom 15.2% were studied at sites in the U.S. Patients were men or women, 18 to 80 years of age, with an historical diagnosis of T2DM who had received a stable dose of metformin monotherapy for at least 2 months prior to screening. Patients with an HbA1c between 7.5% and 10.0% at the end of the screening period entered a 4-week stabilization period. At the conclusion of the stabilization period, eligible patients were equally randomized to 1 of 12 double-blind treatment groups and were instructed to take once daily combinations over 26 weeks of treatment. Treatment groups were the following:

1. Placebo n=129	5. A12.5 alone n=128	9. A25 alone n=129
2. P15 alone n=130	6. A12.5/P15 n=130	10. A25/P15 n=130
3. P30 alone n=129	7. A12.5/P30 n=130	11. A25/P30 n=130
4. P45 alone n=120	8. A12.5/P45 n=130	12. A25/P45 n=130

Randomization was stratified by two factors: (1) HbA1c at week -1 (HbA1c < 9.0 vs. ≥ 9.0; and (2) geographic region (Mexico and Central/South America, Western Europe, Australia and New Zealand, USA, and Rest of World). A 26-week treatment period was followed by an end of treatment visit (or early termination visit), and a 2-week follow-up period. The study period was from May 31, 2006 to March 17, 2008.

Study PI-002: Study PI-002 was conducted in 655 randomized patients, of whom 33.3% were studied at sites in the U.S. Patients were men or women with a diagnosis of T2DM, 18 to 80 years of age, who had failed treatment with diet and exercise for at least 2 months prior to screening and had received less than 7 days of any anti-diabetic therapy within 3 months prior to screening, with HbA1c between 7.5% and 11.0%. A screening period of up to 2 weeks was followed by a 4-week run-in/stabilization period. At the conclusion of the run-in/stabilization period, patients were randomly assigned to one of four treatment groups in a 1:1:1:1 ratio as follows:

1. A25 alone	n=164
2. P30 alone	n=163
3. A12.5/P30	n=164
4. A25/P30	n=164

Randomization was stratified by two factors: (1) HbA1c at week -1 (HbA1c < 9.0 vs. ≥ 9.0; and (2) geographic region (Mexico and Central/South America; Western Europe, Australia and New Zealand; USA; and Rest of World). A 26-week treatment period was followed by an end of treatment visit (or early termination visit), and a 2-week follow-up period. The study period was from November 2, 2006 to February 13, 2008. The biometrics review team reviewed the study protocol as a Special Protocol Assessment and made the recommendation to include the two monotherapy arms in the study (instead of a single placebo arm). The purpose of the recommendation was to enable a comparison of the higher dose arm (A25/P30) to each of its individual components, A25 and P30. This recommendation was communicated to the applicant in a letter dated 6/2/2006, and the applicant agreed to this change in design.

Study 009: Study 009 was conducted in 493 randomized patients, of whom 67.1% were studied at sites in the U.S. Patients were men and women from 18 to 80 years of age, who were currently receiving treatment with a TZD either alone or in combination with metformin or a sulfonylurea (SU), with an HbA1c concentration between 7.0 and 10.0. A screening period of up to 2 weeks was followed by a 4-week run-in/stabilization period. At the conclusion of the run-in/stabilization period, patients were randomly assigned to one of three treatment groups in a 1:2:2 allocation as follows:

Randomized therapy	Background therapy
1. Placebo n=97 2. A12.5 n=197 3. A25 n=199	Pioglitazone (15, 30 or 45 mg once daily) with or without metformin or a sulfonylurea (OADs)

Randomization was stratified by three factors: (1) HbA1c at week -1 (HbA1c < 8.0%, HbA1c ≥ 8.0%; (2) geographic region (Mexico and Central/South America; Western Europe, Australia and New Zealand; USA; Rest of World; and (3) background treatment regimen (pioglitazone alone, pioglitazone plus metformin, or pioglitazone plus a sulfonylurea.) A 26-week treatment period was followed by an end of treatment visit (or early termination visit), and a 2-week follow-up period. The study period was from February 24, 2006 to August 2, 2007.

Study OLE-012: An additional, long-term, open-label extension study, OLE-012, enrolled patients from any of the Phase 3 studies, including the five studies described in NDA 022271/0, and Studies PI-001 and PI-002. Patients who required protocol-defined hyperglycemic rescue from any of the phase 3 studies received alogliptin 25 mg qd, while patients 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

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 1. Individual study reports were submitted for each study.

TABLE 1 Data sources for studies

Document: NDA 022426.0
CDER EDR link: \\CDSESUB1\N022426\
Company: Takeda
Drug: Alogliptin
Received: September 19, 2008

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1. Subject disposition

The pattern of disposition in each study supports the efficacy of the Alo/Pio combination product in comparison with placebo and with each component on its own (TABLE 2). In Study PI-001, the placebo group had the lowest percentage of patients who completed the study and the arms with the Alo/Pio combinations had the highest percentage of completions. In Study PI-002, the Alo alone arm and Pio alone arm had a lower percentage of completions than the Alo/Pio combination arms. In Study 009, the Pio background arm had a lower percentage of completions than the Alo add-on arm. In all three studies, the arm(s) with Alo/Pio combinations had the lowest percentage of patients who met the criteria for hyperglycemic rescue (TABLE 3) than either the Pio alone arms (Studies 001 and 002), the Pio background arm (Study 009) or the placebo arm (in Study 001).

In the statistical review of NDA 022271/0 I discussed the relationship between the primary efficacy endpoint and the criteria used to intervene with additional diabetes medication. I concluded that the estimate of the primary efficacy endpoint based on the Full Analysis Set (Intention-to-Treat) population using HbA1c carried forward from the point of rescue or discontinuation was a reasonable estimate of the net effect of alogliptin. However, I noted that the disproportionate incidence of rescue in patients with higher baseline HbA1c compared to patients with lower baseline HbA1c meant that estimates of change from baseline in HbA1c in subgroups defined by baseline HbA1c are not useful and should not be reported in the label. I do not cover this issue further in this review.

TABLE 2 Patient disposition in each study

Study PI-001 (26 weeks) metformin background therapy	**Placebo**	**Alogliptin alone (A12.5)[1] (A25)**	**Pioglitazone alone (P15) (P30) (P45)**	**Alogliptin + Pioglitazone (A12.5/P15) (A12.5/P30) (A12.5/P45) (A25/P15) (A25/P30) (A25/P45)**	**Total**
Randomized	129	257	388	780	1554
Full Analysis Set	129	257	387	780	1553
Completed	70 (54.3%)[2]	198 (77.0%)	284 (73.2%)	680 (87.2%)	1232 (79.3%)
Rescued[3]	41 (31.8%)	34 (13.2%)	43 (11.1%)	28 (3.6%)	146 (9.4%)
Discontinued	18 (14.0%)	25 (9.7%)	61 (15.7%)	72 (9.2%)	176 (11.3%)
Study PI-002 (26 weeks) no background therapy		**Alogliptin alone (A25)**	**Pioglitazone alone (P30)**	**Alogliptin + Pioglitazone (A12.5/P30) (A25/P30)**	**Total**
Randomized		164	163	328	655
Full Analysis Set		164	163	327	654
Completed		126 (76.8%)	126 (77.3%)	262 (79.9%)	514 (78.5%)
Rescued		8 (11.0%)	10 (6.1%)	10 (3.0%)	38 (5.8%)
Discontinued		20 (12.2%)	27 (16.6%)	56 (17.1%)	103 (15.7%)
Study 009 (26 weeks) background therapy: pioglitazone ± OADs			**Pioglitazone alone (P*[4])**	**Alogliptin + Pioglitazone (A12.5/P*) (A25/P*)**	**Total**
Randomized			97	396	493
Full Analysis Set			97	396	493
Completed			71 (73.2%)	313 (79.0%)	384 (77.9%)
Rescued			12 (12.4%)	37 (9.3%)	49 (9.9%)
Discontinued			14 (14.4%)	46 (11.6%)	60 (12.2%)

Notes:

[1] Dose arms are combined as shown in parentheses

[2] Percentages are calculated from the randomized patients

[3] Patient meets the hyperglycemic rescue criteria defined for the study. 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.

[4] Study 009 was an add-on study with pioglitazone as background therapy. Doses were 15 mg, 30 mg and 45 mg qd.

Sources: Study PI-001 Clinical Report, Table 15.1.1; Study PI-002 Clinical Report, Table 15.1.1; Study 009 Clinical Report, Table 15.1.1

TABLE 3 Criteria for hyperglycemic rescue

Time Frame	Study PI-001	Study PI-002	Study 009
After 7 days but prior to Week 4 visit	FPG ≥ 300 mg/dL		FPG ≥ 275 mg/dL
From the Week 4 visit but prior to Week 8 visit	FPG ≥ 275 mg/dL	FPG ≥ 310 mg/dL	FPG ≥ 250 mg/dL
From the Week 8 visit, but prior to Week 12 visit	FPG ≥ 250 mg/dL	FPG ≥ 275 mg/dL	FPG ≥ 225 mg/dL
From Week 12 to end of treatment	HbA1c ≥ 8.5 and ≤ 0.5 reduction in HbA1c as compared with the baseline HbA1c	HbA1c ≥ 8.5 and ≤ 0.5 reduction in HbA1c as compared with the baseline HbA1c	HbA1c ≥ 8.5 and ≤ 0.5 reduction in HbA1c as compared with the baseline HbA1c

Note: The criteria refer to the value from a single sample as determined by the central laboratory and confirmed by a second sample drawn within 5 days after the first
Sources: Protocols for Studies PI-001, PI-002 and 009

3.1.2. Patient demographic and baseline characteristics

Certain patient demographic and baseline characteristics were fairly similar across the three studies (TABLE 4). Each study had approximately 50% males and 50% females. The majority of patients were Caucasian, ranging from 71% to 80% among the studies. The average age in each study ranged from 53 to 55 years old among the studies, with the majority of patients younger than 65 years. The average body mass index ranged from 31 to 33 kg/m^2 among the studies.

Differences among studies reflect differences in the target populations with respect to the progression of diabetes. Study PI-002 had the shortest mean duration of diabetes, and was designed to enroll patients who had failed diet and exercise. The other two studies, with longer mean duration of diabetes, enrolled patients who were on other background therapies. The differences between studies in average baseline HbA1c and in the cutpoint used to stratify the randomization for baseline HbA1c also reflected this difference among the target populations.

TABLE 4 Patient demographic and baseline characteristics in the randomized patients in each study

	Study PI-001 metformin background therapy n=1554	Study PI-002 no background therapy n=655	Study 009 pioglitazone ± OAD background therapy n=493
Age (years)			
Mean ± SD	54.4 ± 9.5	52.6 ± 10.9	55.4 ± 10.0
Range	22 to 80	21 to 79	24 to 80
≥ 65 years (n, %)	232 (14.9%)	98 (15.0%)	85 (17.2%)
Sex			
Male (n, %)	697 (44.9%)	320 (48.9%)	287 (58.2%)
Female (n, %)	857 (55.1%)	335 (51.1%)	206 (41.8%)
Race			
Caucasian	1096 (70.5%)	526 (80.3%)	366 (74.2%)
Black	68 (4.4%)	38 (5.8%)	45 (9.1%)
Asian	120 (7.7%)	57 (8.7%)	53 (10.8%)
Native American	5 (0.3%)	1 (0.2%)	3 (0.6%)
Pacific Islander	---	1 (0.2%)	1 (0.2%)
Other	265 (17.1%)	32 (4.9%)	25 (5.1%)
Ethnicity			
Hispanic/Latino	745 (48.0%)	248 (37.9%)	80 (16.2%)
Not Hispanic/Latino	808 (52.0%)	407 (62.1%)	413 (83.8%)
Diabetes duration (yr)			
Mean ± SD	6.2 ± 5.4	3.2 ± 3.7	7.6 ± 5.7
Range	0.3 to 39.0	0.1 to 23.0	0.4 to 37.0
BMI (kg/m^2)			
Mean ± SD	31.2 ± 5.1	31.1 ± 5.4	32.8 ± 5.7
Range	21.6 to 44.9	22.6 to 53.0	23.0 to 45.3
HbA1c at baseline			
Mean ± SD	8.5 ± 0.7	8.8 ± 1.0	8.0 ± 0.9
Range	6.7 to 10.9	6.6 to 11.6	6.6 to 12.7
< 8.0%[1]			252 (51.1%)
≥ 8.0%			241 (48.9%)
< 9.0%	1107 (71.3%)	366 (56.0%)	
≥ 9.0%	446 (28.7%)	288 (44.0%)	

Notes:

[1] Baseline HbA1c: 9.0% was used to stratify randomization in Studies PI-001 and PI-002 and 8.0% was used to stratify randomization in Study 009.

Sources: Table 10.c in the clinical report of each study, and additional analysis by this reviewer

3.1.3. Analysis populations

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

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

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

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

3.1.4. Primary efficacy variable

The primary efficacy variable in all three 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

At the development stage of the two combination studies, the biometrics review team recommended features of the analysis that emphasized the comparison of the alogliptin + pioglitazone combination product to each component on its own (i.e., to alogliptin alone and to pioglitazone alone). In my opinion, this approach accurately reflects the regulatory requirements for evaluating a combination product[3]. The applicant followed this recommendation in part. Exceptions are noted for Study PI-001. The applicant did provide sufficient information to enable me to conduct the analysis recommended by the biometrics review team.

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

Study PI-001: The primary analysis model included study treatment and geographic region as class effects, and baseline HbA1c and baseline metformin dose as continuous covariates. To evaluate the Alo/Pio combination, the applicant used a sequence of two comparisons. First, a linear combination of the three Alo/Pio arms with the 25 mg dose of alogliptin, A25/P45, A25/P30 and A25/P15, were compared to the linear combination of the three arms P45, P30 and P15. The linear combination was constructed from the least squares means of the primary analysis of covariance model. A statistically significant result at the α=0.05 level would lead, by the gate-keeping strategy, to a similar evaluation of the 12.5 mg dose of alogliptin.

At the development stage, the biometrics review team disagreed with this approach for two reasons; (1) the proposed approach did not include a comparison to the alogliptin only arms; and (2) the proposed approach involved a combination of results across study arms. Instead, they recommended an evaluation consisting of pairwise comparisons of study arms. For example, the A25/P45 arm would be compared to the A25 arm and to the P45 arm in two pairwise comparisons. This approach can be envisioned as a sequence twelve comparisons, structured as six sets of two pair-wise comparisons. Each set consists of one of the alogliptin + pioglitazone arms compared to the alogliptin arm at the pertinent dose and compared to the pioglitazone arm at the pertinent dose.

These methods were discussed in a meeting with Takeda on 2/8/2006. The position of the biometrics review team is included in the minutes of this meeting, and is quoted below in the response to Question 3. Question 3 was sent in by the applicant as part of the meeting briefing documents, and the response was included in the meeting minutes, sent on 2/22/2006:

> Question 3: *Does the Agency agree that the methodology proposed for the primary and supportive analyses would be sufficient to support the registration of the fixed-dose combination product?*
>
> FDA Response: The Agency stated that the secondary (individual cell) comparisons on the primary endpoint should be considered primary and may be conducted at nominal significance levels. The sponsor expressed concern that in contrast to the proposed primary analysis comparing SYR-322 and pioglitazone combination therapy, and pioglitazone monotherapy (pooled across pioglitazone doses), the cell-to-cell comparisons may fail due to a lack of statistical power. FDA acknowledged that according to the sample size calculations, individual cells were powered at 90% to detect a treatment difference of 0.47% which the sponsor confirmed. Takeda commented that overall power (all comparisons being significant) was much lower than 90% due to the large number of comparisons and the fairly small treatment effect (0.3%) expected for some comparisons. FDA responded that both statistical and clinical judgment are essential with respect to assessing the efficacy of different dose combinations. For example, if all the comparisons were significant except for one comparison at p = .06, FDA would be comfortable with declaring efficacy particularly if the borderline p-value was not associated with the lowest doses.

- FDA agreed that dose surface response methods (to better understand the response at different dose combinations) would be an adequate supportive analysis.
- Takeda requested a commitment that a statistical "trend" for comparisons of individual cells would constitute confirmation of efficacy. The Agency did not commit to this.
- The sponsor was asked to submit a complete protocol for FDA review and comment that reflected the meeting discussion.
- In summary, FDA did not disagree with the primary analysis but considers the secondary (cell-to-cell) analyses the most important part of the statistical review. These results will be carefully evaluated when assessing efficacy.

Post-meeting comment: The sponsor's proposed analyses address the efficacy of SYR-322 only as add-on therapy to pioglitazone. The analyses do not address the fixed combination aspect of therapy in which the combination must be superior to each monotherapy arm. This point was not explicitly verbalized at the meeting, but it should be emphasized. Although pioglitazone has demonstrated efficacy in previous clinical trials, the efficacy of pioglitazone when used in a fixed combination with SYR-322 must be evaluated relative to SYR-322 monotherapy under the particular circumstances of this clinical trial.

In my opinion, both approaches have advantages and disadvantages. For the applicant's approach to be fully interpretable as an estimate of the contribution of the alogliptin 25 mg component to the combination product, we need to assume that the contribution of alogliptin 25 mg is not influenced by the dose of piogligazone with which it is combined, through the dose range of 15 through 45 mg of pioglitazone. A similar assumption is necessary to interpret the contribution of alogliptin 12.5 mg to the combination product. The approach used by the biometrics team has the advantage of being able to identify potential differences in the contribution of alogliptin at different levels of pioglitazone, but it also has the disadvantage of having less statistical power to do so, because each pairwise comparison is based on two arms, whereas the applicant's approach involves a linear combination of six arms. The advice from the biometrics review team at the protocol stage reflects these considerations.

The applicant maintained the originally proposed analysis plan for the primary analysis, and also provided the pairwise comparisons that would support the approach from the biometrics review team.

I developed a post-hoc approach to conducting the 12 pair-wise comparisons that were needed to evaluate each of the six Alo/Pio combinations. I chose an approach that I believed would reflect the spirit of the gate-keeping approach used by the applicant, the focus on pairwise comparisons of each Alo/Pio combination recommended by the biometrics review team, and the post-hoc nature of the evaluation. I developed the approach prior to looking at the study results. The approach was as follows:

- First, evaluate the A25/P45, A25/P30 and A25/P15 combinations by pairwise comparisons against their respective monotherapy components. Evaluate each comparison with $\alpha=0.05/3=0.0167$.

- If both pairwise comparisons for a combination are statistically significant, then conclude that both the alogliptin and pioglitazone components make a significant contribution to the efficacy of the combination.

- If all three combinations at the 25 mg dose of alogliptin are statistically significant, then conclude overall that alogliptin 25 mg in combination with pioglitazone 15, 30 or 45 mg make a significant contribution to the efficacy of the combination. Continue by evaluating the three combinations at the 12.5 dose of alogliptin in the same way.

I used a Bonferroni correction as a conservative approach to my post-hoc evaluation, considering that although I did not look at these study results prior to developing the approach, I was likely to have been influenced by reviewing the INDs and NDAs associated with alogliptin. The Bonferroni correction that I selected represents my view that in this post-hoc evaluation, the set of three Alo/Pio combinations at each alogliptin dose level represents a family of comparisons. Within each Alo/Pio combination, the stipulation that both pairwise comparisons need to be statistically significant reflects the regulatory requirement that both components should contribute to the effectiveness of the combination product. The gate-keeping step between the three combinations at the 25 mg level of alogliptin and the three combinations at the 12.5 mg level reflects the applicant's gate-keeping approach of evaluating the lower dose of alogliptin conditional on the statistical significance of the higher dose.

Study PI-002: The applicant evaluated the A25/P30 combination by comparing it to the A25 and P30 components. Contingent on the statistical significance of these comparisons, the A12.5/P30 arm was compared to the P30 arm (there was no A12.5 arm in the study). The biometrics review team concurred with this approach.

The primary efficacy analysis was conducted using the FAS and an analysis of covariance (ANCOVA) model with change from Baseline in HbA1c at Week 26 (using LOCF) as the response variable. The primary model included study treatment (3 levels) and geographic region (4 levels) as class effects, and baseline HbA1c as a continuous covariate. The primary analysis was a comparison of the average change from baseline in HbA1c at Week 26 for the A25/P30 arm to the average changes for the P30 arm and the A25 arm at the 2-sided 0.05 significance level using contrasts derived from the primary analysis model. If both of these comparisons were statistically significant, then the average change from baseline in HbA1c at Week 26 for the A12.5/P30 arm was compared to the average change for the P30 arm at the 0.05 significance level in a step-down manner using a separate contrast derived from the same model. Using this step-down strategy, no significance level adjustment was made for the multiple comparisons.

Study 009 Add-on to Pio (with TZD, SU and metformin as background therapies): The applicant evaluated alogliptin as an add-on to pioglitazone (along with other background therapies). The biometrics review team concurred with this approach. 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. 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.

3.1.6. Results of the statistical analysis of efficacy

HbA1c at week 26 – baseline: The combination of alogliptin and pioglitazone, in the dosage combinations studied in Studies PI-001 and PI-002, had a statistically significantly greater effect on the average reduction in HbA1c at week 26 compared to either alogliptin alone or pioglitazone alone (TABLE 5 and TABLE 6). The contribution of alogliptin in the combination product was an additional average reduction of HbA1c of approximately 0.5 percent units compared to pioglitazone alone (TABLE 5 and TABLE 6). The contribution of alogliptin 25 mg was fairly similar to the contribution of alogliptin 12.5 mg in the combination product. The contribution of pioglitazone in the combination product was an additional average reduction of HbA1c that ranged from 0.4 to 0.9, compared to alogliptin alone. The range in contributions did not appear to be related to pioglitazone dose or to alogliptin dose. Studies PI-001 and PI-002 were not powered or intended to quantify the differences between doses of the same drug or between the two drug components.

The add-on effect of alogliptin, with pioglitazone as background therapy, was an average reduction of 0.5 for the alogliptin 12.5 mg dose and 0.6 for the alogliptin 25 mg dose, at week 26 (Study 009; TABLE 7). These results are similar to the effect of alogliptin in combination with pioglitazone in Studies PI-001 and PI-002.

The effect of alogliptin on the average reduction of HbA1c, estimated from Studies PI-001, PI-001 and 009 is similar to the effect estimated from the four other Phase 3 studies, reviewed under NDA 022271/0, which evaluated alogliptin 12.5 mg and 25 mg against placebo, either as a monotherapy, or as an add-on therapy to sulfonylurea, metformin or insulin.

3.1.7. Other Efficacy Endpoints

Fasting plasma glucose (FPG): Results from FPG supported the efficacy of the alogliptin + pioglitazone combination in the range of doses used in Studies PI-001, PI-002 and 009. Both alogliptin and pioglitazone contributed to the reduction in FPG at week 26 compared to baseline in the two combination studies (TABLE 5, TABLE 6). In Study 009, both alogliptin dose arms had a greater average reduction in FPG at week 26 than the arm with pioglitazone background therapy (TABLE 7). In the two combination studies, the contribution of pioglitazone 30 mg and 45 mg to the average reduction in FPG was greater than the contribution of alogliptin 12.5 mg or 25 mg. However, I note that Studies PI-001 and PI-002 were not powered or intended to quantify differences between the two drug components.

Body weight: In the combination studies, the alogliptin component was not associated with a statistically significant average change in body weight at week 26 compared to baseline (TABLE 11 and TABLE 12; "statistical significance" refers to the nominal p-value of each comparison). In contrast, the pioglitazone component was associated with a statistically significant average weight gain at week 26, ranging from 1.3 kg to 3.4 kg between the two studies and across the dose arms. The average weight gain with the 30 mg dose of pioglitazone was similar to the average weight gain with the 45 mg dose, and was somewhat greater than the average weight gain with the 15 mg dose.

In the add-on study, the alogliptin component was not associated with a statistically significant change in body weight at week 26 (TABLE 13). These findings are consistent with the results from the other Phase 3 studies of alogliptin reviewed in NDA 022271/0. The large majority of patients in each of these Phase 3 studies, 84% to 94%, stayed within ± 5% of their baseline body weight at week 26.

TABLE 5 Study PI-001: Statistical results for primary HbA1c endpoint at week 26 (primary efficacy FAS population with LOCF)

Metformin baseline therapy			N		Baseline mean ± SD		Adjusted mean change from baseline at Week 26 endpoint ± SE		Difference in adjusted mean change, Trt 1 – Trt 2	
Trt 1	**vs.**	**Trt 2**	**Trt 1**	**Trt 2**	**Trt 1**	**Trt 2**	**Trt 1**	**Trt 2**	**LS Mean (95% CI)**	**P-value**
1. Applicant's method[1]										
A25[P25|P30|P15]	vs.	[P25|P30|P15]	390	387	8.5 ± 0.7	8.5 ± 0.7	-1.42 ± 0.05	-0.89 ± 0.05	-0.53 (-0.66 to -0.41)	<0.001
Decision: A25/Pio combination is superior to Pio comparator. Next, evaluate the A12.5 combination.										
A12.5[P12.5|P30|P15]	vs.	[P25|P30|P15]	390	387	8.5 ± 0.7	8.5 ± 0.7	-1.43 ± 0.05	-0.89 ± 0.05	-0.54 (-0.67 to -0.41)	<0.001
Decision: A12.5/Pio combination is superior to Pio comparator.										
2. This reviewer's method[2]										
A25/P45	vs.	P45	126	126	8.6 ± 0.7	8.5 ± 0.7	-1.60 ± 0.08	-1.00 ± 0.08	-0.61 (-0.83 to -0.39)	<0.001
	vs.	A25	126	123	8.6 ± 0.7	8.6 ± 0.7	-1.60 ± 0.08	-0.90 ± 0.08	-0.70 (-0.92 to -0.48)	<0.001
Decision: A25/P45 combination is superior to A25 and P45 components separately.										
A25/P30	vs.	P30	124	123	8.5 ± 0.7	8.5 ± 0.7	-1.39 ± 0.08	-0.92 ± 0.08	-0.47 (-0.79 to -0.25)	<0.001
	vs.	A25	124	123	8.5 ± 0.7	8.6 ± 0.7	-1.39 ± 0.08	-0.90 ± 0.08	-0.49 (-0.71 to -0.27)	<0.001
Decision: A25/P30 combination is superior to A25 and P30 components separately.										
A25/P15	vs.	P15	127	127	8.5 ± 0.7	8.5 ± 0.7	-1.27 ± 0.08	-0.80 ± 0.08	-0.52 (-0.74 to -0.30)	<0.001
	vs.	A25	127	123	8.5 ± 0.7	8.6 ± 0.7	-1.27 ± 0.08	-0.90 ± 0.08	-0.37 (-0.59 to -0.15)	0.001
Decision: A25/P15 combination is superior to A25 and P15 components separately. Next, evaluate the A12.5 combinations										
A12.5/P45	vs.	P45	127	126	8.6 ± 0.7	8.5 ± 0.7	-1.55 ± 0.08	-1.00 ± 0.08	-0.55 (-0.77 to -0.33)	<0.001
	vs.	A12.5	127	122	8.6 ± 0.7	8.6 ± 0.7	-1.55 ± 0.08	-0.64 ± 0.08	-0.91 (-1.13 to -0.68)	<0.001
Decision: A12.5/P45 combination is superior to A12.5 and P45 components separately.										
A12.5/P30	vs.	P30	128	123	8.5 ± 0.7	8.5 ± 0.7	-1.39 ± 0.08	-0.92 ± 0.08	-0.47 (-0.70 to -0.25)	<0.001
	vs.	A12.5	128	122	8.5 ± 0.7	8.6 ± 0.7	-1.39 ± 0.08	-0.64 ± 0.08	-0.76 (-0.98 to -0.53)	<0.001
Decision: A12.5/P30 combination is superior to A12.5 and P30 components separately.										
A12.5/P15	vs.	P15	130	127	8.5 ± 0.7	8.5 ± 0.7	-1.34 ± 0.08	-0.75 ± 0.08	-0.59 (-0.81 to -0.38)	<0.001
	vs.	A12.5	130	122	8.5 ± 0.7	8.6 ± 0.7	-1.34 ± 0.08	-0.64 ± 0.08	-0.70 (-0.93 to -0.48)	<0.001
Decision: A12.5/P15 combination is superior to A12.5 and P15 components separately.										

Notes:

[1] Applicant's method: Evaluate the linear combination of (A25/P45, A25/P30 and A25/P15) to the linear combination of (P45, P30, and P15) at α=0.05. If this contrast is significant, evaluate a similar linear combination constructed for A12.5, also at α=0.05.

[2] This reviewer's method: Evaluate A25/P45 against the components A25 and P45, using α=0.05/3 = 0.0167. Do the same for A25/P30 and A25/P15. If these evaluations are all significant, continue the evaluation with A12.5/P45, A12.5/P30 and A12.5/P15, also at α=0.05/3 = 0.0167.

Sources: Study PI-001 clinical report, Table 11.a and Table 11.b

TABLE 6 Study PI-002: Statistical results for primary HbA1c endpoint at week 26 (primary efficacy FAS population with LOCF)

No background therapy			N		Baseline mean ± SD		Adjusted mean change from baseline at Week 26 endpoint ± SE		Difference in adjusted mean change, Trt 1 – Trt 2	
Trt 1	**vs.**	**Trt 2**	**Trt 1**	**Trt 2**	**Trt 1**	**Trt 2**	**Trt 1**	**Trt 2**	**LS Mean (95% CI)**	**P-value**
Applicant's method[1]										
A25/P30	vs.	P30	164	163	8.8 ± 1.0	8.8 ± 1.0	-1.71 ± 0.08	-1.15 ± 0.08	-0.56 (-0.78 to -0.33)	<0.001
	vs.	A25	164	164	8.8 ± 1.0	8.8 ± 1.0	-1.71 ± 0.08	-0.96 ± 0.08	-0.75 (-0.98 to -0.53)	<0.001
			Decision: A25/P30 combination is superior to A25 and P30 components separately. Next, evaluate A12.5/P30.							
A12.5/P30	vs.	P30	163	163	8.9 ± 1.0	8.8 ± 1.0	-1.56 ± 0.08	-1.15 ± 0.08	-0.40 (-0.63 to -0.18)	<0.001
			Decision: A12.5/P30 combination is superior to the P30 component.							

Note:
[1] Evaluate A25/P30 against the components A25 and P30, using α=0.05. If both of these evaluations are both significant, then evaluate A12.5/P30 against the P30 arm, using α=0.05.
Source: Study PI-002 clinical report, Table 11.a

TABLE 7 Study 009: Statistical results for primary HbA1c endpoint at week 26 (primary efficacy FAS population with LOCF)

Pio ± OADs background therapy			N		Baseline mean ± SD		Adjusted mean change from baseline at Week 26 endpoint ± SE		Difference in adjusted mean change, Trt 1 – Trt 2	
Trt 1	**vs.**	**Trt 2**	**Trt 1**	**Trt 2**	**Trt 1**	**Trt 2**	**Trt 1**	**Trt 2**	**LS Mean (95% CI)**	**P-value**
Applicant's method[1]										
A25	vs.	placebo	195	95	8.0 ± 8.0	8.0 ± 8.0	-0.80 ± 0.06	-0.19 ± 0.08	-0.61 (-0.80 to -0.41)	<0.001
			Decision: A25 is superior to placebo (with Pio background therapy). Next, evaluate A12.5.							
A12.5	vs.	placebo	196	95	8.1 ± 8.1	8.0 ± 8.0	-0.66 ± 0.06	-0.19 ± 0.08	-0.47 (-0.67 to -0.28)	<0.001
			Decision: A12.5 is superior to placebo (with Pio background therapy)							

Note:
[1] Evaluate A25 against the placebo, using α=0.05. If this evaluation is significant, then evaluate A12.5 against the placebo, using α=0.05.
Source: Study 009 clinical report, Table 11.a

TABLE 8 Study PI-001: Statistical results for fasting plasma glucose at week 26 (primary efficacy FAS population with LOCF)

Metformin background therapy			N		Baseline mean ± SD		Adjusted mean change from baseline at Week 26 endpoint ± SE		Difference in adjusted mean change, Trt 1 – Trt 2	
Trt 1	vs.	Trt 2	Trt 1	Trt 2	Trt 1	Trt 2	Trt 1	Trt 2	LS Mean (95% CI)	P-value[1]
A25/P45	vs.	P45	127	129	178.1 ± 45.3	180.6 ± 53.6	-52.7 ± 3.5	-32.4 ± 3.5	-20.3 (-30.1 to -10.6)	<0.001
	vs.	A25	127	126	178.1 ± 45.3	184.3 ± 49.2	-52.7 ± 3.5	-18.6 ± 3.5	-34.2 (-44.0 to -24.2)	<0.001
A25/P30	vs.	P30	126	125	178.7 ± 46.4	175.1 ± 43.0	-41.7 ± 3.5	-28.8 ± 3.6	-12.9 (-22.7 to -3.1)	0.010
	vs.	A25	126	126	178.7 ± 46.4	184.3 ± 49.2	-41.7 ± 3.5	-18.6 ± 3.5	-23.2 (-33.0 to -13.4)	<0.001
A25/P15	vs.	P15	130	127	179.2 ± 45.4	176.6 ± 46.6	-38.0 ± 3.5	-23.6 ± 3.5	-14.4 (-24.1 to -4.7)	0.004
	vs.	A25	130	126	179.2 ± 45.4	184.3 ± 49.2	-38.0 ± 3.5	-18.6 ± 3.5	-19.5 (-29.2 to -9.7)	<0.001
A12.5/P45	vs.	P45	128	129	174.3 ± 49.1	180.6 ± 53.6	-51.3 ± 3.5	-32.4 ± 3.5	-18.9 (-28.6 to -9.2)	<0.001
	vs.	A12.5	128	122	174.3 ± 49.1	183.4 ± 49.8	-51.3 ± 3.5	-13.2 ± 3.6	-38.1 (-47.9 to -28.2)	<0.001
A12.5/P30	vs.	P30	129	125	179.6 ± 46.8	175.1 ± 43.0	-42.2 ± 3.5	-28.8 ± 3.6	-13.4 (-23.2 to -3.6)	0.007
	vs.	A12.5	129	122	179.6 ± 46.8	183.4 ± 49.8	-42.2 ± 3.5	-13.2 ± 3.6	-29.1 (-38.9 to -19.2)	<0.001
A12.5/P15	vs.	P15	129	127	184.0 ± 49.2	176.6 ± 46.6	-42.0 ± 3.5	-23.6 ± 3.5	-18.4 (-28.1 to -8.7)	<0.001
	vs.	A12.5	129	129	184.0 ± 49.2	183.4 ± 49.8	-42.0 ± 3.5	-13.2 ± 3.6	-28.8 (-38.7 to -19.0)	<0.001

Notes:
[1] p-values are unadjusted for multiple comparisons
Source: Study PI-001 clinical report, Table 11 f

TABLE 9 Study PI-002: Statistical results for fasting plasma glucose at week 26 (primary efficacy FAS population with LOCF)

No background therapy			N		Baseline mean ± SD		Adjusted mean change from baseline at Week 26 endpoint ± SE		Difference in adjusted mean change, Trt 1 – Trt 2	
Trt 1	vs.	Trt 2	Trt 1	Trt 2	Trt 1	Trt 2	Trt 1	Trt 2	LS Mean (95% CI)	P-value[1]
A25/P30	vs.	P30	162	157	184.5 ± 49.7	189.4 ± 54.3	-50.2 ± 3.3	-37.3 ± 3.3	-12.9 (-22.0 to -3.8)	0.006
	vs.	A25	162	162	184.5 ± 49.7	188.8 ± 51.2	-50.2 ± 3.3	-25.8 ± 3.3	-24.5 (-33.5 to -15.4)	<0.001
A12.5/P30	vs.	P30	162	157	198.7 ± 60.1	189.4 ± 54.3	-48.5 ± 3.3	-37.3 ± 3.3	-11.2 (-20.3 to -2.0)	0.017

Note:
[1] p-values are unadjusted for multiple comparisons
Source: Study PI-002 clinical report, Table 11.d

TABLE 10 Study 009: Statistical results for fasting plasma glucose at week 26 (primary efficacy FAS population with LOCF)

Pio ± OADs background therapy			N		Baseline mean ± SD		Adjusted mean change from baseline at Week 26 endpoint ± SE		Difference in adjusted mean change, Trt 1 – Trt 2	
Trt 1	vs.	Trt 2	Trt 1	Trt 2	Trt 1	Trt 2	Trt 1	Trt 2	LS Mean (95% CI)	P-value[1]
A25	vs.	placebo	197	97	169.5 ± 46.3	171.7 ± 51.2	-19.9 ± 2.7	-5.7 ± 3.8	-14.1 (-23.3 to -5.0)	0.003
A12.5	vs.	placebo	196	97	173.4 ± 46.2	171.7 ± 51.2	-19.7 ± 2.7	-5.7 ± 3.8	-13.9 (-23.1 to -4.8)	0.003

Note:
[1] p-values are unadjusted for multiple comparisons
Source: Study 009 clinical report, Table 11.d

TABLE 11 Study PI-001: Statistical results for body weight at week 26 (primary efficacy FAS population with LOCF)

Metformin background therapy			N		Baseline mean ± SD		Adjusted mean change from baseline at Week 26 endpoint ± SE		Difference in adjusted mean change, Trt 1 – Trt 2	
Trt 1	vs.	Trt 2	Trt 1	Trt 2	Trt 1	Trt 2	Trt 1	Trt 2	LS Mean (95% CI)	P-value[1]
A25/P45	vs.	P45	126	124	82.5 ± 18.4	81.6 ± 16.9	2.3 ± 0.3	1.7 ± 0.3	0.6 (-0.2 to -1.4)	0.141
	vs.	A25	126	123	82.5 ± 18.4	82.9 ± 18.4	2.3 ± 0.3	-0.7 ± 0.3	2.9 (2.1 to 3.7)	<0.001
A25/P30	vs.	P30	123	122	85.6 ± 18.9	85.1 ± 20.4	2.1 ± 0.3	1.9 ± 0.3	0.2 (-0.6 to 1.0)	0.602
	vs.	A25	123	123	85.6 ± 18.9	82.9 ± 18.4	2.1 ± 0.3	-0.7 ± 0.3	2.8 (2.0 to 3.9)	<0.001
A25/P15	vs.	P15	124	122	82.7 ± 16.5	84.4 ± 18.7	1.3 ± 0.3	0.9 ± 0.3	0.3 (-0.5 to 1.1)	0.428
	vs.	A25	124	123	82.7 ± 16.5	82.9 ± 18.4	1.3 ± 0.3	-0.7 ± 0.3	1.9 (1.1 to 2.7)	<0.001
A12.5/P45	vs.	P45	122	124	84.9 ± 19.0	81.6 ± 16.9	2.3 ± 0.3	1.7 ± 0.3	0.7 (-0.2 to 1.5)	0.115
	vs.	A12.5	122	122	84.9 ± 19.0	84.6 ± 19.3	2.3 ± 0.3	0.0 ± 0.3	2.3 (1.5 to 3.1)	<0.001
A12.5/P30	vs.	P30	125	122	83.3 ± 18.2	85.1 ± 20.4	1.9 ± 0.3	1.9 ± 0.3	0.0 (-0.8 to 0.8)	0.980
	vs.	A12.5	125	122	83.3 ± 18.2	84.6 ± 19.3	1.9 ± 0.3	0.0 ± 0.3	1.9 (1.1 to 2.7)	<0.001
A12.5/P15	vs.	P15	127	122	85.6 ± 18.6	84.4 ± 18.7	1.3 ± 0.3	0.9 ± 0.3	0.3 (-0.5 to 1.1)	0.449
	vs.	A12.5	127	122	85.6 ± 18.6	84.6 ± 19.3	1.3 ± 0.3	0.0 ± 0.3	1.3 (0.5 to 2.1)	0.002

Notes:
[1] p-values are unadjusted for multiple comparisons
Sources: Study PI-001 clinical report, Table 15.2.7.1b

TABLE 12 Study PI-002: Statistical results for body weight at week 26 (primary efficacy FAS population with LOCF)

No background therapy			N		Baseline mean ± SD		Adjusted mean change from baseline at Week 26 endpoint ± SE		Difference in adjusted mean change, Trt 1 – Trt 2	
Trt 1	**vs.**	**Trt 2**	**Trt 1**	**Trt 2**	**Trt 1**	**Trt 2**	**Trt 1**	**Trt 2**	**LS Mean (95% CI)**	**P-value[1]**
A25/P30	vs.	P30	155	147	83.2 ± 19.0	84.9 ± 16.4	3.1 ± 0.3	2.2 ± 0.3	1.0 (0.1 to 1.8)	0.025
	vs.	A25	155	159	83.2 ± 19.0	86.1 ± 18.6	3.1 ± 0.3	-0.3 ± 0.3	3.4 (2.6 to 4.2)	<0.001
A12.5/P30	vs.	P30	154	147	83.4 ± 20.3	84.9 ± 16.4	2.5 ± 0.3	2.2 ± 0.3	0.3 (-0.5 to 1.2)	0.448

Note:
[1] p-values are unadjusted for multiple comparisons
Source: Study PI-002 clinical report, Table 11 h

TABLE 13 Study 009: Statistical results for body weight at week 26 (primary efficacy FAS population with LOCF)

Pio ± OADs background therapy			N		Baseline mean ± SD		Adjusted mean change from baseline at Week 26 endpoint ± SE		Difference in adjusted mean change, Trt 1 – Trt 2	
Trt 1	**vs.**	**Trt 2**	**Trt 1**	**Trt 2**	**Trt 1**	**Trt 2**	**Trt 1**	**Trt 2**	**LS Mean (95% CI)**	**P-value[1]**
Applicant's method[1]										
A25	vs.	placebo	189	94	94.8 ± 20.6	95.7 ± 22.3	1.1 ± 0.3	1.0 ± 0.3	0.1 (-0.7 to 0.8)	0.900
A12.5	vs.	placebo	193	94	92.7 ± 20.8	95.7 ± 22.3	1.5 ± 0.2	1.0 ± 0.3	0.4 (-0.4 to 1.2)	0.294

Note:
[1] p-values are unadjusted for multiple comparisons
Source: Study 009 clinical report, Table 15.2.7.1

3.2 Evaluation of Safety

An evaluation of the safety of alogliptin and the alogliptin + pioglitazone combination product is included in the clinical reviews by Dr. Valerie Pratt, under NDA 022271/0 and this NDA. As a contribution to Dr. Pratt's review, I compared the incidence of major adverse cardiovascular events (MACE) and cardiovascular adverse events (CAE) between alogliptin- and comparator-treated patients, in a stratified meta-analysis of eight Phase 2 and Phase 3 studies reported in these two NDAs. This analysis is included in Dr. Pratt's clinical review, under NDA 022271/0. The results, along with results provided by the applicant, illustrated the extent to which the estimates of the upper 95% confidence bound of the risk ratio (alogliptin vs. comparator) were sensitive to choice of method, study population and definition of endpoint. This upper bound is compared to non-inferiority margins of 1.8 and 1.3, as specified in the 2008 guidance, "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes." These margins represent critical decision points regarding the cardiovascular safety of a diabetes therapy.

The evaluation of cardiovascular risk associated with alogliptin is the focus of ongoing review by the Division, and is likely to involve an additional cardiovascular safety study as well as an assessment of additional safety information from studies that were ongoing at the time of this review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Across all three studies, subgroups defined by gender, race, ethnicity and age were fairly similar with respect to the effect of alogliptin in the combination product, or to the effect of alogliptin compared to pioglitazone as background therapy. The applicant evaluated changes from baseline in HbA1c for these subgroups through the use of summary statistics. I did not conduct additional statistical analyses for this review. A more detailed evaluation of the effect of subgroups defined by gender, race and ethnicity is available in the review of alogliptin under NDA 022271/0. In this review, I also concluded that the effect of alogliptin was fairly similar among these subgroups.

4.2 Other Special/Subgroup Populations

Additional subgroups were not evaluated in this review. A more detailed review of the efficacy of alogliptin in subgroups defined by disposition status (rescued or discontinued vs. completed), baseline HbA1c, and baseline BMI is included in the statistics review of alogliptin under NDA 022271/0.

TABLE 14 Study PI-001: Mean change from baseline in HbA1c at week 26 by demographic subgroup (FAS/LOCF)

Subgroup	Pio Alone (N=387)	A12.5 + Pio (N=390)	A25 + Pio (N=390)
Sex			
Male	-0.76 (n=170)	-1.33 (n=171)	-1.39 (n=163)
Female	-0.97 (n=206)	-1.49 (n=214)	-1.46 (n=214)
Age			
<65 years	-0.88 (n=317)	-1.42 (n=327)	-1.44 (n=379)
≥65 years	-0.85 (n=59)	-1.40 (n=58)	-1.37 (n=58)
≥75 years	-1.06 (n=7)	-2.30 (n=2)	-1.45 (n=2)
Race			
American Indian/Alaska native	NE (n=0)	-2.27 (n=3)	-2.10 (n=2)
Asian	-0.69 (n=30)	-1.86 (n=22)	-1.68 (n=28)
Black or African American	-0.88 (n=22)	-1.48 (n=14)	-1.15 (n=10)
Native Hawaiian/Pacific Islander	NE (n=0)	NE (n=0)	NE (n=0)
White	-0.84 (n=258)	-1.29 (n=290)	-1.34 (n=269)
Other	-1.09 (n=66)	-1.86 (n=56)	-1.70 (n=68)
Ethnicity			
Hispanic/Latino	-0.97 (n=189)	-1.60 (n=182)	-1.49 (n=177)
Not Hispanic/Not Latino	-0.78 (n=187)	-1.26 (n=203)	-1.38 (n=200)

Source: Study PI-001 Clinical Report, Table 11.o

TABLE 15 Study PI-002: Mean change from baseline in HbA1c at week 26 by demographic subgroup (FAS/LOCF)

Subgroup	A25 Alone (N=164)	P30 Alone (N=163)	A12.5 + P30 (N=163)	A25 + P30 (N=164)
Sex				
Male	-1.03 (n=74)	-1.08 (n=86)	-1.29 (n=78)	-1.46 (n=68)
Female	-0.89 (n=86)	-1.21 (n=67)	-1.85 (n=80)	-1.89 (n=90)
Age				
<65 years	-0.94 (n=140)	-1.16 (n=134)	-1.57 (n=124)	-1.77 (n=135)
≥65 years	-1.08 (n=20)	-1.03 (n=19)	-1.57 (n=34)	-1.32 (n=23)
≥75 years	-1.00 (n=1)	-1.70 (n=1)	-0.95 (n=2)	-1.55 (n=4)
Race				
American Indian/Alaska native	-0.90 (n=1)	NE (n=0)	NE (n=0)	NE (n=0)
Asian	-0.92 (n=14)	-1.24 (n=15)	-1.95 (n=15)	-1.93 (n=12)
Black or African American	-1.36 (n=8)	-0.90 (n=8)	-1.75 (n=8)	-1.27 (n=11)
Native Hawaiian/Pacific Islander	NE (n=0)	NE (n=0)	-1.10 (n=1)	NE (n=0)
White	-0.94 (n=131)	-1.14 (n=123)	-1.54 (n=128)	-1.70 (n=124)
Other	-0.82 (n=6)	-1.23 (n=7)	-1.07 (n=6)	-1.97 (n=11)
Ethnicity				
Hispanic/Latino	-1.03 (n=60)	-1.27 (n=59)	-1.58 (n=56)	-1.86 (n=59)
Not Hispanic/Not Latino	-0.91 (n=100)	-1.06 (n=94)	-1.57 (n=102)	-1.62 (n=99)

Source: Study PI-001 Clinical Report, Table 11.m

TABLE 16 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 Pioglitazone ± OADs background therapy	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									
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)

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

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In my opinion, the collective evidence from the two Phase 3 combination studies supports the contribution of both alogliptin and piogliptin to the efficacy of the combination product, at the dose levels tested (alogliptin 12.5 mg and 25 mg; pioglitazone 15, 30 and 45 mg). Results for the primary efficacy endpoint, HbA1c at week 26 as a change from baseline, are consistent with results from secondary efficacy endpoints, such as fasting plasma glucose. Results from the combination studies are also consistent with results from five Phase 3 studies, reviewed under NDA 022271/0, which evaluated alogliptin either as a monotherapy, or as an add-on therapy to sulfonylurea, metformin, pioglitazone or insulin.

A statistical issue that occurred in the review of this submission concerned the evaluation of a combination product. At the development stage of the two combination studies, the biometrics review team recommended features of the design and analysis that emphasized the comparison of the alogliptin + pioglitazone combination product to each component on its own (i.e., to alogliptin alone and to pioglitazone alone). The applicant followed these recommendations in part, and designed the studies appropriately to support an evaluation of the combination product. The applicant also provided sufficient summary information for me to follow up with a post-hoc approach that involved a structured set of pairwise comparisons. The two approaches resulted in the same study conclusions, supporting the efficacy of the alogliptin and pioglitazone components of the combination.

5.2 Conclusions

The contribution of alogliptin in the combination product was an additional average reduction of HbA1c of approximately 0.5 percent units compared to pioglitazone alone. The contribution of alogliptin 25 mg was fairly similar to the contribution of alogliptin 12.5 mg in the combination product. The combination studies were not powered or intended to quantify the differences between doses of the same drug or between the two drug components. Results for fasting plasma glucose at week 26 also supported the efficacy of the combination product in comparison to either alogliptin alone or pioglitazone alone, in the range of doses that were evaluated. Subgroups defined by gender, race, ethnicity and age (< 65 and ≥ 65 years) were fairly similar with respect to the effect of alogliptin in the combination product.

In the combination studies, the alogliptin component was not associated with a statistically significant average change in body weight at week 26 compared to baseline. In contrast, the pioglitazone component was associated with a statistically significant average weight gain at week 26, ranging from 1.3 kg to 3.4 kg between the two studies and across the dose arms. The

findings for body weight in this review are consistent with the results from the Phase 3 studies of alogliptin reviewed in NDA 022271/0.

The evaluation of cardiovascular risk associated with alogliptin is the focus of ongoing review by the Division. The evaluation of safety is included in the clinical review by Dr. Valerie Pratt.

5.3 Recommendations for Labeling

Recommendations for labeling are not included in this review. For general recommendations for reporting statistical results in the Clinical Studies of the package insert, see the statistical review of NDA 022271/0.

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 022426/0
DMEP/JMarchick, VPratt, HJoffe, MParks
OB DBII/JDerr, JTSahlroot, TPermutt
OB/RTiwari, ENevius, LPatrician

c:\NDA\NDA 022426_0 statistical review.doc

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22426	ORIG 1		ALOGLIPTIN/PIOGLITAZONE TABLET

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

/s/

JANICE A DERR
07/31/2009

JON T SAHLROOT
08/05/2009

THOMAS J PERMUTT
08/07/2009
concur