CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022426Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MEMO TO FILE

NDA #:	22426
Sponsor:	Takeda
Drug:	(b) (4) (Alogliptin/Pioglitazone FDC tablets)
Submission Date:	July 25, 2011
Memo Date:	January 24, 2012
Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Jayabharathi Vaidyanathan, Ph.D. (Acting)
RE:	Labeling Comments

Labeling Comments

(~~**double strikethrough text**~~ indicates deletion and red text indicates addition.)

All the relevant labeling comments related to alogliptin in Nesina (NDA 22271) and approved labeling of Actos should properly be reflected in (b) (4) labeling. In addition, there are couple editorial comments:

12.3 Pharmacokinetics

Absorption and Bioavailability

Alogliptin/Pioglitazone

In bioequivalence studies of (b) (4) the AUC and maximum concentration (C_{max}) of both the alogliptin and the pioglitazone component following a single dose of the combination tablet (12.5 mg/15 mg or 25 mg/45 mg) were bioequivalent to alogliptin (12.5 mg or 25 mg) concomitantly administered with pioglitazone (15 mg or 45 mg respectively) tablets under fasted conditions in healthy subjects.

Administration of (b) (4) 25 mg/45 mg with food resulted in no significant change in overall exposure of alogliptin or pioglitazone. (b) (4) may therefore be administered with or without food.

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/s/

SANG M CHUNG
01/24/2012

JAYABHARATHI VAIDYANATHAN
01/24/2012

Memo to File: Clinical Pharmacology

NDA #:	22426
Sponsor:	Takeda
Drug:	(b) (4) (Alogliptin/Pioglitazone FDC tablets)
Submission Date:	July 25, 2011
Memo Date:	January 18, 2012
Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Jayabharathi Vaidyanathan, Ph.D. (Acting)
RE:	Re-submission

The submission is to address the issues identified in the Agency's Complete Response Letter dated on September 2, 2009. There were two FDA comments related to the clinical pharmacology perspective in the letter as follows. The sponsor has properly addressed both comments: Comment No. 3 through the alogliptin re-submission (NDA 22271) and Comment No. 4 through the prior discussion with the Agency. The clinical pharmacology review for the original submission by Dr. Jain Ritesh dated June 8, 2009 indicates that there was no review issue at the time except the pending OSI inspection. According to the OSI review dated on July 30, 2009 indicates that the pivotal bioequivalence study was acceptable for agency review.

In conclusion, there is no pending clinical pharmacology review issue and FDA comments related to clinical pharmacology have been properly addressed by the sponsor. The NDA is acceptable from a clinical pharmacology perspective.

FDA Comments related to the clinical pharmacology perspectives:

FDA Comment No. 3

In Study SYR-322-006, entitled "An Open-Label, Parallel-Group Comparison Study of Single-Dose Pharmacokinetics of SYR110322 in Subjects with Mild or Moderate Renal Impairment and Healthy Volunteers," submitted to NDA 22-271, mean exposure to alogliptin, as assessed by the area under the time-concentration curve (AUC), was increased by approximately 70% in patients with mild renal impairment compared to patients with normal renal function. This finding suggests there may be a need to adjust the dosage of alogliptin in patients with mild renal impairment. In your complete response to both NDAs 22-271 and 22-426, you should include analyses of the controlled phase 2/3 program comparing safety and tolerability in patients with normal renal function to those with mild renal impairment. Present the data in two ways; one using the Cockcroft-Gault formula to categorize renal function and another using the Modification of Diet in Renal Disease (MDRD) equation to categorize renal function.

FDA Comment No. 4

In NDA 22-426, greater incidences of elevations in blood urea nitrogen, serum creatinine and urinary albumin/creatinine ratios were observed with the combination alogliptin/pioglitazone treatment group compared to the individual alogliptin and pioglitazone treatment groups. In addition, more subjects in the combination drug treatment group experienced a shift from normal to mild or moderate renal impairment, as calculated by both the Cockcroft-Gault and MDRD formulas, when compared to the individual treatment groups. These observations raise concern in your proposed dosage strengths, which do not include a fixed-dose combination tablet containing alogliptin 6.25 mg, a dosage strength that you have specifically developed under NDA 22-271 for patients with severe renal impairment or end-stage renal disease. It is likely that patients with severe renal impairment will be prescribed the fixed-dose combination of alogliptin and pioglitazone and that patients with type 2 diabetes with mild or moderate renal disease will progress to more severe renal impairment while prescribed this drug product. Consequently, you will need to manufacture dosage strengths that include alogliptin 6.25 mg and conduct any additional clinical trials necessary to support the approval of these lower dosage strength tablets under NDA 22-426.

Takeda Response

For the albumin:creatinine ratio, mean baseline values were much higher than normal range (0-20 μg/mg) for all groupings: the combination, pioglitazone, and alogliptin groupings, respectively, due largely to a few outliers in each of the treatment groups. Median baseline values, therefore, were only slightly higher than normal range for all groupings. Baseline values for urine albumin:creatinine ratio were only available for 65.3%, 64.7%, and 63.9% of subjects in the combination, pioglitazone, and alogliptin groupings, respectively, as a result of several subjects having albumin results too low to be detected by the standard assay method.

Median changes from Baseline, however, were small and similar among groupings. Shifts from normal at Baseline to high at Endpoint were similar across groupings. Because several subjects had albumin results too low to be detected, sample sizes of subjects with both a Baseline and a postbaseline value were rather small. The overall percentages of subjects with an abnormal ratio were generally similar across groupings within each criteria category.

At the Type B meeting held on February 2010, the Agency confirmed the acceptability of not manufacturing the lower dosage strength of alogliptin 6.25 mg in the alogliptin/pioglitazone FDC product due to the low expected commercial use for that strength. The product labeling addresses that the appropriate dosage strengths for severe renally impaired patients or patients with ESRD are not available in the fixed dose combination product.

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/s/

SANG M CHUNG
01/18/2012

JAYABHARATHI VAIDYANATHAN
01/18/2012

ONDQA (Biopharmaceutics) Review

NDA Resubmission: 22-426
Submission Dates: 7/25/11 & Amendment (SDN-042) 12/13/11
Product: [redacted] (alogliptin/pioglitazone) tablets, 12.5/15mg, 12.5/30mg, 12.5/45mg, 25/15mg, 25/30mg and 25/45mg mg
Type of Submission: Amendment to Pending NDA Resubmission
Applicant: Takeda
Reviewer: Tapash K. Ghosh, Ph.D.

SUBMISSION:
Based upon Takeda Global Research & Development's (TGRD) amendment to NDA 22-426 (SDN-031, dated July 27, 2011), and FDA's follow-up emails dated August 9, 2011 and December 7, 2011, via this amendment (SDN-042 dated December 13, 2011) Takeda officially committed to the following:

1. To further evaluate the pioglitazone dissolution specification (using the new 50 rpm/PEAK vessel dissolution method) by collecting product release and stability data for pioglitazone dissolution from SYR-322-4833 tablets at both 15 and 30 minutes for one year after product approval, while maintaining the current specification of Q=[redacted] in 30 minutes (as the interim pioglitazone dissolution specification).

2. In the course of this one year evaluation period post-approval, Takeda will collect release data for multiple commercial lots and stability data at testing intervals up to 24 months.

3. At the end of the one year period, if the additional dissolution data clearly support the pioglitazone dissolution specification change [redacted] Takeda will commit to implementing the revised [redacted] specification of Q=[redacted] in 15 minutes (from Q=[redacted] in 30 minutes). This change will be reported in a supplement to the NDA.

4. However, if the additional data do not support the [redacted] change in the pioglitazone dissolution specification to Q=[redacted] in 15 minutes, Takeda will provide, in a supplement to the NDA, the additional dissolution data and the justification for maintaining the specification at Q=[redacted] at 30 minutes as the final dissolution acceptance criteria for pioglitazone.

RECOMMENDATION:
The Applicant's commitment (described above) is acceptable. From the Biopharmaceutics viewpoint, NDA 22-426 (Resubmission) for alogliptin/pioglitazone fixed-dose combination tablets is recommended for approval.

Tapash K. Ghosh, Ph. D.
Primary Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

TAPASH K GHOSH
12/22/2011

ANGELICA DORANTES
12/22/2011

ONDQA (Biopharmaceutics) Review

NDA:	22-426
Submission Dates:	07/27/2011 (S-031)
Product:	SYR-322-4833 (alogliptin/pioglitazone) tablets, 12.5/15mg, 12.5/30mg, 12.5/45mg, 25/15mg, 25/30mg and 25/45mg mg
Type of Submission:	Amendment to Pending Original NDA
Sponsor:	Takeda
Reviewer:	Tapash K. Ghosh, Ph.D.

Background: SYR-322-4833 Tablets are round, biconvex film-coated tablets produced in six dosage strengths; 12.5mg+15mg, 12.5mg+30mg, 12.5mg+45mg, 25mg+15mg, 25mg+30mg and 25mg+45mg of alogliptin and pioglitazone, respectively.

In response to the amendment to NDA 22-426 for SYR-322-4833 tablets dated May 31, 2011 (S028) that includes information related to a proposed change in drug product dissolution method, FDA's email dated July 14, 2011, requested the sponsor to adopt a Q= (b) (4) at 15 minutes for pioglitazone using the proposed dissolution method with PEAK vessels at 50 rpm. In that e-mail, the Agency advised the sponsor to contact the Agency with supportive data at 15 minutes for pioglitazone if problems arise in adhering to the above specifications.

The purpose of this submission is to respond to the sponsor's response to the Agency's above proposal. The following summarizes the sponsor's responses:

1. Takeda has demonstrated that the pioglitazone specification of Q= (b) (4) in 30 minutes is fully justified and capable of discriminating important product differences/changes. Takeda requests FDA's concurrence.

The Agency's Response: *We do not agree with this proposal because the data presented show that a Q = (b) (4) at 15 minute can be met for pioglitazone.*

2. If the Agency does not concur with point #1 above, Takeda will commit to further evaluate product release and stability data for pioglitazone dissolution from SYR-322-4833 tablets at both 15 and 30 minutes for one year after product approval, while maintaining the current specification of Q= (b) (4) in 30 minutes.

a. In the course of this one year evaluation period post-approval, Takeda would collect release data for multiple commercial lots and stability data at testing intervals up to 24 months.

b. At the end of the one year period, if the additional data clearly support the specification change, Takeda would commit to implementing and reporting the revised (b) (4) specification from Q= (b) (4) in 30 minutes to Q= (b) (4) in 15 minutes in the first Annual Report.

c. However, if the additional data do not support the change in the dissolution specification to Q=(b) (4) in 15 minutes, Takeda would provide, for the Agency's review, the data and the justification for maintaining the specification at Q=(b) (4) at 30 minutes.

The Agency's Response: *The sponsor's 2nd proposal is acceptable.*

Recommendation: The sponsor's revised dissolution method using Apparatus 2 with PEAK vessels at 50 rpm is acceptable. However, based on the dissolution profiles submitted by the sponsor using Apparatus 2 with PEAK vessels at 50 rpm, the Agency recommends the following dissolution condition for SYR-322-4833 Tablets (e.g., for both alogliptin and pioglitazone) with the following dissolution specifications:

Medium: 900 mL of pH 2.2 Sörensen buffer (without deaeration)
Apparatus: 2 with PEAK vessels
Paddle rotation speed: 50 rpm
Alogliptin: Q = (b) (4) *of the labeled amount dissolved in 15 minutes.*
Pioglitazone: Q = (b) (4) *of the labeled amount dissolved in **30** minutes for one year after product approval.*

In essence, Takeda will commit to further evaluate product release and stability data for pioglitazone dissolution from SYR-322-4833 tablets at both 15 and 30 minutes for one year after product approval, while maintaining the current specification of Q=(b) (4) in 30 minutes.

a. In the course of this one year evaluation period post-approval, Takeda would collect release data for multiple commercial lots and stability data at testing intervals up to 24 months.

b. At the end of the one year period, if the additional data clearly support the specification change, Takeda would commit to implementing and reporting the revised (b) (4) specification from Q=(b) (4) in 30 minutes to Q=(b) (4) in 15 minutes in the first Annual Report.

c. However, if the additional data do not support the change in the dissolution specification to Q=(b) (4) in 15 minutes, Takeda would provide, for the Agency's review, the data and the justification for maintaining the specification at Q=(b) (4) at 30 minutes.

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. _____

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/s/

TAPASH K GHOSH
07/28/2011

PATRICK J MARROUM
08/02/2011

ONDQA (Biopharmaceutics) Review

NDA:	22-426
Submission Dates:	05/31/11 (S-028)
Product:	SYR-322-4833 (alogliptin/pioglitazone) tablets, 12.5/15mg, 12.5/30mg, 12.5/45mg, 25/15mg, 25/30mg and 25/45mg mg
Type of Submission:	Amendment to Pending Original NDA
Sponsor:	Takeda
Reviewer:	Tapash K. Ghosh, Ph.D.

Background: SYR-322-4833 Tablets are round, biconvex film-coated tablets produced in six dosage strengths; 12.5mg+15mg, 12.5mg+30mg, 12.5mg+45mg, 25mg+15mg, 25mg+30mg and 25mg+45mg of alogliptin and pioglitazone, respectively. During the review of the original NDA, the sponsor was asked to address to the following comments:

- The sponsor's proposed operating conditions for routine dissolution testing of SYR-322-4833 tablets is not acceptable from "rpm" point of view. The Agency recommended dissolution condition for SYR-322-4833 Tablets (for both alogliptin and pioglitazone) is described below:

Medium: 900 mL of pH 2.2 Sörensen buffer (without deaeration)
Apparatus 2
Paddle rotation speed: 50 rpm

- The sponsor's proposed Q values for Pioglitazone should be changed from Q = (b) (4) to Q = (b) (4) in 30 minutes at the rpm of 50 rpm.

The comments were conveyed to the sponsor via CMC information request letter dated June 9, 2009. In response to that, the sponsor committed, as a Phase IV agreement, to evaluate a paddle speed change in the drug product dissolution method. TGRD agreed that if the additional 50 rpm data confirmed that the method is reliable and compatible with the agreed specifications, the method change would be implemented within 1 year after product approval and reported in the first NDA Annual Report.

(b) (4)

[redacted] Other test method parameters and the Q specifications remain unchanged.

The current amendment to NDA 22-426 for SYR-322-4833 tablets includes information related to a proposed change in drug product dissolution method and has been reviewed.

Recommendation: The sponsor's revised dissolution method using Apparatus 2 with PEAK vessels at 50 rpm is acceptable. However, based on the profiles dissolution profiles submitted by the sponsor using Apparatus 2 with PEAK vessels at 50 rpm, it appears that Pioglitazone can meet Q = [redacted] of the labeled amount also at 15 minutes unless the sponsor can justify otherwise. Therefore, the Agency recommends the following dissolution condition for SYR-322-4833 Tablets (e.g., for both alogliptin and pioglitazone) with the following dissolution specifications:

Medium: 900 mL of pH 2.2 Sörensen buffer (without deaeration)
Apparatus: 2 with PEAK vessels
Paddle rotation speed: 50 rpm
Alogliptin: Q = [redacted] of the labeled amount dissolved in 15 minutes.
*Pioglitazone: Q = [redacted] of the labeled amount dissolved in **15** minutes.*

In essence, the sponsor is requested to adopt a Q = [redacted] at **15** minutes for pioglitazone using the proposed dissolution method with PEAK vessels at 50 rpm. The sponsor is advised to contact the Agency with supportive data at 15 minutes for pioglitazone if problems arise in adhering to the above specifications.

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. _____

DEVELOPMENT OF DISSOLUTION CONDITIONS (PROPOSED PEAK VESSEL / 50 RPM METHOD)

Background and Investigation into Issue with (b) (4) rpm Method

(b) (4)

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Discussion:

Based on the results of the original method development studies, stability studies, and modified method experiments, the sponsor's proposed operating conditions for routine dissolution testing of SYR-322-4833 tablets are shown below.

Medium: 900 mL of pH 2.2 Sörensen buffer (without deaeration) *Apparatu: 2 with PEAK vessels* *Paddle rotation speed: 50 rpm* ***Alogliptin**: Q = (b) (4) of the labeled amount is dissolved in 15 minutes.* ***Pioglitazone**: Q = (b) (4) of the labeled amount is dissolved in **30** minutes.*

The sponsor's revised dissolution method using Apparatus 2 with PEAK vessels at 50 rpm is acceptable. However, based on the profiles (Figure 52), it appears that Pioglitazone can meet Q = (b) (4) of the labeled amount also at 15 minutes unless the sponsor can justify otherwise. Therefore, the Agency recommends the following dissolution condition for SYR-322-4833 Tablets (e.g., for both alogliptin and pioglitazone) with the following dissolution specifications:

Medium: 900 mL of pH 2.2 Sörensen buffer (without deaeration)
Apparatus: 2 with PEAK vessels
Paddle rotation speed: 50 rpm
Alogliptin: Q = (b) (4) of the labeled amount dissolved in 15 minutes.
*Pioglitazone: Q = (b) (4) of the labeled amount dissolved in **15** minutes.*

In essence, the sponsor is requested to adopt a Q = (b) (4) at **15** minutes for pioglitazone using the proposed dissolution method with PEAK vessels at 50 rpm. The sponsor is advised to contact the Agency with supportive data at 15 minutes for pioglitazone if problems arise in adhering to the above specifications.

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TAPASH K GHOSH
07/11/2011

PATRICK J MARROUM
07/11/2011

ONDQA (Biopharmaceutics) Review

NDA:	22-426
Submission Dates:	06/16/09 (S-015); 06/18/09 (S-016); 6/30/09 (S-017)
Product:	SYR-322-4833 (alogliptin/pioglitazone) tablets, 12.5/15mg, 12.5/30mg, 12.5/45mg, 25/15mg, 25/30mg and 25/45mg mg
Type of Submission:	Original NDA Amendment
Sponsor:	Takeda
Reviewer:	Tapash K. Ghosh, Ph.D.

Background: SYR-322-4833 Tablets are round, biconvex film-coated tablets produced in six dosage strengths; 12.5mg+15mg, 12.5mg+30mg, 12.5mg+45mg, 25mg+15mg, 25mg+30mg and 25mg+45mg of alogliptin and pioglitazone, respectively. During review of the original NDA, the sponsor was asked to address to the following comment:

- The sponsor's proposed operating conditions for routine dissolution testing of SYR-322-4833 tablets is not acceptable from "rpm" point of view. The Agency recommended dissolution condition for SYR-322-4833 Tablets (for both alogliptin and pioglitazone) is described below:

Medium: 900 mL of pH 2.2 Sörensen buffer (without deaeration)
Apparatus 2
Paddle rotation speed: 50 rpm

- The sponsor's proposed Q values for Pioglitazone should be changed from Q = (b) (4) to Q = (b) (4) in 30 minutes at the rpm of 50 rpm.

The comments were conveyed to the sponsor via CMC information request letter dated June 9, 2009. In response to that the sponsor submitted Supplements 15, 16 and 17 and they are reviewed here.

Recommendation: The Agency recommends the following dissolution condition for SYR-322-4833 Tablets (e.g., for both alogliptin and pioglitazone) with the following dissolution specifications:

Medium: 900 mL of pH 2.2 Sörensen buffer (without deaeration)
Apparatus 2
Paddle rotation speed: 50 rpm
***Alogliptin**: NLT (b) (4) (Q) of the labeled amount is dissolved in 15 minutes.*
***Pioglitazone**: NLT (b) (4) (Q) of the labeled amount is dissolved in 30 minutes.*

The sponsor is advised to contact the Agency if problems arise in adhering to these specifications.

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. _____

(b) (4)

Overall Conclusion: Upon review of Supplements 15, 16 and 17 to the Original NDA 22426, the Agency still recommends the following dissolution condition for SYR-322-4833 Tablets (e.g., for both alogliptin and pioglitazone) with the following dissolution specifications:

Medium: 900 mL of pH 2.2 Sörensen buffer (without deaeration) *Apparatus 2* *Paddle rotation speed: 50 rpm*

Alogliptin: NLT (b) (4) *(Q) of the labeled amount is dissolved in 15 minutes.*
Pioglitazone: NLT (b) (4) *(Q) of the labeled amount is dissolved in 30 minutes.*

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

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/s/

TAPASH K GHOSH
08/25/2009

PATRICK J MARROUM
08/25/2009

NDA: 22-426	Submission Date(s): 09/19/2008
Brand Name	(b) (4)
Generic Name	Alogliptin/Pioglitazone FDC tablets
Reviewer	Ritesh Jain, Ph.D.
Team Leader (Acting)	Wei Qiu, Ph.D.
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Takeda
Submission Type; Code	Original NDA 505(b)(1); Standard
Formulation; Strength(s)	(b) (4) Tablets (SYR-322-4833); 25 mg alogliptin/15 mg pioglitazone, 25 mg alogliptin/ 30 mg pioglitazone, 25 mg alogliptin/45 mg pioglitazone 12.5 mg alogliptin/15 mg pioglitazone, 12.5 mg alogliptin/30 mg pioglitazone, 12.5 mg alogliptin/45 mg pioglitazone.
Proposed Indication	Fixed Dose Combination product is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes.

List of Figures and Tables:

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the clinical pharmacology data submitted under NDA 22-426, dated 09/19/2008, and finds it acceptable provided 1) the DSI inspection find the Pivotal BE study acceptable.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The purpose of this application (NDA 22-426) is to develop immediate release oral fixed dose combination (FDC) tablets of alogliptin and pioglitazone. Alogliptin is an orally active inhibitor of dipeptidyl peptidase-4 (DPP-4) that is being developed by Takeda as a novel antihyperglycemic agent. An NDA for alogliptin (NDA 22-271) was submitted on 27 December 2007 and is under review by the Agency. Pioglitazone (ACTOS®) is a peroxisome proliferator-activated receptor-gamma (PPARγ) agonist that is a member of the thiazolidinedione (TZD) class of oral antihyperglycemic agents and has been commercially available since 1999.

The FDC product (b) (4) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes (b) (4) will be marketed in six strengths for once daily oral administration. The six dosage strengths of alogliptin (SYR-322)/pioglitazone (AD-4833) are 12.5mg/15mg, 12.5mg/30mg, 12.5mg/45mg, 25mg/15mg, 25mg/30mg, and 25mg/45mg. The drug products are (b) (4) immediate release, round, biconvex film-coated tablets for once daily oral administration to adult's patients with type 2 diabetes mellitus.

The phase 3 program consisted of 2 double-blind randomized clinical studies designed to assess the efficacy and safety of (1) alogliptin 12.5 and 25 mg co-administered with pioglitazone 30 mg QD for the treatment of T2DM as an adjunct to diet and exercise (322OPI-002) and (2) alogliptin 12.5 and 25 mg co-administered with pioglitazone 15, 30, or 45 mg QD for the treatment of T2DM as add-on therapy to metformin (322OPI-001). In addition, a third phase 3 study (322-009 submitted in NDA 22-271), which investigated alogliptin as an add-on to pioglitazone therapy, is used in support of the safety and efficacy evaluation.

In this current NDA application two studies related to clinical pharmacology were submitted. The studies are:

1) A pivotal bioequivalence study with the highest and lowest proposed dosage strengths of FDC tablets (alogliptin 12.5 mg + pioglitazone 15 mg and alogliptin 25 mg + pioglitazone 45 mg).
2) Food-Effect Study with the highest proposed dosage strength of FDC tablet (alogliptin 25 mg + pioglitazone 45 mg).

In the clinical Phase 3 program, sponsor used individual tablets of alogliptin and pioglitazone that were co-administered. Pivotal bioequivalence study was conducted using the (b) (4) formulation to establish the bioequivalence of alogliptin and pioglitazone when dosed as FDC product (SYR-322-4833) and as individual tablets. The highest and lowest dosage strengths of FDC product (25 mg alogliptin/ 45 mg pioglitazone and 12.5 mg alogliptin/15 mg pioglitazone) were used. Biowaiver assessment of the intermediate dosage strengths (25 mg alogliptin/15 mg pioglitazone, 25 mg alogliptin/ 30 mg pioglitazone, 12.5 mg alogliptin/30 mg pioglitazone, 12.5 mg alogliptin/45 mg pioglitazone) is deferred to the Office of New Drug Quality Assessment (ONDQA).

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When dosed as the FDC product in the pivotal BE study, both alogliptin and pioglitazone met the standards for bioequivalence to the individual tablets given concurrently. The bioequivalence of alogliptin and pioglitazone when dosed orally as individual tablets and as the proposed commercial formulation of the FDC product (SYR-322-4833 (b) (4)) were determined in a pivotal, open-label, randomized, 4-sequence, 4-period crossover study in 72 healthy adult (≥18 years of age) subjects (322OPI-101).

Summaries of the pharmacokinetic parameters of alogliptin 12.5 mg and pioglitazone 15 mg following administration as individual tablets and as a combination product are presented in **Table 1**. The 90% CIs for the ratios of the LS means for AUC (0-tlqc), AUC (0-inf), and C_{max} values of both alogliptin and pioglitazone were within the 80% to 125% range. Therefore, the low dose FDC product (12.5 mg/15 mg) tablet met the standards for bioequivalence to the alogliptin 12.5 mg and pioglitazone 15 mg individual tablets.

Table 1: Pharmacokinetic Parameters and Bioequivalence Statistics of Alogliptin 12.5 mg and Pioglitazone 15 mg When Administered as Individual Tablets and as FDC product (SYR-322-4833 (b) (4)).

PK parameters	Geometric Least Squares Mean		Ratio T/R*100 (90% CI)
	SYR-322-4833 (b) (4) (12.5 mg +15 mg) (Test)	Alogliptin 12.5 mg + Pioglitazone 15 mg (Reference)	
Alogliptin (Plasma)			
C_{max} (ng/mL)	48.23	50.28	95.94 (91.83-100.23)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	826.84	824.23	100.32 (99.00-101.65)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	904.72	904.17	100.06 (98.6-101.4)
Pioglitazone (Serum)			
C_{max} (ng/mL)	612.22	626.25	97.76 (91.82-104.08)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	5707.70	5774.19	98.85 (95.42-102.404)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	6399.01	6429.75	99.52 (96.58-102.55)

Summaries of the pharmacokinetic parameters of alogliptin 25 mg and pioglitazone 45 mg following administration as individual tablets and as a FDC product are presented in **Table 2**.

Table 2: Pharmacokinetic Parameters and Bioequivalence Statistics of Alogliptin 25 mg and Pioglitazone 45 mg When Administered as Individual Tablets and as FDC product (SYR-322-4833 (b) (4)).

PK parameters	Geometric Least Squares Mean		Ratio T/R*100 (90% CI)
	SYR-322-4833 (b) (4) (25 mg +45 mg) (Test)	Alogliptin 25 mg + Pioglitazone 45 mg (Reference)	
Alogliptin (Plasma)			
C_{max} (ng/mL)	104.10	106.15	98.07 (93.33-103.06)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	1582.33	1601.99	98.77 (97.58-99.98)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	1694.76	1719.46	98.56 (97.40-99.74)
Pioglitazone (Serum)			
C_{max} (ng/mL)	1276.53	1303.92	97.90 (89.34-107.28)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	14978.78	14369.87	104.24 (98.62-110.18)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	16789.67	15961.30	105.19 (98.19-112.69)

The 90% CIs for the ratios of the LS means for AUC (0-tlqc), AUC (0-inf), and C_{max} values for both alogliptin and pioglitazone were within the 80% to 125% range. Therefore, the SYR-322-4833 (b) (4) (25 mg/45 mg) tablet met the standards for bioequivalence to the alogliptin 25 mg and pioglitazone 45 mg individual tablets.

Food-Effect Study

The effect of high fat meal on the single-dose pharmacokinetics of the proposed FDC product at highest dose strength (SYR-322-4833 (b) (4) 25mg/45 mg) was examined in a randomized, open-label, single-dose, 2-sequence, 2-period crossover study (322OPI-006) in 24 healthy adult (≥18 years of age) subjects. Subjects were randomized to 1 of 2 treatment sequences and received SYR-322-4833 (b) (4) after an overnight fast and immediately after consuming a high-fat meal. All doses were administered orally. Summaries of the pharmacokinetic parameters of alogliptin and pioglitazone following administration in fed and fasted states are presented in **Table 3.**

Table 3: Pharmacokinetic Parameters of Alogliptin and Pioglitazone When Administered as FDC product (SYR-322-4833 (b) (4)) in Fed and Fasted States

PK parameters	Geometric Least Squares Mean		Ratio T/R*100 (90% CI)
	SYR-322-4833 (b) (4) 25 mg +45 mg (Fed) (T)	SYR-322-4833 (b) (4) 25 mg +45 mg (Fasted) (R)	
Alogliptin (Plasma)			
C_{max} (ng/mL)	104.44	94.77	110.21(101.61-119.54)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	1508.08	1484.57	101.58 (99.02-104.21)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	1630.19	1607.20	101.43(99.05-103.87)
T_{max} (hr)	3.00	2.00	
Pioglitazone (Serum)			
C_{max} (ng/mL)	1531.59	1478.31	103.60 (90.49-118.61)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	14493.66	14561.85	99.53 (90.87-109.02)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	15210.31	15696.40	96.90 (87.05-107.87)
T_{max} (hr)	4.00	2.00	

The 90% CIs for the ratios (fed/fasted) of the LS means for AUC (0-24), AUC (0-tlqc), AUC (0-inf), and C_{max} of alogliptin and of pioglitazone were within the 80% to 125% range, indicating no effect of food on total or peak exposures in subjects who received SYR-322-4833 (b) (4) 25 mg/45 mg. Median T_{max} increased by approximately 2 hours when SYR-322-4833 (b) (4) 25 mg/45 mg was administered under fed conditions compared with administration under fasted conditions.

In conclusion, the clinical pharmacology aspects of SYR-322-4833 (b) (4) were appropriately characterized and this NDA 22-426 is acceptable.

2 Question-Based Review (QBR)

2.1 General Attributes of the Drug and Drug Product

SYR-322-4833 (b) (4) is a biconvex film-coated fixed dose combination (FDC) tablet of **alogliptin and pioglitazone**. FDC tablet will be marketed in six strengths for once daily administration. The six fixed dosage strengths of alogliptin (SYR-322) and pioglitazone (AD-4833) are 12.5mg/15mg, 12.5mg/30mg, 12.5mg/45mg, 25mg/15mg, 25mg/30mg, and 25mg/45mg. An NDA for alogliptin (original NDA 22-271) was submitted on 27 December 2007 and is under review by the Agency. Pioglitazone (ACTOS®) is a peroxisome proliferator-activated receptor-gamma (PPARγ) agonist and has been commercially available since 1999 in US.

Individual Drugs:

Alogliptin: Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4) enzyme, and is under review (NDA 22-271) for the treatment of type-2 diabetes. Alogliptin exposure increase was proportional to alogliptin dose increase after multiple dosing (25 mg-400 mg). Mean time to reach C_{max} (T_{max}), clearance (CL/F), volume of distribution (Vd/F), and half-life following 25 mg single dose administration were 1-2 hour, 16.9 L/h, 609.6 L, and 25.6 hour, respectively. Food did not significantly affect the alogliptin exposure. For further details please refer to the original review of NDA 22-271 by Dr. Chung Sang DFS dated 08/28/2008.

Pioglitazone: Pioglitazone (ACTOS®) is a peroxisome proliferator-activated receptor-gamma (PPARγ) agonist that is a member of the thiazolidinedione (TZD) class of oral antihyperglycemic agents and has been commercially available since 1999 in US. Following oral administration, in the fasting state, peak concentrations of pioglitazone were observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption. Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and Biopharmaceutics of the drug?

The purpose of this application (NDA 22-426) is to develop immediate release oral fixed dose combination (FDC) tablets of alogliptin and pioglitazone. Alogliptin is an orally active inhibitor of dipeptidyl peptidase-4 (DPP-4) that is being developed by Takeda as a novel antihyperglycemic agent. An NDA for alogliptin (original NDA 22-271) was submitted on 27 December 2007 and is under review by the Agency. Pioglitazone

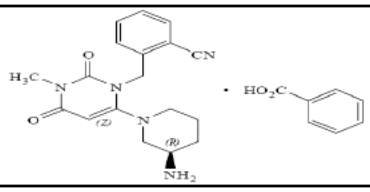
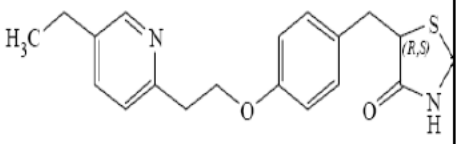
(ACTOS®) is a peroxisome proliferator-activated receptor-gamma (PPARγ) agonist that is a member of the thiazolidinedione (TZD) class of oral antihyperglycemic agents and has been commercially available since 1999.

The FDC product is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes. FDC product will be marketed in six strengths for once daily administration. The six dosage strengths of alogliptin (SYR-322) and pioglitazone (AD-4833) are 12.5mg/15mg, 12.5mg/30mg, 12.5mg/45mg, 25mg/15mg, 25mg/30mg, and 25mg/45mg. The drug products are (b) (4) immediate release, round, biconvex film-coated tablets for once daily oral administration to adult's patients with type 2 diabetes mellitus. Within this application, the nonclinical and clinical pharmacology profiles of the combination product are based largely on the information contained in the previously submitted marketing applications for the individual drug products. In the P-IND meeting dated Feb 08 2006 the sponsor asked the Agency's input on their clinical pharmacology program. The FDA had following recommendations for the proposed fixed dose combination product:

"FDA agreed with TGRD that with the above study, 2-way bioequivalence, crossover studies looking at the highest dose combination (45 mg/25 mg) and the lowest dose combination (15 mg/12.5 mg) would be adequate to establish bioequivalence between the fixed dose combination tablet and its individual components. FDA reaffirmed that establishing bioequivalence on the remaining combination dose strengths can be waived, and a 6-way dose proportionality study would not be necessary, as long as dose proportionality between the 12.5 mg and 25 mg dose strengths of SYR-322 has been established. TGRD agreed to conduct a dose proportionality study with the two dose strengths of SYR-322, if such a study had not been previously performed"

In the current Phase 3 clinical program, sponsor used individual tablets of alogliptin and pioglitazone that were co-administered. Pivotal bioequivalence study was conducted using the (b) (4) formulation to establish the bioequivalence of alogliptin and pioglitazone when dosed as FDC product (SYR-322-4833) and as individual tablets. The highest and lowest dosage strengths of FDC product (25 mg alogliptin/ 45 mg pioglitazone and 12.5 mg alogliptin/15 mg pioglitazone) were used. Biowaiver assessment of the intermediate dosage strengths (25 mg alogliptin/15 mg pioglitazone, 25 mg alogliptin/ 30 mg pioglitazone, 12.5 mg alogliptin/30 mg pioglitazone, 12.5 mg alogliptin/45 mg pioglitazone) is deferred to the Office of New Drug Quality Assessment (ONDQA). Food-Effect Study with the highest proposed dosage strength of FDC tablet (alogliptin 25 mg + pioglitazone 45 mg) was also conducted in this submission.

2.1.2 *What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?*

	Alogliptin	Pioglitazone
Description	White to off-white crystalline powder	Odorless white crystalline powder
Chemical Name	2-({6-[(3*R*)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methyl) benzonitrile monobenzoate	[(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride
Molecular Formula	C18H21N5O2·C7H6O2	C19H20N2O3S·HCl
Molecular Weight	461.51	392.90
Structural Formula		
Solubility	It is soluble in dimethylsulfoxide, sparingly soluble in water and methanol, slightly soluble in ethanol, and very slightly soluble in octanol and isopropyl acetate.	It is soluble in *N,N* dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

Formulation: In addition to the active Ingredients (Alogliptin and Pioglitazone) FDC tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, lactose monohydrate, hypromellose (b) (4), polyethylene glycol (b) (4), titanium dioxide, talc, ferric oxide (yellow and/or red), and printing ink (Red A1 or Gray F1). The composition of the formulations for the different alogliptin/pioglitazone fixed dose combination tablets are shown in the table 4 below:

Table 4: Composition of SYR-322 4833 (b) (4) Tablets

Component	Quantity per Tablet (mg)					
	12.5 mg+15 mg	12.5 mg+30 mg	12.5 mg+45 mg	25 mg+15 mg	25 mg+30 mg	25 mg+45 mg
Alogliptin benzoate (As the free base)	17 (12.5)	17 (12.5)	17 (12.5)	34 (25)	34 (25)	34 (25)
Mannitol	(b) (4)					
Cellulose, microcrystalline						
Hydroxypropylcellulose						
Croscarmellose sodium						
Magnesium stearate						
Pioglitazone hydrochloride (As the free base)	16.53 (15)	33.06 (30)	49.59 (45)	16.53 (15)	33.06 (30)	49.59 (45)
Lactose monohydrate	(b) (4)					
Film-Coating	(b) (4)					
Hypromellose	(b) (4)					
Talc						
Titanium dioxide						
Iron oxide yellow	(b) (4)					
Iron oxide red	(b) (4)					
	(b) (4)					
Printing Ink	(b) (4)					
Printing ink Red A1						
Printing ink Gray F1						
	(b) (4)					

2.1.3 What is the mechanism of action and therapeutic indication?

The FDC tablets (alogliptin/pioglitazone) are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes. The mechanisms of action of individual components are explained below:

Alogliptin: Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4) enzyme. The DPP-4 enzymes are responsible for the breakdown of incretin hormones namely the glucagon-like peptide–1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous hormonal system involved in the physiological regulation of glucose and insulin homeostasis. One of the important

physiologic functions of GLP-1 and GIP is the stimulation of glucose-dependent insulin secretion from the pancreas. GLP-1 also suppresses glucagon secretion from pancreatic alpha cells leading to reduced hepatic glucose production.

Pioglitazone: Pioglitazone (ACTOS®) is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. ACTOS® decreases insulin resistance in the periphery and in the liver resulting in increased insulin dependent glucose disposal and decreased hepatic glucose output. Pioglitazone is a potent agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism. Pioglitazone is an approved drug and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

2.1.4 What are the proposed dosage and route of administration?

Sponsor is proposing six different strengths of FDC (Alogliptin/Pioglitazone) tablets for once daily oral administration. The strengths are 25 mg alogliptin/15 mg pioglitazone, 25 mg alogliptin/30 mg pioglitazone, 25 mg alogliptin/45 mg pioglitazone, 12.5 mg alogliptin/15 mg pioglitazone, 12.5 mg alogliptin/30 mg pioglitazone, 12.5 mg alogliptin/45 mg pioglitazone.

2.1.5 Is any DSI (Division of Scientific Investigation) inspection requested for any of the clinical studies?

Yes. DSI inspection is request for the pivotal BE study (Study # 322OPI-101).

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The phase 3 program consisted of 2 double-blind randomized clinical studies designed to assess the efficacy and safety of (1) alogliptin 12.5 and 25 mg co-administered with pioglitazone 30 mg QD for the treatment of T2DM as an adjunct to diet and exercise (322OPI-002) and (2) alogliptin 12.5 and 25 mg co-administered with pioglitazone 15, 30, or 45 mg QD for the treatment of T2DM as add-on therapy to metformin (322OPI-001). In addition, a third phase 3 study (322-009 submitted in NDA 22-271), which investigated alogliptin as an add-on to pioglitazone therapy, is used in support of the safety and efficacy evaluation.

Clinical Pharmacology studies conducted in this application consists of 1) a pilot relative bioavailability study with the (b) (4) formulation (322OPI-007) 2) A pivotal bioequivalence study using the (b) (4) formulation to establish the bioequivalence of alogliptin and pioglitazone when dosed as FDC (SYR-322-4833) and as individual tablets. In this study the highest and lowest dosage strengths of SYR-322-4833 (25 mg/ 45 mg and 12.5 mg/15 mg) were used (322OPI-101). 3) A food effect study using the highest dosage strength (25 mg/45 mg) of FDC tablets (322OPI-006).

2.2.2 What are the basic pharmacokinetic characteristics of Alogliptin and Pioglitazone?

Please refer to section 2.1. For further details refer to NDA 22-271 for alogliptin and NDA 21-073 for pioglitazone.

2.2.3 Are the active moieties in the plasma appropriately identified and measured?

Yes. Please refer to the section 2.6 for details of the bioanalytical method.

2.2.4 Exposure Response

2.2.4.1 What are the characteristics of the dose-response relationships for efficacy?

Please refer to Dr. Chung Sang review for the exposure-response, dose-response relationship for alogliptin. Also refer to NDA 21-073 for pioglitazone dose-response, exposure-response relationship. In this NDA, the efficacy of the FDC combination product is supported by two pivotal Phase 3 studies in subject with T2DM. Study 322OPI-002 was designed to support the use of FDC product in adults with T2DM as an adjunct to diet and exercise or and study 322OPI-001 as add-on to maximized metformin therapy. In the clinical Phase 3 program, sponsor used individual tablets of alogliptin and pioglitazone that were co-administered.

Study 322OPI-002: Co-administration of individual Alogliptin 25mg + pioglitazone 30mg tablet achieved a significantly ($P<0.001$) greater LS mean decrease from Baseline in HbA1c at Week 26 compared with the alogliptin 25 mg alone and pioglitazone 30 mg alone groups. The alogliptin 12.5mg + pioglitazone 30mg group also exhibited a

significantly (P<0.001) greater LS mean decrease in HbA1c at Week 26 compared with the pioglitazone 30mg alone group. Overall, the alogliptin 25mg + pioglitazone 30mg group achieved a greater LS mean reduction in HbA1c at Week 26 compared with the alogliptin 12.5mg + pioglitazone 30mg (-1.71% vs -1.56%, respectively).

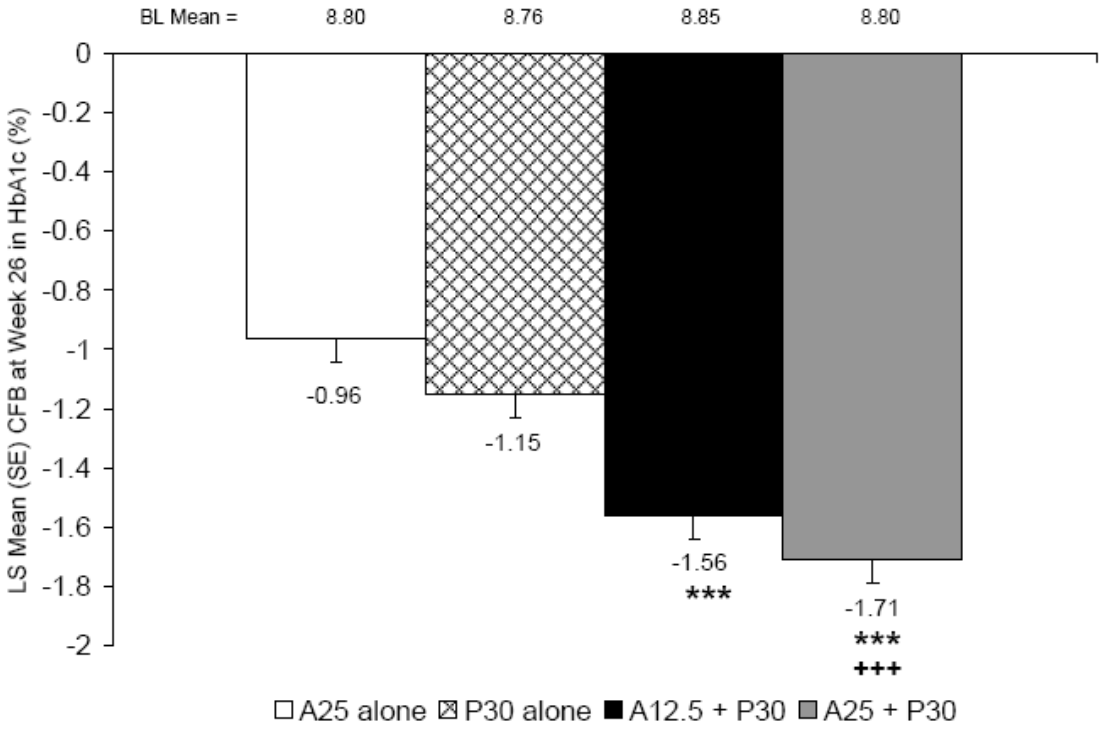


Figure 1: LS Mean Change from baseline in HbA1c (%) at week 26 (Study 322OPI-002)

Study 322OPI-001: In subjects with inadequate glycemic control on maximized metformin therapy, the co-administration of alogliptin12.5 mg + pioglitazone and alogliptin 25 + pioglitazone groupings had significantly greater LS mean reductions in HbA1c compared with the Pioglitazone alone grouping, and all of the individual combination groups achieved significantly greater LS mean reductions in HbA1c when compared to the corresponding doses of alogliptin and pioglitazone given alone. The HbA1c reductions observed at Week 26 between the alogliptin 12.5 mg + pioglitazone grouping and the alogliptin 25 mg + pioglitazone grouping were similar.

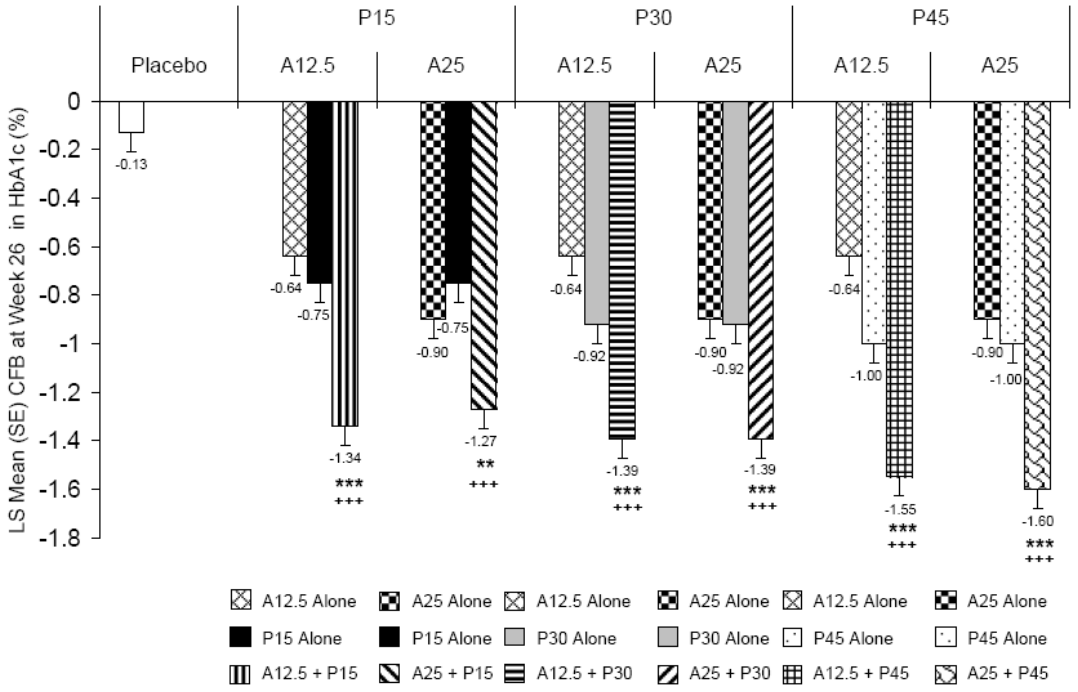


Figure 2: Change from baseline in HbA1c (%) at week 26 (Study 322OPI-001)

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The intrinsic factors were not evaluated in this NDA. The intrinsic factors for the individual components alogliptin and pioglitazone were previously described in the corresponding CP reviews of these submissions.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.4.1.1 Drug-Drug Interaction

No drug interaction between alogliptin and pioglitazone was conducted in this NDA. However in NDA 22-271 a drug interaction study between alogliptin and pioglitazone was conducted and no drug interaction was found between them. For further detail please refer to Clinical Pharmacology Review by Dr. Chung Sang for NDA 22-271.

2.4.1.2 Food effect

The effect of food on the single-dose pharmacokinetics of the proposed commercial formulation of the FDC product (SYR-322-4833 (b) (4)) was examined in a randomized, open-label, single-dose, 2-sequence, 2-period crossover study (322OPI-006) in 24 healthy adult (≥18 years of age) subjects. Summaries of the pharmacokinetic parameters of alogliptin and pioglitazone following administration in fed (high-fat meal) and fasted states are presented in **Table 5.**

Table 5: Pharmacokinetic Parameters of Alogliptin and Pioglitazone When Administered as FDC product (SYR-322-4833 (b) (4)) in Fed and Fasted States

PK parameters	Geometric Least Squares Mean		Ratio T/R*100 (90% CI)
	SYR-322-4833 (b) (4) 25 mg +45 mg (Fed) (T)	SYR-322-4833 (b) (4) 25 mg +45 mg (Fasted) (R)	
Alogliptin (Plasma)			
C_{max} (ng/mL)	104.44	94.77	110.21(101.61-119.54)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	1508.08	1484.57	101.58 (99.02-104.21)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	1630.19	1607.20	101.43(99.05-103.87)
T_{max} (hr)	3.00	2.00	
Pioglitazone (Serum)			
C_{max} (ng/mL)	1531.59	1478.31	103.60 (90.49-118.61)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	14493.66	14561.85	99.53 (90.87-109.02)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	15210.31	15696.40	96.90 (87.05-107.87)
T_{max} (hr)	4.00	2.00	

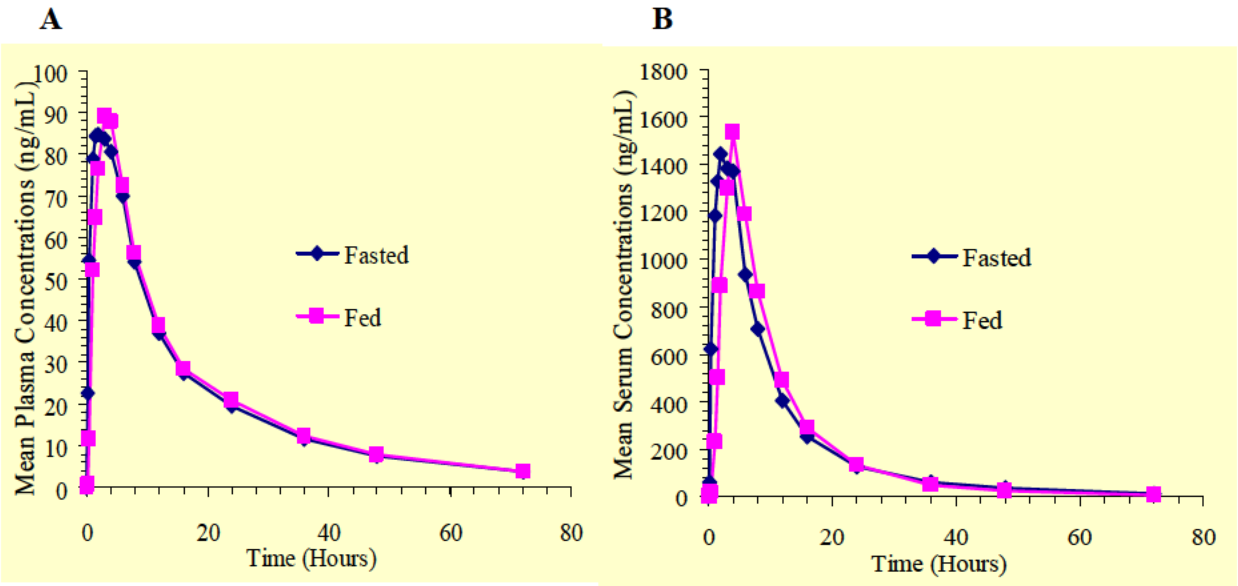


Figure 3: Mean Plasma Concentrations of Alogliptin vs Time (A) and Mean Serum Concentration of Pioglitazone vs Time (B) under Fasted and Fed Conditions: Linear Scale

The 90% CIs for the ratios (fed/fasted) of the LS means for AUC (0-24), AUC (0-tlqc), AUC (0-inf), and C_{max} of alogliptin and of pioglitazone were within the 80% to 125% range, indicating no effect of food on total or peak exposures in subjects who received SYR-322-4833 (b) (4) 25 mg/45 mg. Median T_{max} increased by approximately 2 hours when SYR-322-4833 (b) (4) 25 mg/45 mg was administered under fed conditions compared with administration under fasted conditions.

2.5 General Biopharmaceutics

2.5.1 Is the proposed to-be-marketed fixed dose formulation bioequivalent to the individual alogliptin and pioglitazone formulations?

In the clinical Phase 3 program, sponsor used individual tablets of alogliptin and pioglitazone that were co-administered. Pivotal bioequivalence study was conducted using the (b) (4) formulation to establish the bioequivalence of alogliptin and pioglitazone when dosed as FDC product (SYR-322-4833) and as individual tablets. The highest and lowest dosage strengths of FDC product (25 mg/45 mg and 12.5 mg/15 mg) were used. Biowaiver assessment of the intermediate dosage strengths (25 mg alogliptin/15 mg pioglitazone, 25 mg alogliptin/ 30 mg pioglitazone, 12.5 mg alogliptin/30 mg pioglitazone, 12.5 mg alogliptin/45 mg pioglitazone) is deferred to the Office of New Drug Quality Assessment (ONDQA).

Study 322OPI-101: Summaries of the pharmacokinetic parameters of lowest strengths of alogliptin 12.5 mg and pioglitazone 15 mg following administration as individual tablets and as a combination product are presented in **Table 6**. The 90% CIs for the ratios of the LS means for AUC (0-tlqc), AUC (0-inf), and C_{max} values of both alogliptin and pioglitazone were within the 80% to 125% range. Therefore, the SYR-322-4833 (b) (4) (12.5 mg + 15 mg) tablet met the standards for bioequivalence to the alogliptin 12.5 mg and pioglitazone 15 mg individual tablets No statistically significant differences for the median T_{max} values for either alogliptin or pioglitazone were observed between the SYR-322-4833 (b) (4) (12.5 + 15 mg) tablet and the alogliptin 12.5 mg and pioglitazone 15 mg individual tablets.

Table 6: Pharmacokinetic Parameters and Bioequivalence Statistics of Alogliptin 12.5 mg and Pioglitazone 15 mg When Administered as Individual Tablets and as FDC product (SYR-322-4833 (b) (4)).

PK parameters	Geometric Least Squares Mean		Ratio T/R*100 (90% CI)
	SYR-322-4833 (b) (4) (12.5 mg +15 mg) (Test)	Alogliptin 12.5 mg + Pioglitazone 15 mg (Reference)	
Alogliptin (Plasma)			
C_{max} (ng/mL)	48.23	50.28	95.94 (91.83-100.23)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	826.84	824.23	100.32 (99.00-101.65)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	904.72	904.17	100.06 (98.6-101.4)
¥T_{max}(Hr)	3.00	2.99	
Pioglitazone (Serum)			
C_{max} (ng/mL)	612.22	626.25	97.76 (91.82-104.08)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	5707.70	5774.19	98.85 (95.42-102.404)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	6399.01	6429.75	99.52 (96.58-102.55)
¥T_{max}(Hr)	1.77	1.50	

¥ Tmax is reported as median

Summaries of the pharmacokinetic parameters of highest strength of alogliptin 25 mg and pioglitazone 45 mg following administration as individual tablets and as a combination product are presented in **Table 7**.

Table 7: Pharmacokinetic Parameters and Bioequivalence Statistics of Alogliptin 25 mg and Pioglitazone 45 mg When Administered as Individual Tablets and as FDC product (SYR-322-4833 (b) (4)).

PK parameters	Geometric Least Squares Mean		Ratio T/R*100 (90% CI)
	SYR-322-4833 (b) (4) (25 mg +45 mg) (Test)	Alogliptin 25 mg + Pioglitazone 45 mg (Reference)	
Alogliptin (Plasma)			
C_{max} (ng/mL)	104.10	106.15	98.07 (93.33-103.06)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	1582.33	1601.99	98.77 (97.58-99.98)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	1694.76	1719.46	98.56 (97.40-99.74)
¥T_{max}(Hr)	2.50	2.98	
Pioglitazone (Serum)			
C_{max} (ng/mL)	1276.53	1303.92	97.90 (89.34-107.28)
$AUC_{0\text{-}tlqc}$ (ng.hr/mL)	14978.78	14369.87	104.24 (98.62-110.18)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	16789.67	15961.30	105.19 (98.19-112.69)
¥T_{max}(Hr)	3.00	2.00	

¥ T_{max} is reported as median

The 90% CIs for the ratios of the LS means for AUC (0-tlqc), AUC (0-inf), and C_{max} values for both alogliptin and pioglitazone were within the 80% to 125% range. Therefore, the SYR-322-4833 (b) (4) (25 mg + 45 mg) tablet met the standards for bioequivalence to the alogliptin 25 mg and pioglitazone 45 mg individual tablets. A statistically significant difference between the SYR-322-4833 (b) (4) (25 + 45 mg) tablet and the individual alogliptin 25 mg and pioglitazone 45 mg tablets was observed for the median T_{max} value of pioglitazone ($P<0.001$) but not alogliptin ($P=0.830$). However this change in T_{max} will be not considered clinically significant, since SYR-322-4833 (b) (4) will be administered chronically.

2.6 Analytical

2.6.1 How are the active moieties identified and measured in the plasma/serum?

Concentrations of alogliptin in plasma and urine, and concentrations of pioglitazone in serum were measured using validated high-performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS).

2.6.2 What bioanalytical methods are used to assess concentrations?

Alogliptin concentrations in plasma and pioglitazone concentrations in serum were quantified using HPLC-MS/MS methods (validated under various project codes). Alogliptin plasma samples were extracted using protein precipitation with acetonitrile. Extracted samples were evaporated to dryness and reconstituted and analyzed by HPLC-MS/MS. Validated concentration ranges for alogliptin are 1.00 to 1000 ng/mL in plasma and 5.0 to 5000 ng/mL in urine. Pioglitazone serum samples were extracted using solid phase extraction. Extracted samples were evaporated to dryness and reconstituted and analyzed by HPLC-MS/MS. Validated concentration ranges for pioglitazone are 25.0 to 2500 ng/mL. A brief summary of the different bioanalytical methods used is shown in the **Table 8** below. Accepted validation indicates that method met the FDA guidance "Bioanalytical Method Validation" recommendations, and was therefore acceptable.

Table 8: Assay Validation Results for Alogliptin and Pioglitazone

	Alogliptin	**Pioglitazone**
Standard Curve Range	1.00 ng/mL- 1000 ng/mL	25 ng/mL-2500 ng/mL
QC Sample Concentrations	1, 2.5, 50, 800 ng/mL	74.9, 300, 480, 1000, 2000 ng/mL
Precision (%CV) (Run 3WXN2)	Intra-Day: 2.35% to 6.72 % Inter-Day: 4.53% to 9.26%	Intra-Day: 1.2% to 5.2 % Inter-Day: 5.3% to 7.3%
Accuracy (%)	Intra-Day: 99.6% to 102.5% Inter-Day: 98.2% to 103.1%	Intra-Day: 97.7% to 110.8% Inter-Day: 98.8% to 103.9%
Internal Standard	SYR110322B-d4 Lot No: 031704D	AD-4875 Lot No: A-9218-11-08
Reference Standard	SYR110322S Lot No: 03CDW002	AD-4833 (Pioglitazone) Lot No: HS01
Specificity	No Interference	No Interference
Recovery	~63% (Drug) ~63% (Internal Standard)	~94.4% (Drug) ~103.8 % (Internal Standard)
Stability	Benchtop Stability: 25 hours Freeze/ Thaw Stability: 4 FT Cycle Long Term Matrix Stability: 8 Days at -20°C¥	Benchtop Stability: 72 hours Freeze/ Thaw Stability: 6 FT Cycle Long Term Matrix Stability: 72 Days -20°C ¥

¥***Note: Data presented is based on the original validation report (Alogliptin Validation Report Revision 1 LCMS 307.4 and for Pioglitazone Validation Report 1000-0519-1). Several amendments been made to the original report showing the higher long term stability.***

3 DETAILED LABELING RECOMMENDATION

None

Reviewer's Comment: No labeling reviews were done at this time. Labeling recommendations will be made upon the approval of Alogliptin.

43 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 INDIVIDUAL STUDY REVIEW

4.2.1 Bioequivalence Study SYP-322OPI-101

Title: An Open-Label, Randomized, 4-Period Crossover Study to Determine the Bioequivalence of the Phase 3 SYR-322 Tablets (12.5 and 25 mg) and Pioglitazone (15 and 45 mg) When Administered as Individual Tablets and as Combination Products

Investigator and Study Center(s):
James Kissling, MD
MDS Pharma Services
621 Rose Street
Lincoln, NE 68502

Study Sponsor:
Takeda Global Research & Development Center, Inc.

Bioanalytical Analysis:
(b) (4)

Study Period: 25 August 2007 to 09 October 2007

Objective:

- The primary objective of this study was to determine the bioequivalence of SYR-322 (hereafter referred to as alogliptin) and pioglitazone when administered as individual tablets and as a combination product. Two different dose strengths of the combination product were evaluated: SYR-322-4833 (b) (4) 12.5 mg + pioglitazone 15 mg and SYR-322-4833 (b) (4) 25 mg + pioglitazone 45 mg.

- The secondary objective of this study was to evaluate the safety of alogliptin and pioglitazone when administered as individual tablets and as a combination product.

Study Design:

The current trial was a single-center, open-label, randomized, 4-sequence, 4-period crossover study to determine the bioequivalence of SYR-322-4833 (b) (4) (Fixed Dose Combination Product) and the individual alogliptin and pioglitazone tablets.

Subjects were screened for enrollment within 2 to 28 days before the first dose of study drug in accordance with predefined entrance criteria. Subjects were randomized to 1 of 4 sequences (18 subjects per sequence) during which they received a single oral dose of each treatment as shown below:

Treatment A: SYR-322-4833 (b) (4) (FDC, 12.5 mg alogliptin + 15 mg pioglitazone)
Treatment B: Aloglitpin 12.5 mg + Pioglitazone 15 mg
Treatment C: SYR-322-4833 (b) (4) (FDC, 25 mg alogliptin + 45 mg pioglitazone)
Treatment D: Aloglitpin 25 mg + Pioglitazone 45 mg

Table 1: Trial Design

Pretreatment Period			Treatment Period (a)								
Screening	Check-in		Period 1		Period 2		Period 3		Period 4		
Days -28 to -2	Day -1	Randomization	Day 1 Dosing	Days 2 to 7	Day 1 Dosing	Days 2 to 7	Day 1 Dosing	Days 2 to 7	Day 1 Dosing	Days 2 to 3	Day 4 Final Visit/ET
		Sequence I (n=18)	A	WO	B	WO	C	WO	D	WO	
		Sequence II (n=18)	B		C		D		A		
		Sequence III (n=18)	C		D		A		B		
		Sequence IV (n=18)	D		A		B		C		

A=SYR-322-4833 (b) (4) (12.5 mg + 15 mg) (test treatment), B=alogliptin 12.5 mg + pioglitazone 15 mg (reference treatment), C=SYR-322-4833 (b) (4) (25 mg + 45 mg) (test treatment), D=alogliptin 25 mg + pioglitazone 45 mg (reference treatment), ET=Early Termination, WO=Washout.
(a) Subjects were confined to the clinic from Day -1 of Treatment Period 1 through Day 4 of Treatment Period 1 and from Day 7 of Treatment Periods 1, 2, and 3 through Day 4 of Treatment Periods 2, 3, and 4, respectively.

A washout interval of 7 days (beginning immediately after dosing on Day 1 of each Period) separated the doses of each study period. The subjects stayed in the clinic until after their 72 hour post dose pharmacokinetic sample on Day 4 of each Period. The total duration of the study for a subject who completes all treatments is 26 days, including Check-in (Day -1 of treatment period 1).

Subjects received randomized treatment on Day 1 of each Treatment Period. Subjects fasted overnight for at least 8 hours before each dose of study drug was administered and for 4 hours after each dose. Subjects were allowed to consume water without restriction, except for 1 hour before and after dosing.

Blood samples (3 mL for alogliptin and 5 mL for pioglitazone) for the determination of the concentrations of alogliptin and pioglitazone in plasma and serum, respectively, were collected on Day 1 within 0.25 hours prior to dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours post dose during each treatment period.

Study Population:

Seventy two healthy volunteers were enrolled in this study. **Table 2** below shows the demographics of the enrolled patients.

Table 2: Baseline Demographics of Study Population

Characteristic	Treatment Sequence				Overall N=72
	Sequence I ABCD n=18	Sequence II BCDA n=18	Sequence III CDAB n=18	Sequence IV DABC n=18	
Sex, n (%)					
Male	10 (55.6)	14 (77.8)	11 (61.1)	11 (61.1)	46 (63.9)
Female	8 (44.4)	4 (22.2)	7 (38.9)	7 (38.9)	26 (36.1)
Mean age (SD), yr	32.8 (13.28)	30.3 (10.98)	34.7 (10.56)	34.9 (12.74)	33.2 (11.83)
Race, n (%)					
American Indian or Alaska Native	0	0	1 (5.6)	0	1 (1.4)
Asian	1 (5.6)	0 (0.0)	2 (11.1)	0	3 (4.2)
Black	1 (5.6)	2 (11.1)	4 (22.2)	0	7 (9.7)
White	16 (88.9)	16 (88.9)	11 (61.1)	18 (100.0)	61 (84.7)
Hispanic ethnicity, n (%)	2 (11.1)	3 (16.7)	2 (11.1)	2 (11.1)	9 (12.5)
Mean weight (SD), kg	76.8 (9.14)	73.4 (12.33)	69.7 (12.73)	74.8 (12.58)	73.7 (11.84)
Mean height (SD), cm	175.4 (10.26)	175.9 (7.09)	173.3 (8.29)	172.5 (9.97)	174.3 (8.92)
Mean BMI (SD), kg/m^2	25.0 (2.70)	23.6 (2.82)	23.1 (3.22)	25.1 (3.05)	24.2 (3.02)

Source: Table 15.1.2.2
A=SYR-322-4833 (b) (4) (12.5 mg + 15 mg) (test treatment), B=alogliptin 12.5 mg + pioglitazone 15 mg (reference treatment), C=SYR-322-4833 (b) (4) (25 mg + 45 mg) (test treatment), D=alogliptin 25 mg + pioglitazone 45 mg (reference treatment).

Investigational Product and Dose Selection:

Subjects were assigned randomly to 1 of 4 treatment sequences Each treatment sequence included Treatments A, B, C, and D as shown in Table 3. Study drugs were administered orally with 240 mL of water after an 8-hour fast. Subjects were required to continue fasting for 4 hours after dosing.

Table 3: Treatment Scheme by Treatment Period

Sequence	Treatments	Treatment Period			
		Period 1	Period 2	Period 3	Period 4
I	ABCD	SYR-322-4833 (b) (4) (12.5 mg + 15 mg)	Alogliptin 12.5 mg + pioglitazone 15 mg	SYR-322-4833 (b) (4) (25 mg + 45 mg)	Alogliptin 25 mg + pioglitazone 45 mg
II	BCDA	Alogliptin 12.5 mg + pioglitazone 15 mg	SYR-322-4833 (b) (4) (25 mg + 45 mg)	Alogliptin 25 mg + pioglitazone 45 mg	SYR-322-4833 (b) (4) (12.5 mg + 15 mg)
III	CDAB	SYR-322-4833 (b) (4) (25 mg + 45 mg)	Alogliptin 25 mg + pioglitazone 45 mg	SYR-322-4833 (b) (4) (12.5 mg + 15 mg)	Alogliptin 12.5 mg + pioglitazone 15 mg
IV	DABC	Alogliptin 25 mg + pioglitazone 45 mg	SYR-322-4833 (b) (4) (12.5 mg + 15 mg)	Alogliptin 12.5 mg + pioglitazone 15 mg	SYR-322-4833 (b) (4) (25 mg + 45 mg)

A and C=test treatments, B and D=reference treatments (b) (4)

The investigational products used in this study are listed in **Table 4**.

Table 4: Batch number of product used in this trial

Drug	Lot No.	Expiration/Retest Date
SYR-322-4833 (b) (4) (12.5 mg + 15 mg) tablet	Z644B027	29 Feb 2008
SYR-322-4833 (25 mg + 45 mg) tablet	Z644G027	29 Feb 2008
Alogliptin 12.5 mg phase 3 tablet	6J080	31 Jan 2008
Alogliptin 25 mg phase 3 tablet	6J082	31 Jan 2008
Pioglitazone hydrochloride (ACTOS®) 15 mg commercial tablet	C13008	30 Nov 2009
Pioglitazone hydrochloride (ACTOS) 45 mg commercial tablet	A12951	31 Oct 2009

(b) (4)

SYR-322-4833 (b) (4) was supplied in 75 cc, white, square, high-density polyethylene bottles (b) (4) Each bottle contained 30 tablets. Alogliptin was supplied in 60 cc pharmaceutical round, white, high-density polyethylene bottles (b) (4) Each bottle contained 35 tablets Pioglitazone hydrochloride (ACTOS®) was supplied in the commercial packaging. Each bottle contained 30 tablets. Each bottle of SYR-322-4833 (b) (4) and alogliptin bore a single-panel label with pertinent study information. Each bottle of pioglitazone bore a supplemental label with pertinent information.

Bioanalysis:

Alogliptin: Quantitative assessment of Alogliptin in plasma was done using validated LC/MS/MS method. The lower limit of the quantification of the assay was 1.0 ng/mL. The calibration curves for alogliptin were analysed at concentration range of 1 ng/mL to 250 ng/mL. The precision of the assay, as determined from analysis of quality control (QC) samples ranged between 5.71 and 3.73%. The mean accuracy (% Bias) ranged between -7.28% to –5.48%. Between-batch precision (%CV) results of the calibration standards was less between 2.60 % to 5.52% and accuracy (%Bias) ranged from -1.81 to 1.06 %.

Pioglitazone: Quantitative assessment of Pioglitazone in human serum was done using validated LC/MS/MS method. The lower limit of the quantification of the assay was 25 ng/mL. The calibration curves for alogliptin were analysed at concentration range of 25 ng/mL to 2500 ng/mL. The precision of the assay, as determined from analysis of quality control (QC) samples ranged between 4.5 and 2.7%. The mean accuracy (% Bias) ranged between -2.1% to –5.0%. Between-batch precision (%CV) results of the calibration standards was less between 2.2 % to 2.8% and accuracy (%Bias) ranged from -4.0 to 3.6 %.

Data Analysis:

All data analyses were performed using SAS (Version 9.1, SAS Institute, Cary, NC). Pharmacokinetic parameters were derived using noncompartmental methods with WinNonlin® Professional Version 5.1 (Pharsight Corp., Mountain View, CA).

The following pharmacokinetic parameters were derived from plasma concentration data for alogliptin and serum concentration data for pioglitazone under different treatment conditions:

- AUC (0-24): Area under the plasma/serum concentration-time curve from time 0 to 24 hours.
- AUC (0-tlqc): Area under the plasma/serum concentration-time curve from time 0 to time of last quantifiable concentration (tlqc).
- AUC(0-inf): Area under the plasma/serum concentration-time curve from time 0 to infinity
- C_{max}: Maximum observed plasma/serum concentration.
- T_{max}: Time to reach C_{max}.
- λz : Terminal elimination rate constant.
- $T_{1/2}$: Terminal elimination half-life.
- CL/F: Apparent clearance after oral administration (CL/F)
- Fe Fraction of drug excreted in urine, calculated as Fe=(Ae[0-t]/dose)x100 (alogliptin only).
- CLr Renal clearance, calculated as CLr=Ae(0-t)/AUC(0-t) (alogliptin only)
- Ae(0-24) Total amount of drug excreted in urine from 0 to 24 hours (alogliptin only).

An analysis of variance (ANOVA) with fixed effects for sequence, period, treatment and random effect for subject nested within sequence was performed on the natural logarithms of AUC(0-tlqc), AUC(0-inf), and C_{max} of pioglitazone and alogliptin. The Wilcoxon signed rank test was performed on T_{max}. Within the context of the ANOVA for the natural logarithms of C_{max}, AUC(0-inf), and AUC(0-tlqc), the 90% confidence intervals (CI) for the ratio of the test treatment least squares (LS) mean of pioglitazone/alogliptin combination tablet (Treatment A or C) compared with the reference treatment LS mean of the pioglitazone tablet and alogliptin tablet (Treatment B or D) were provided. The 90% CIs were obtained by taking the antilogarithm of the 90% CI for the difference between the LS means on the natural logarithmic scale. If the 90% CIs for C_{max}, AUC(0-tlqc), and AUC(0-inf) of pioglitazone and alogliptin were within the

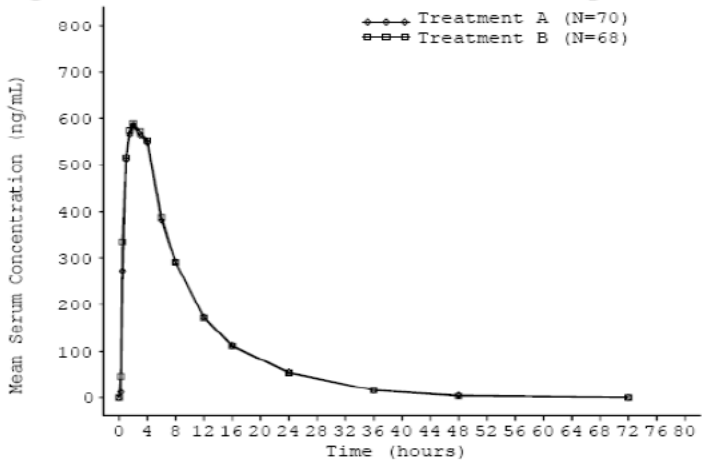
(80% to 125%) interval, bioequivalence between test and reference treatments was claimed.

Pharmacokinetics Results:

Bioequivalence Assessment of Alogliptin 12.5 mg and Pioglitazone 15 mg Administered as Individual Tablets and as Combination Tablets

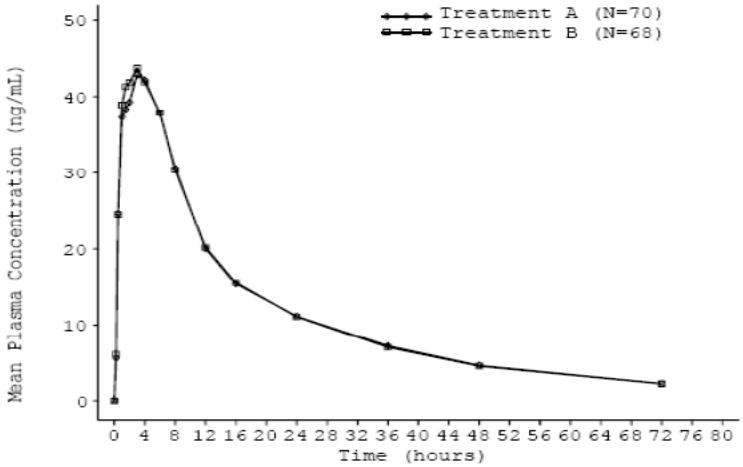
Linear plots of mean serum concentrations of pioglitazone and mean plasma concentrations of alogliptin are presented in **Figures 1 and 2**, respectively.

Figure 1: Mean Serum Concentrations of Pioglitazone vs Time: Treatment A (Test) and Treatment B (Reference).



Source: Figure 15.2.5.
Treatment A=SYR-322-4833 (b) (4) (12.5 mg + 15 mg) (test treatment).
Treatment B=alogliptin 12.5 mg + pioglitazone 15 mg (reference treatment).

Figure 2: Mean Plasma Concentrations of Alogliptin vs Time: Treatment A (Test) and Treatment B (Reference).



Source: Figure 15.2.2.
Treatment A=SYR-322-4833 (b) (4) (12.5 mg + 15 mg) (test treatment).
Treatment B=alogliptin 12.5 mg + pioglitazone 15 mg (reference treatment).

Descriptive statistics and statistical analysis for serum pharmacokinetic parameters of pioglitazone and plasma and urine pharmacokinetic parameters of alogliptin are presented in **Table 5**.

Table 5: Pharmacokinetic Parameters and Statistical Analysis of Alogliptin 12.5 mg and Pioglitazone 15 mg After Administration as Individual Tablet (Reference) and as Fixed Dose Combination Tablets (Test)

	Arithmetic Mean (%CV)		LS Mean		
Analyte Parameter (units)	Treatment A: SYR-322-4833 (b) (4) (12.5 mg + 15 mg) (T)	Treatment B: Alogliptin 12.5 mg + Pioglitazone 15 mg (R)	Treatment A: SYR-322-4833 (b) (4) (12.5 mg + 15 mg) (T)	Treatment B: Alogliptin 12.5 mg + Pioglitazone 15 mg (R)	Ratio T/R·100 (90% CI) (a)
Pioglitazone (Serum)					
AUC(0-tlqc) (ng·hr/mL)	6020.95 (34.091)	6045.21 (32.158)	5707.70	5774.19	98.85 (95.42, 102.40)
AUC(0-inf) (ng·hr/mL)	6708.60 (30.675)	6727.18 (29.957)	6399.01	6429.75	99.52 (96.58, 102.55)
Cmax (ng/mL)	653.56 (33.98)	656.32 (29.53)	612.22	626.25	97.76 (91.82, 104.08)
Tmax (hr) (b,c)	1.77 (0.483, 4.050)	1.50 (0.500, 4.017)	1.77	1.50	NA
Alogliptin (Plasma)					
AUC(0-tlqc) (ng·hr/mL)	837.39 (16.969)	835.82 (17.886)	826.84	824.23	100.32 (99.00, 101.65)
AUC(0-inf) (ng·hr/mL)	916.35 (17.540)	915.78 (17.580)	904.72	904.17	100.06, (98.68, 101.46)
Cmax (ng/mL)	50.30 (31.194)	52.52 (31.581)	48.23	50.28	95.94 (91.83, 100.23)
Tmax (hr) (b,d)	3.00 (0.500, 6.00)	2.99 (0.500, 6.067)	3.00	2.99	NA
Alogliptin (Urine)					
Ae(0-24) (mg)	5.41 (18.768)	5.28 (20.179)	NA	NA	NA
CLr (L/hr)	9.74 (23.175)	9.46 (24.592)	NA	NA	NA
Fe (%)	43.28 (18.768)	42.20 (20.179)	NA	NA	NA

Sources: Tables 15.2.1.2, 15.2.1.3, 15.2.1.6, 15.2.1.7, and 15.2.1.10.
T=test treatment, R=reference treatment, NA=Not applicable.
N=68 for AUC(0-tlqc); Cmax, and Tmax of serum pioglitazone; N=59 for AUC(0-inf) of serum pioglitazone.
N=68 for AUC(0-tlqc); Cmax, and Tmax of plasma alogliptin; N=66 for AUC(0-inf) of plasma alogliptin.
N=68 for urine parameters of alogliptin.
(a) Ratios and CIs are presented as percentages.
(b) Tmax is reported as median (minimum, maximum).
(c) P=0.264.
(d) P=0.586.

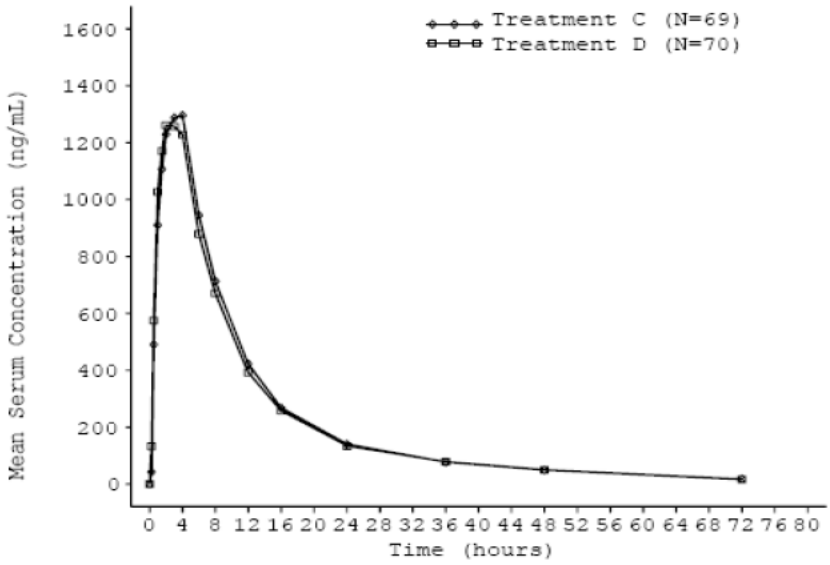
The 90% CIs for the ratios of the LS means for the AUC and C_{max} values of both alogliptin and pioglitazone were within the 80% to 125% range. Therefore, the SYR-322-4833 (b) (4) (12.5 mg + 15 mg) tablet was bioequivalent to the alogliptin 12.5 mg and pioglitazone 15 mg individual tablets.

No statistically significant differences for the median T_{max} values for either alogliptin or pioglitazone were observed between the SYR-322-4833 (b) (4) (12.5 + 15 mg) tablet and the alogliptin 12.5 mg and pioglitazone 15 mg individual tablets.

Bioequivalence Assessment of Alogliptin 25 mg and Pioglitazone 45 mg Administered as Individual Tablets and as Combination Tablets:

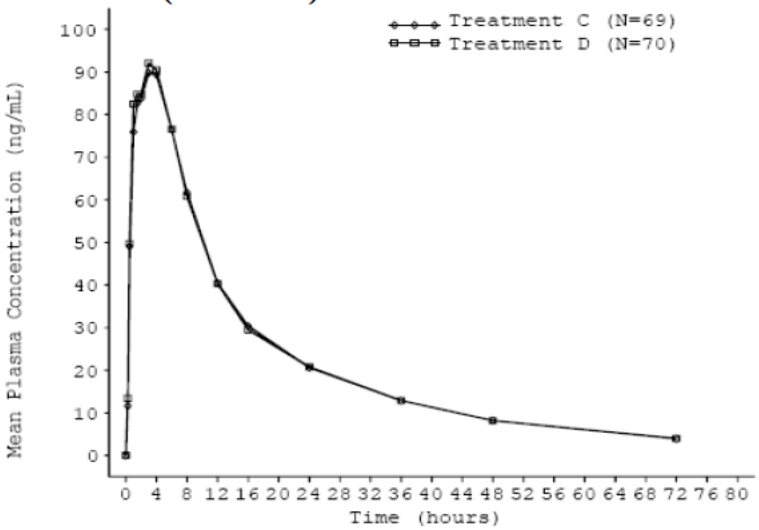
Linear plots of mean serum concentrations of pioglitazone and mean plasma concentrations of alogliptin are presented in Figures 3 and 4, respectively.

Figure 3: Mean Serum Concentrations of Pioglitazone vs Time: Treatment C (Test) and Treatment D (Reference).



Source: Figure 15.2.6.
C=SYR-322-4833 (b) (4) (25 mg + 45 mg) (test treatment).
D=Alogliptin 25 mg + pioglitazone 45 mg (reference treatment).

Figure 4: Mean Plasma Concentrations of Alogliptin vs Time: Treatment C (Test) and Treatment D (Reference).



Source: Figure 15.2.3.
C=SYR-322-4833 (b) (4) (25 mg + 45 mg) (test treatment).
D=Alogliptin 25 mg + pioglitazone 45 mg (reference treatment).

Descriptive statistics and statistical analysis for the serum pharmacokinetic parameters of pioglitazone and plasma and urine pharmacokinetic parameters of alogliptin are presented in Table 6.

Table 6: Pharmacokinetic Parameters and Statistical Analysis of Alogliptin 25 mg and Pioglitazone 45 mg After Administration as Individual Tablet (Reference) and as Fixed Dose Combination Tablets (Test)

Analyte Parameter (units)	Arithmetic Mean (%CV)		LS Mean		
	Treatment C: SYR-322-4833 (b) (4) (25 mg + 45 mg) (T)	Treatment D: Alogliptin 25 mg + Pioglitazone 45 mg (R)	Treatment C: SYR-322-4833 (b) (4) (25 mg + 45 mg) (T)	Treatment D: Alogliptin 25 mg + Pioglitazone 45 mg (R)	Ratio T/R·100 (90% CI) (a)
Pioglitazone Serum					
AUC(0-tlqc) (ng·hr/mL)	15891.52 (34.284)	15041.50 (30.501)	14978.78	14369.87	104.24 (98.62, 110.18)
AUC(0-inf) (ng·hr/mL)	17858.57 (32.415)	16786.47 (30.633)	16789.67	15961.30	105.19 (98.19, 112.69)
Cmax (ng/mL)	1411.62 (40.38)	1390.04 (33.15)	1276.53	1303.92	97.90 (89.34, 107.28)
Tmax (hr) (b,c)	3.00 (1.000, 8.000)	2.00 (0.500, 6.000)	3.00	2.00	NA
Alogliptin Plasma					
AUC(0-tlqc) (ng·hr/mL)	1602.86 (16.300)	1620.66 (15.716)	1582.331	1601.99	98.77 (97.58, 99.98)
AUC(0-inf) (ng·hr/mL)	1715.91 (16.213)	1741.05 (16.401)	1694.756	1719.46	98.56 (97.40, 99.74)
Cmax (ng/mL)	107.51 (23.655)	110.79 (29.32)	104.10	106.15	98.07 (93.33, 103.06)
Tmax (hr) (b,d)	2.50 (0.500, 6.000)	2.98 (0.500, 8.000)	2.50	2.98	NA
Alogliptin Urine					
Ae(0-24) (mg)	10.81 (23.392)	11.54 (19.397)	NA	NA	NA
CLr (L/hr)	9.77 (26.618)	10.40 (23.723)	NA	NA	NA
Fe (%)	43.24 (23.392)	46.18 (19.397)	NA	NA	NA

Sources: Tables 15.2.1.2, 15.2.1.4, 15.2.1.6, 15.2.1.8, and 15.2.1.10.
T=test treatment, R=reference treatment, NA=Not applicable.
N=67 for AUC(0-tlqc), N=47 for AUC(0-inf), and N=68 for Cmax and Tmax of serum pioglitazone.
N=67 for AUC(0-tlqc), N=66 for AUC(0-inf), and N=68 for Cmax and Tmax of plasma alogliptin.
N=68 for Fe and Ae(0-24), and N=67 for CLr of urine alogliptin.
(a) Ratios and CIs are presented as percentages.
(b) Tmax is reported as median (minimum, maximum).
(c) P<0.001.
(d) P=0.830.

The 90% CIs for the ratios of the LS means for the AUC and C_{max} values for both alogliptin and pioglitazone were within the 80% to 125% range. Therefore, the SYR-322-4833 (b) (4) (25 mg + 45 mg) tablet was bioequivalent to the alogliptin 25 mg and pioglitazone 45 mg individual tablets.

A statistically significant difference between the SYR-322-4833 (b) (4) (25 + 45 mg) tablet and the individual alogliptin 25 mg and pioglitazone 45 mg tablets was observed for the median T_{max} value of pioglitazone (P<0.001) but not alogliptin (P=0.830).

Summary of Pharmacokinetic Results:

- Both of the SYR-322-4833 (b) (4) tablet strengths were bioequivalent to the individual alogliptin and pioglitazone tablets as all of the 90% CIs for the ratios of the LS means for the exposure parameters were within the 80% to 125% range.

- No statistically significant differences for the median T_{max} values for either alogliptin or pioglitazone were observed between the SYR-322-4833 (b) (4) (12.5 + 15 mg) tablet and the alogliptin 12.5 mg and pioglitazone 15 mg individual tablets.

- A statistically significant difference between the SYR-322-4833 (b) (4) (25 + 45 mg) tablet and the individual alogliptin 25 mg and pioglitazone 45 mg tablets was observed for the median T_{max} value of pioglitazone ($P<0.001$) but not alogliptin ($P=0.830$).

Safety Conclusions:

- Thirty-six of 72 subjects (50.0%) experienced at least 1 adverse event. The most commonly reported adverse events were headache, reported by 16/72 subjects (22.2%), constipation (4/72 subjects, 5.6%) and cough (4/72 subjects, 5.6%).

- Fifteen subjects (20.8%) experienced at least 1 adverse event that was considered by the investigator to be possibly related to study drug. No adverse events were considered to be probably or definitely related to study drug.

- The majority of adverse events were judged by the investigator to be mild in intensity (24/72 subjects [33.3%]). The remaining adverse events were judged to be of moderate intensity (12/72 subjects [16.7%]). No adverse events were severe in intensity.

- No subjects were withdrawn from the study due to adverse events. No deaths, SAEs, or other significant adverse events occurred.

- No clinically significant changes in ECGs or clinical laboratory examination results were reported. Three subjects had vital signs values and 3 subjects had physical examination results that were reported as adverse events, all of which were considered by the investigator to be mild in intensity and not related to study drug.

Overall Conclusions:

- The SYR-322-4833 (b) (4) (12.5 mg + 15 mg) tablet met the standards for bioequivalence to the individual alogliptin 12.5 mg and pioglitazone 15 mg tablets for the AUC and C_{max} of both pioglitazone and alogliptin.

- The SYR-322-4833 (b) (4) (25 mg + 45 mg) tablet met the standards for bioequivalence to the individual alogliptin 25 mg and pioglitazone 45 mg tablets for the AUC and C_{max} of both pioglitazone and alogliptin.

- SYR-322-4833 (b) (4), alogliptin, and pioglitazone were well tolerated as administered in this study.

Reviewer's Comment:

The overall study design and data analysis seems reasonable and acceptable.

4.2.2 Food Effect Study 01-06-TL-322OPI-006

Title: An Open-Label, Randomized, Crossover Study to Determine the Effects of Food on the Pharmacokinetics of the Proposed Commercial Formulation of a Fixed Dose Combination of SYR-322 and Pioglitazone HCl in Healthy Male and Female Subjects

Investigator and Study Center(s):
James Kissling, MD
MDS Pharma Services
621 Rose Street
Lincoln, NE 68502

Study Sponsor:
Takeda Global Research & Development Center, Inc.

Bioanalytical Analysis:
(b) (4)

Study Period: 31 July 2007 to 21 August 2007

Objective:

- The primary objective of this study was to evaluate the effect of food on the pharmacokinetics of the proposed commercial formulation of a fixed-dose combination of SYR-322 (alogliptin) and pioglitazone hydrochloride (HCl) (SYR-322-4833 (b) (4) 25 mg + 45 mg)

- The secondary objective of this study was to evaluate the safety of SYR-322-4833 (b) (4) 25 mg + 45 mg under fed and fasted conditions.

Study Design:

The current trial was a phase 1, single-center, open-label, randomized, 2-period crossover study that was designed to evaluate the effect of food on the pharmacokinetics of SYR-322-4833 (b) (4).

Subjects were assigned randomly to 1 of 2 treatment sequences (12 subjects per sequence) and received a single oral dose of SYR-322-4833 (b) (4) 25 mg + 45 mg in the fasted state (reference treatment) and a single oral dose of SYR-322-4833 (b) (4) 25 mg + 45 mg in the fed state (test treatment).

Subjects were randomized immediately prior to dosing on Day 1 of Treatment Period 1. Subjects were confined to the clinic from Day -1 of Treatment Period 1 through Day 4 of Treatment Period 1 and from Day 7 of Treatment Period 1 through Day 4 of Treatment Period 2.

Each subject received treatment in both the fed and fasted states. A 7-day washout interval, which began immediately after dosing on Day 1 of Period 1, separated the 2 Treatment Periods. Subjects were discharged from the clinic on Day 4 of Period 1, readmitted on the evening prior to dosing in Period 2 (Day 7 of Period 1), and discharged from the study after the 72-hour pharmacokinetic sample was collected and all study exit procedures were completed on Day 4 of Period 2 (**Table 1**).

Table 1: Trial Design

<table>
<tr><th colspan="2">Pretreatment Period</th><th colspan="5">Treatment Period (a,b)</th></tr>
<tr><th>Screening</th><th>Baseline/Check-in</th><th colspan="2">Period 1 (c)</th><th colspan="3">Period 2</th></tr>
<tr><td>Days -28 to -2</td><td>Day -1</td><td>Day 1
Dosing</td><td>Days 2 to 7</td><td>Day 1
Dosing</td><td>Days 2 to 3</td><td>Day 4
Study Exit</td></tr>
<tr><td rowspan="2"></td><td rowspan="2"></td><td>A
(N=12)</td><td rowspan="2">Washout</td><td>B</td><td rowspan="2">Washout</td><td rowspan="2"></td></tr>
<tr><td>B
(N=12)</td><td>A</td></tr>
</table>

A=SYR-322-4833 (b) (4) 25 mg + 45 mg under fasted conditions (reference treatment).
B=SYR-322-4833 (b) (4) 25 mg + 45 mg after a high-fat meal (test treatment).

For fed treatment, subjects were required to fast for 10 hours prior to consuming a high fat, high-calorie meal prior to dosing. The meal consisted of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk, and contained approximately 800 to 1000 calories with approximately 50% of the caloric content coming from fat.

For fasted treatment, subjects were required to fast for 10 hours prior to dosing. All subjects received study drug with 240 mL of water and were required to drink all of the water provided with the dose. Subjects were required to fast for at least 4 hours after dosing.

Blood samples (4 mL each) for the determination of alogliptin concentrations in plasma were collected on Day 1 within 0.25 hours prior to dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours post dose during each treatment period.

Blood samples (5 mL each) for the determination of pioglitazone concentrations in serum were collected on Day 1 within 0.25 hours prior to dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours post dose during each treatment period.

Study Population:

Twenty four healthy volunteers were enrolled in this study. The mean age of the study population was 28.4 years. **Table 2** below shows the demographics of the enrolled patients**.**

Table 2: Baseline Demographics of Study Population.

Table 10.a Summary of Demographic and Other Baseline Characteristics

Characteristic	Treatment Sequence AB n=12	Treatment Sequence BA n=12	All Subjects N=24
Sex, n (%)			
Male	7 (58.3)	9 (75.0)	16 (66.7)
Female	5 (41.7)	3 (25.0)	8 (33.3)
Mean age (SD), years	26.7 (8.41)	30.2 (11.85)	28.4 (10.21)
Race, n (%)			
Asian	0	1 (8.3)	1 (4.2)
Black or African American	1 (8.3)	1 (8.3)	2 (8.3)
White	11 (91.7)	10 (83.3)	21 (87.5)
Ethnicity, n (%)			
Hispanic or Latino	2 (16.7)	0	2 (8.3)
Not Hispanic or Latino	10 (83.3)	12 (100.0)	22 (91.7)
Mean weight (SD), kg	77.64 (14.173)	85.05 (16.060)	81.35 (15.289)
Mean height (SD), cm	173.2 (8.99)	175.5 (10.01)	174.3 (9.38)
Mean BMI (SD), kg/m^2	25.79 (3.821)	27.46 (3.625)	26.63 (3.741)

Investigational Product and Dose Selection:

Treatment consisted of a single oral dose of SYR-322-4833 (b) (4) 25 mg + 45 mg administered under fasted (10 hours) conditions (reference treatment) and a single oral dose of SYR-322-4833 (b) (4) 25 mg + 45 mg administered under fed conditions (test treatment). A 7-day washout interval, which began immediately after dosing on Day 1 of Period 1, separated the 2 treatments. Subjects were assigned randomly to 1 of 2 treatment sequences using the randomization schedule as shown in **Table 3**.

Table 3: Randomization Scheme

Sequence	Period 1	Period 2
AB	SYR-322-4833 (b) (4) 25 mg + 45 mg fasted	SYR-322-4833 (b) (4) 25 mg + 45 mg fed
BA	SYR-322-4833 25 mg + 45 mg fed	SYR-322-4833 25 mg + 45 mg fasted

A=reference treatment, B=test treatment.

SYR-322-4833 (b) (4) 25 mg + 45 mg was supplied in 75 cc, white, square, high-density polyethylene bottles (b) (4) Each bottle contained 30 tablets and bore a 1-panel label containing pertinent study information.

Table 4: Batch number of product used in this trial

Study Drug	Lot No.	Retest Date
SYR-322-4833 (b) (4) 25 mg + 45 mg	Z644G027	29 February 2008

Bioanalysis:

Alogliptin: Quantitative assessment of Alogliptin in plasma was done using validated LC/MS/MS method. The lower limit of the quantification of the assay was 1.0 ng/mL. The calibration curves for alogliptin were analysed at concentration range of 1 ng/mL to 250 ng/mL. The precision of the assay, as determined from analysis of quality control (QC) samples ranged between 2.72 and 6.03%. The mean accuracy (% Bias) ranged between 0.594% to 3.95%. Between-batch precision (%CV) results of the calibration standards was less between 3.20 % to 5.53% and accuracy (%Bias) ranged from -1.68 to 1.58 %.

Pioglitazone: Quantitative assessment of Pioglitazone in human serum was done using validated LC/MS/MS method. The lower limit of the quantification of the assay was 25 ng/mL. The calibration curves for alogliptin were analysed at concentration range of 25 ng/mL to 2500 ng/mL. The precision of the assay, as determined from analysis of quality control (QC) samples ranged between 3.8 and 2.6%. The mean accuracy (% Bias) ranged between -5.5% to 4.3 %. Between-batch precision (%CV) results of the calibration standards was less between 1.9 % to 4.1% and accuracy (%Bias) ranged from -7.4 to 3.2 %.

Data Analysis:

All data analyses were performed using SAS (Version 9.1, SAS Institute, Cary, NC). Pharmacokinetic parameters were derived using noncompartmental methods with WinNonlin® Professional Version 5.1 (Pharsight Corp., Mountain View, CA).

The following pharmacokinetic parameters were derived from plasma concentration data for alogliptin and serum concentration data for pioglitazone under fed and fasted conditions:

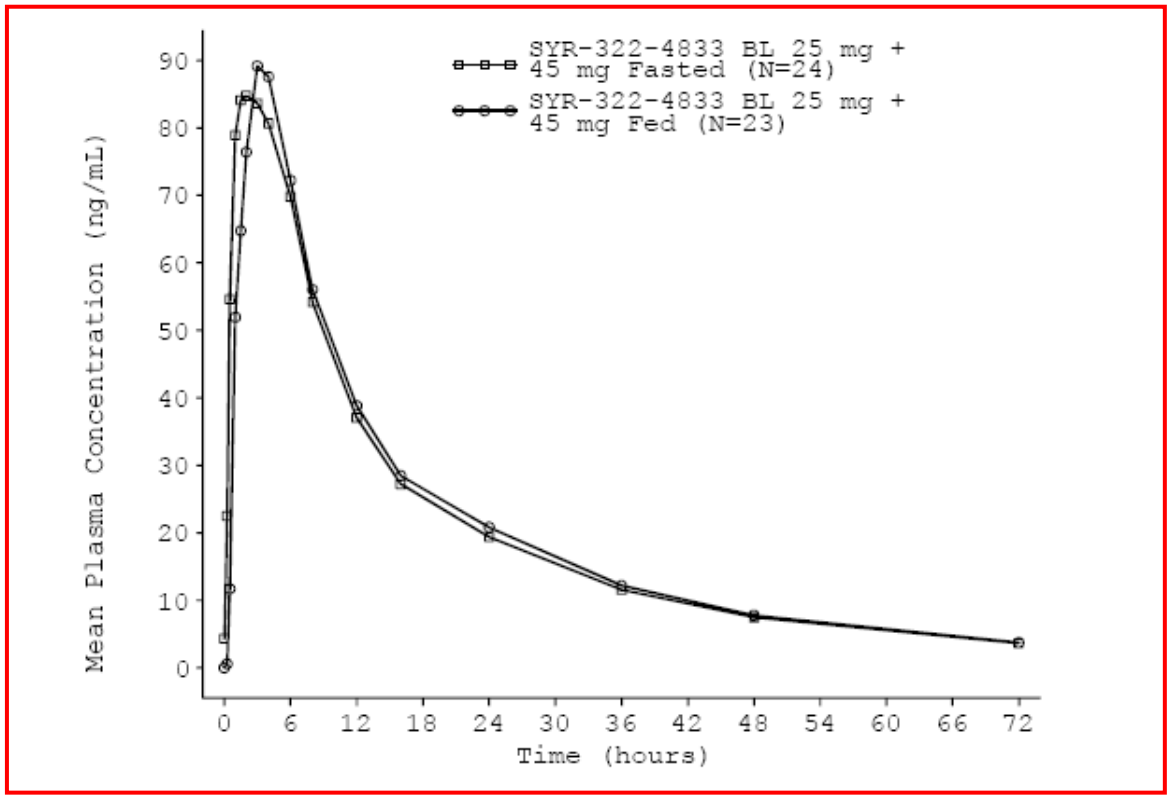
- AUC (0-24): Area under the plasma/serum concentration-time curve from time 0 to 24 hours.
- AUC (0-tlqc): Area under the plasma/serum concentration-time curve from time 0 to time of last quantifiable concentration (tlqc).
- AUC(0-inf): Area under the plasma/serum concentration-time curve from time 0 to infinity
- C_{max}: Maximum observed plasma/serum concentration.
- T_{max}: Time to reach C_{max}.
- λz : Terminal elimination rate constant.
- $T_{1/2}$: Terminal elimination half-life.
- CL/F: Apparent clearance after oral administration (CL/F)

Statistical inferences to compare the pharmacokinetic parameters of alogliptin and pioglitazone under fed conditions (test treatment) relative to alogliptin and pioglitazone under fasted conditions (reference treatment) were based on an analysis of variance (ANOVA) model with fixed effects for sequence, period, and treatment and a random effect for subject nested within sequence. The natural logarithmic-transformed values of AUC(0-24), AUC(0-tlqc), AUC(0-inf), and C_{max} were the dependent variables in the ANOVA model. The Wilcoxon signed-rank test was used to compare T_{max} between the 2 treatments.

Pharmacokinetics Results:

Linear plots of the mean plasma concentrations of alogliptin under fasted and fed conditions are presented in **Figure 1**.

Figure 1: Mean Plasma Concentrations of Alogliptin vs Time under Fasted and Fed Conditions: Linear Scale



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Descriptive statistics and statistical analysis of plasma and urine pharmacokinetic parameters of alogliptin under fasted and fed conditions are presented in **Table 5**.

Table 5: Summary of Plasma and Urine Pharmacokinetic Parameters of Alogliptin

Parameter (units)	Arithmetic Mean (%CV) SYR-322-4833 (b) (4) 25 mg + 45 mg fed (T) N=23	Arithmetic Mean (%CV) SYR-322-4833 (b) (4) 25 mg + 45 mg fasted (R) N=23	LS Mean SYR-322-4833 (b) (4) 25 mg + 45 mg fed (T) N=23	LS Mean SYR-322-4833 (b) (4) 25 mg + 45 mg fasted (R) N=23	Ratio T/R-100 (90% CI) (a)
Alogliptin (Plasma) (b)					
AUC(0-24) (ng·hr/mL)	1063.57 (16.051)	1067.73 (19.852)	1050.08	1048.30	100.17 (97.15, 103.28)
AUC(0-tlqc) (ng·hr/mL)	1519.95 (12.835)	1500.95 (15.129)	1508.08	1484.57	101.58 (99.02, 104.21)
AUC(0-inf) (ng·hr/mL)	1640.61 (11.847)	1621.70 (13.790)	1630.19	1607.20	101.43 (99.05, 103.87)
Cmax (ng/mL)	109.60 (36.325)	99.61 (35.190)	104.44	94.77	110.21 (101.61, 119.54)
Tmax (hr) (c)	3.00 (1.000, 6.000)	2.00 (0.250, 4.067)	3.00	2.00	—
λz (1/hr)	0.03 (18.088)	0.032 (18.064)	—	—	—
T1/2 (hr)	21.61 (17.720)	22.23 (16.533)	—	—	—
CL/F (L/hr)	15.44 (11.890)	15.68 (13.043)	—	—	—
Alogliptin (Urine) (b)					
Ae(0-24) (mg)	10.89 (19.738)	11.25 (17.926)	—	—	—
CLr(0-24) (L/hr)	10.38 (21.699)	10.79 (20.334)	—	—	—
Fe(0-24) (%)	43.55 (19.738)	45.01 (17.926)	—	—	—

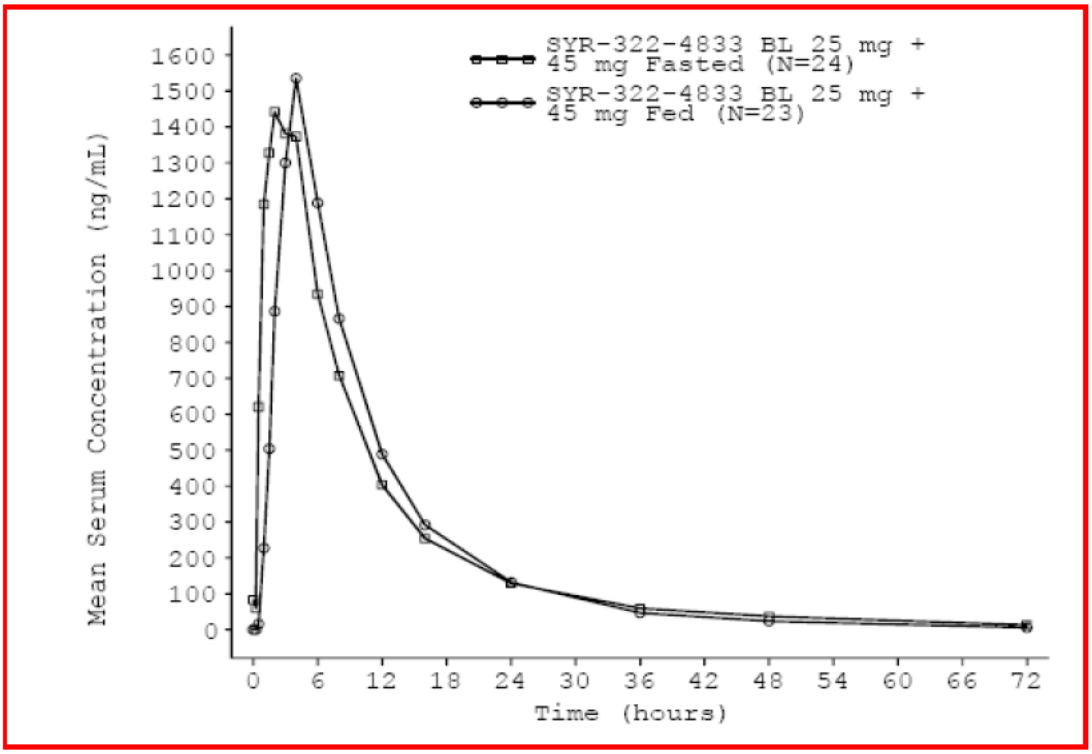
Source: Tables 15.2.1.2, 15.2.1.5, and 15.2.1.8.
R=reference treatment, T=test treatment, —=not applicable.
(a) Ratios and CIs are presented as percentages.
(b) Subject 014 had only a partial profile during Period 1 and no data for Period 2 (early termination).
(c) Tmax is presented as median (minimum, maximum). P=0.290.

The 90% CIs for the ratios (fed/fasted) of the LS means for AUC(0-24), AUC(0-tlqc), AUC(0-inf), and C_{max} of alogliptin were contained entirely within the 80% to 125% range, indicating no effect of food on total or peak exposure to alogliptin.

Median alogliptin T_{max} increased by approximately 1 hour when SYR-322-4833 (b) (4) 25 mg + 45 mg was administered under fed conditions compared with administration under fasted conditions; the difference in T_{max} between the 2 treatments was not statistically significant (P=0.290). Mean λz, T1/2, and CL/F of alogliptin were similar for both treatments. Ae (0-24), CLr (0-24), and Fe (0-24) of alogliptin were similar following administration of SYR-322-4833 (b) (4) 25 mg + 45 mg under fed and fasted conditions.

Linear plot of the mean serum concentrations for pioglitazone under fasted and fed conditions are presented in **Figure 2.**

Figure 2: Mean Plasma Concentrations of Pioglitazone vs Time under Fasted and Fed Conditions: Linear Scale



Descriptive statistics and the statistical analyses of the serum pharmacokinetic parameters of pioglitazone under fasted and fed conditions are presented in **Table 6**.

Table 6: Summary of Plasma Pharmacokinetic Parameters of Pioglitazone

	Arithmetic Mean (%CV)		LS Mean		
	SYR-322-4833 (b) (4)		SYR-322-4833 (b) (4)		
Parameter (units)	25 mg +45 mg fed (T) N=23 (a)	25 mg +45 mg fasted (R) N=23 (b)	25 mg +45 mg fed (T) N=23 (a)	25 mg +45 mg fasted (R) N=23 (b)	Ratio T/R-100 (90% CI) (c)
AUC(0-24) (ng·hr/mL)	13849.54 (35.585)	13692.83 (38.707)	13030.94	12799.11	101.81 (92.48, 112.09)
AUC(0-tlqc) (ng·hr/mL)	15371.41 (36.056)	15680.94 (40.026)	14493.66	14561.85	99.53 (90.87, 109.02)
AUC(0-inf) (ng·hr/mL)	16605.73 (33.061)	17197.87 (40.345)	15210.31	15696.40	96.90 (87.05, 107.87)
Cmax (ng/mL)	1605.17 (29.69)	1562.61 (34.39)	1531.59	1478.31	103.60 (90.49, 118.61)
Tmax (hr) (d)	4.00 (2.000, 6.067)	2.00 (1.000, 4.000)	4.00	2.00	—
λz (1/hr)	0.088 (53.784)	0.059 (63.609)	—	—	—
T1/2 (hr)	14.04 (111.316)	21.64 (103.561)	—	—	—
CL/F (L/hr)	3.00 (36.639)	3.12 (47.003)	—	—	—

Source: Tables 15.2.1.4 and 15.2.1.6.
R=reference treatment, T=test treatment, — =not applicable.
(a) N=20 for AUC(0-inf) and CL/F; N=21 for T1/2.
(b) N=19 for AUC(0-inf) and CL/F; N=22 for T1/2.
(c) Ratios and CIs are presented as percentages.
(d) Tmax is presented as median (minimum, maximum). P<0.001.

The 90% CIs for the ratios (fed/fasted) of the LS means for AUC(0-24), AUC(0-tlqc), AUC(0-inf), and C_{max} of pioglitazone were contained entirely within the 80% to 125% range, indicating no effect of food on total or peak exposure to pioglitazone. However, median pioglitazone T_{max} increased by approximately 2 hours when SYR-322-4833 (b) (4) 25 mg + 45 mg was administered under fed conditions compared with administration under fasted conditions; the difference in T_{max} between the 2 treatments was statistically significant (P<0.001). Mean CL/F of pioglitazone was similar for both treatments.

Summary of Pharmacokinetic Results:

- The 90% CIs for the ratios (fed/fasted) of the LS means for AUC(0-24), AUC(0-tlqc), AUC(0-inf), and C_{max} of alogliptin were contained entirely within the 80% to 125% range, indicating no effect of food on total or peak exposure to alogliptin in subjects who received SYR-322-4833 (b) (4) 25 mg + 45 mg.

- The 90% CIs for the ratios (fed/fasted) of the LS means for AUC(0-24), AUC(0-tlqc), AUC(0-inf), and C_{max} of pioglitazone were also contained entirely within the 80% to 125% range, indicating no effect of food on total or peak exposure to pioglitazone in subjects who received SYR-322-4833 (b) (4) 25 mg + 45 mg.

- Median alogliptin T_{max} increased by approximately 1 hour when SYR-322-4833 (b) (4) 25 mg + 45 mg was administered under fed conditions compared with administration under fasted conditions.

- Median pioglitazone T_{max} increased by approximately 2 hours when SYR-322-4833 (b) (4) 25 mg + 45 mg was administered under fed conditions compared with administration under fasted conditions.

Safety Conclusions:

- Fourteen of 24 subjects (58.3%) experienced at least 1 treatment-emergent adverse event.

- Ten of 24 subjects (41.7%) experienced at least 1 treatment-emergent adverse event following fasted treatment, and 8 of 23 subjects (34.8%) experienced at least 1 treatment emergent adverse event following fed treatment.

- Adverse events that were experienced by more than 1 subject were headache (5 of 24 subjects [20.8%]), fatigue (4 of 24 subjects [16.7%]), upper respiratory tract infection (4 of 24 subjects [16.7%]), constipation (2 of 24 subjects [8.3%]), vessel puncture site pain (2 of 24 subjects [8.3%]), and pharyngolaryngeal pain (2 of 24 subjects [8.3%]).

- The majority of adverse events were considered by the investigator to be not related to study drug. Five of 24 subjects (20.8%) experienced 1 or more of the following adverse events that were considered possibly related to study drug: fatigue (3 subjects), headache (1 subject), and upper abdominal pain (1 subject). No adverse events were judged by the investigator to be probably or definitely related to study treatment.

- All adverse events were considered by the investigator to be of mild intensity. One subject(Subject 014) prematurely discontinued the study, due to an adverse event of vessel puncture site pain following treatment with SYR-322-4833 (b) (4) 25 mg + 45 mg under fasted conditions during Period 1. The investigator considered this event to be mild in intensity and not related to study drug. No deaths, SAEs, or other significant adverse events occurred.

- One subject had a clinically significant abnormal chemistry test result that was reported as an adverse event of alkaline phosphatase increased. This event was experienced following fasted treatment; the investigator considered the event to be mild in intensity and not related to study drug. Liver transaminases and bilirubin were within the normal range. No hematology test result, urinalysis result, vital sign measurement, physical examination observation, or ECG result was reported as an adverse event.

Overall Conclusions:

- Total and peak exposure to alogliptin and pioglitazone were not altered when administered as a single dose of SYR-322-4833 (b) (4) 25 mg + 45 mg with a high-fat meal compared with administration in the fasted state.

- Median alogliptin T_{max} increased by approximately 1 hour when SYR-322-4833 (b) (4) 25 mg + 45 mg was administered under fed conditions compared with administration under fasted conditions.

- Median pioglitazone T_{max} increased by approximately 2 hours when SYR-322-4833 (b) (4) 25 mg + 45 mg was administered under fed conditions compared with administration under fasted conditions.

- A single dose of SYR-322-4833 (b) (4) 25 mg + 45 mg was well tolerated in healthy subjects under fed and fasted conditions as administered in this study.

Reviewer's Comment:

The overall study design and data analysis seems reasonable and acceptable.

4.3 OCP FILING MEMO

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	22-426	Brand Name	TBD
OCPB Division (I, II, III)	DCP II	Generic Name	Alogliptin/Pioglitazone Fixed Dose Combination Tablets
Medical Division	DMEP	Drug Class	
OCPB Reviewer	Ritesh Jain, Ph.D.	Indication(s)	Treatment of Type-2 Diabetes (T2DM).
OCPB Team Leader	Sally Choe, Ph.D.	Dosage Form	Tablet; 25/15, 25/30, 25/45, 12.5/15, 12.5/30, 12.5/45 mg/mg
		Dosing Regimen	25mg/15mg /day through 12.5mg/45mg/day
Date of Submission	09/19/2008	Route of Administration	Oral
Estimated Due Date of OCPB Review	06/5/2009	Sponsor	Takeda Global Research & Development Center, Inc.
PDUFA Due Date	07/22/2009	Priority Classification	S
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X	1		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	X	3		
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		5		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	Yes it is filable
Comments sent to firm ?		
QBR questions (key issues to be considered)	1) Was bioequivalence demonstrated between the proposed to-be-marketed formulation for the intended commercial manufacture and the pivotal clinical trial formulation? 2) What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal type? 3) Was formulation effect demonstrated for this fixed dose combination product?	
Other comments or information not included above	**DSI inspection is requested for the pivotal BE study 322OPI-101**	
Primary reviewer Signature and Date	Ritesh Jain, Ph.D.	
Secondary reviewer Signature and Date	Sally Choe, Ph.D.	

Background:

- This is a New Drug Application (NDA) submission for alogliptin/pioglitazone fixed dose combination tablets.
- The sponsor is proposing 6 different fixed dose combinations of alogliptin/pioglitazone. The doses are (alogliptin/pioglitazone) 25mg/15mg, 25mg/30mg, 25mg/45mg, 12.5mg/15mg, 12.5 mg/30mg, and 12.5mg/45mg.
- Alogliptin is an orally active, selective, and potent inhibitor of dipeptidyl peptidase-4 (DPP-4) that is being developed by TGRD as a novel antihyperglycemic agent.
- An NDA for alogliptin (original NDA 22-271) was submitted on December 27, 2007 and is under review.
- Pioglitazone (ACTOS®) is a peroxisome proliferator-activated receptor-gamma (PPARγ) agonist that is a member of the thiazolidinedione (TZD) class of oral antihyperglycemic agents and has been commercially available since 1999.

Biopharmaceutics Studies:

In this NDA, the sponsor submitted 5 biopharmaceutics related studies. In the clinical studies the sponsor used the phase 3 formulation of alogliptin, which is bioequivalent to the proposed commercial formulation of alogliptin (NDA 22-271) and the commercial formulation of pioglitazone (ACTOS®) individually. The sponsor conducted following biopharmaceutics studies with the proposed commercial fixed dose combination (FDC) tablet to bridge the information between to be marketed product and the individual products used in the clinical studies.

1) **A pilot relative bioavailability study with the highest and lowest strength of proposed commercial (FDC) tablet and individual tablets of alogliptin and pioglitazone. [Study-01-06-TL-322OPI-007]**
   - Open label, randomized, 4-period, 4-sequence, crossover, pilot study in 16 healthy adult subjects.
   - Small-scale batches of the highest and lowest dosage strength of FDC formulation **(SYR-322-4833 (b)(4))** were evaluated: alogliptin 12.5 mg + pioglitazone 15 mg and alogliptin 25 mg + pioglitazone 45 mg.
   - The relative bioavailability of alogliptin and pioglitazone were similar when dosed as SYR-322-4833 (b)(4) (FDC) as compared to when dosed individually at both dosage strengths (See Appendix 1).

2) **A pivotal bioequivalence study with the highest and lowest strength of proposed commercial (FDC) tablet and individual tablets of alogliptin and pioglitazone. [Study-322OPI-101]**
   - Open label, randomized, 4-sequence, 4-period crossover study in 72 healthy subjects
   - In this study the highest and lowest dosage strength of FDC formulation (**SYR-322-4833 (b)(4)**) were evaluated: alogliptin 12.5 mg + pioglitazone 15 mg and alogliptin 25 mg + pioglitazone 45 mg.
   - The 90% CIs for the ratios of the LS means for AUC (0-tlqc), AUC (0-inf), and Cmax values of both alogliptin and pioglitazone were within the 80% to 125% range (APPENDIX 1).

- No statistically significant differences for the median Tmax values for either alogliptin or pioglitazone were observed between the SYR-322-4833 (b)(4) (12.5 + 15 mg) tablet, and the alogliptin 12.5 mg and pioglitazone 15 mg individual tablets.
- A statistically significant difference between the SYR-322-4833 (b)(4) (25 + 45 mg) tablet and the individual alogliptin 25 mg and pioglitazone 45 mg tablets was observed for the median T_{max} value of pioglitazone (P<0.001) but not alogliptin (P=0.830). According to sponsor this difference is not considered clinically significant because SYR-322-4833 is a chronically administered drug.

3) **A single dose food effect study on the proposed commercial formulation.[Study-01-06-TL-322OPI-006]**
   - This is a randomized, open-label, single-dose, 2-sequence, 2-period crossover study in 24 healthy adult subjects.
   - The 90% CIs for the ratios (fed/fasted) of the LS means for AUC(0-24), AUC(0-tlqc), AUC(0-inf), and Cmax of alogliptin and of pioglitazone were within the 80% to 125% range, indicating no effect of food on total or peak exposures in subjects who received SYR-322-4833 (b)(4) 25 mg + 45 mg (APPENDIX 1).
   - Median Tmax increased by approximately 2 hours when SYR-322-4833 (b)(4) 25 mg + 45 mg were administered under fed conditions compared with administration under fasted conditions. The difference in Tmax between the 2 treatments was statistically significant (P<0.001); however, the sponsor claims that this difference is not considered to be clinically relevant as this is a chronically administered drug.

4) **Sponsor also submitted two addition bioequivalence studies. These studies use the FDC tablets but not the proposed commercial FDC tablets. [Study-01-06-TL-322OPI-005(C), 322OPI-102(C)**]
   - Study-01-06-TL-322OPI-005 and study 322OPI-102 were randomized, open-label, 4-sequence, 4-period crossover BE study in 68 and 83 healthy subjects, respectively.
   - Two other different FDC formulations, SYR-322-4833 (b)(4) [study 01-06-TL-322OPI-005(C)] and SYR-322-4833 (b)(4) tablets [study 322OPI-102(C)], were used in these BE studies. These two formulations were different than the formulation used in pivotal BE study.
   - These two FDC formulations, 12.5 mg + 15 mg tablets and FDC 25mg + 45mg tablets, failed to meet the standards for bioequivalence to the alogliptin 12.5 mg and pioglitazone 15 mg and alogliptin 25 mg and pioglitazone 45 mg individual tablets (APPENDIX 1).

Internal Comments:

- In this NDA submission sponsor is proposing 6 fix dose combinations of alogliptin/ pioglitazone (12.5/15, 12.5/30, 12.5/45, 25/15, 25/30, 25/45 mg/mg). Bioequivalence studies were carried out only for highest (25mg/45mg) and the lowest (12.5mg/15mg) fixed dose strength combinations.
- According to sponsor the dose proportionality was established previously for alogliptin and pioglitazone covering the range of the proposed dosage strengths of SRY-322-4833 (b) (4) FDC tablets. Based on these results the sponsor is requesting biowaiver for 4 doses that are not evaluated in the in vivo study. This biowaiver request will be reviewed by ONDQA.
- DSI inspection is requested for the pivotal BE study **322OPI-101**. The site details are as follows:

Clinical Site:

Phase 1 Site (b) (4)
Responsibilities: Phase 1 clinical services (b) (4)

MDS Pharma Services
621 Rose Street
Lincoln, NE 68502
402-437-1158

Analytical Site:

Pharmacokinetic Assays

Site 1:
Responsibilities: Bioanalytical laboratory for alogliptin
(b) (4)

Site 2:
Responsibilities: Bioanalytical laboratory for pioglitazone
(b) (4)

APPENDIX 1

Appendix 2 Summary of Clinical Biopharmaceutic Studies

Study No. Country Objective Design	Drug Lot No.	No. Subjects Entered/ Completed	Mean Age (Range) (yr)	Analyte	Dose (mg)	Dosing	Pharmacokinetic Parameters						
							LS Mean		Median	Arithmetic Mean		Ratio T/R-100 (90% CI))	
							AUC(0-inf)) (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	CL/F (L/hr)	AUC(0-inf)	Cmax
322OPI-005	Alo 12.5 mg 6E044	68/62	32.2 (20-54)	Alo (plasma)	12.5	Individual tablet	840.76	52.07	2.00	19.688	15.07398	96.31 (94.94, 97.70)	84.16 (80.93, 87.51)
United States	Pio 15 mg C12044					FDC	809.73	43.82	2.49	20.076	15.67970		
Bioequivalence	SYR-322-4833 (b) (4) (12.5 mg + 15 mg) Z6447031			Pio (serum)	15	Individual tablet	6006.68	550.24	2.01	9.643	2.57340	104.54 (100.79, 108.44)	124.02 (114.45, 134.39)
Randomized, open-label, 4-sequence, 4-period crossover	Alo 25 mg 6E047					FDC	6279.65	682.41	1.00	7.740	2.47063		
	Pio 45 mg A12114												
	SYR-322-4833 (b) (4) (25 mg + 45 mg) Z6448011			Alo (plasma)	25	Individual tablet	1642.13	116.37	2.00	18.437	15.41374	94.22 (92.96, 95.49)	85.31 (81.49, 89.30)
						FDC	1547.23	99.27	2.98	18.420	16.35181		
				Pio (serum)	45	Individual tablet	14361.00	1129.95	1.52	13.390	3.30294	77.63 (72.22, 83.43)	88.02 (80.00, 96.85)
						FDC	11147.96	994.60	1.02	12.359	4.50901		
322OPI-006	SYR-322-4833 (b) (4) (25 mg + 45 mg) Z644G027	24/23 16/15 M 8/8 F	28.4 (19-54)	Alo (plasma)	25	Fasted	1607.20	94.77	2.00	22.228	15.68149	101.43 (99.05, 103.87)	110.21 (101.61, 119.54)
United States						Fed	1630.19	104.44	3.00	21.607	15.44293		
Food-effect				Pio (serum)	45	Fasted	15696.40	1478.31	2.00	21.635	3.12054	96.90 (87.05, 107.87)	103.60 (90.49, 118.61)
Randomized, open-label, 2-sequence, 2-period, crossover						Fed	15210.31	1531.59	4.00	14.040	2.99844		

Appendix 2 Summary of Clinical Biopharmaceutic Studies (continued)

Study No. Country Objective Design	Drug Lot No.	No. Subjects Entered/ Completed	Mean Age (Range) (yr)	Analyte	Dose (mg)	Dosing	Pharmacokinetic Parameters						
							LS Mean		Median	Arithmetic Mean		Ratio T/R-100 (90% CI))	
							AUC(0-inf)) (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	CL/F (L/hr)	AUC(0-inf)	Cmax
322OPI-007 United States Relative bioavailability Randomized, open-label, 4-sequence, 4-period crossover	Alo 12.5 mg 6E044 Pio 15 mg A12190 SYR-322-4833 (b) (4) (12.5 mg + 15 mg) Z6449011 Alo 25 mg 6E047 Pio 45 mg A12115 SYR-322-4833 (b) (4) (25 mg + 45 mg) Z644A011	16/16 12/12 M 4/4 F	28.8 (19-51)	Alo (plasma)	12.5	Individual tablet	943.69	61.35	1.50	19.004	13.38827	97.89 (96.06, 99.76)	94.66 (86.48, 103.62)
						FDC	923.79	58.07	3.00	19.559	13.66701		
				Pio (serum)	15	Individual tablet	7159.39	635.85	2.50	7.634	2.13678	93.44 (88.53, 98.62)	99.74 (84.13, 118.25)
						FDC	6689.46	634.21	1.53	6.677	2.29403		
				Alo (plasma)	25	Individual tablet	1811.87	122.77	2.00	18.430	13.96326	96.82 (93.66, 100.08)	99.92 (90.54, 110.28)
						FDC	1754.18	122.67	1.50	18.865	14.41238		
				Pio (serum)	45	Individual tablet	17787.78	1383.51	3.00	13.278	2.56445	102.53 (93.39, 112.58)	97.60 (75.86, 125.57)
						FDC	18238.57	1350.28	3.00	10.640	2.57047		
322OPI-101 United States Bioequivalence Randomized, open-label, 4-sequence, 4-period, crossover	Alo 12.5 mg 6J080 Pio 15 mg C13008 SYR-322-4833 (b) (4) (12.5 mg + 25 mg) Z644B027 Alo 25 mg 6J082 Pio 45 mg A12951 SYR-322-4833 (b) (4) (25 mg + 45 mg) Z644G027	72/66 46/43 M 26/23 F	33.2 (19-55)	Alo (plasma)	12.5	Individual tablet	904.17	50.28	2.99	22.922	14.05944	100.06 (98.68, 101.46)	95.94 (91.83, 100.23)
						FDC	904.72	48.23	3.00	22.631	14.05582		
				Pio (serum)	15	Individual tablet	6429.75	626.25	1.50	9.818	2.43504	99.52 (96.58, 102.55)	97.76 (91.82, 104.08)
						FDC	6399.01	612.22	1.77	9.450	2.43563		
				Alo (plasma)	25	Individual tablet	1719.46	106.15	2.98	21.415	14.74178	98.56 (97.40, 99.74)	98.07 (93.33, 103.06)
						FDC	1694.76	104.10	2.50	21.288	14.95689		
				Pio (serum)	45	Individual tablet	15961.30	1303.92	2.00	25.705	2.96712	105.19 (98.19, 112.69)	97.90 (89.34, 107.28)
						FDC	16789.67	1276.53	3.00	19.884	2.86841		

Appendix 2 Summary of Clinical Biopharmaceutic Studies (continued)

Study No. Country Objective Design	Drug Lot No.	No. Subjects Entered/ Completed	Mean Age (Range) (yr)	Analyte	Dose (mg)	Dosing	Pharmacokinetic Parameters						
							LS Mean		Median	Arithmetic Mean		Ratio T/R-100 (90% CI))	
							AUC(0-inf)) (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	CL/F (L/hr)	AUC(0-inf)	Cmax
322OPI-102 United States Bioequivalence Randomized, open-label, 4-sequence, 4-period crossover	Alo 12.5 mg 6J080 Pio 15 mg A13263 SYR-322-4833 (b) (4) (12.5 mg + 15 mg) Z644H011 Alo 25 mg 6J082 Pio 45 mg C13281 SYR-322-4833 (b) (4) (25 mg + 45 mg) Z644J011	83/51	35.6 (18-55)	Alo (plasma)	12.5	Individual tablet	841.47	49.42	2.00	23.517	14.95244	97.08 (95.73, 98.45)	89.82 (85.47, 94.41)
						FDC	816.94	44.39	2.01	22.769	15.40681		
				Pio (serum)	15	Individual tablet	6445.58	613.07	1.50	9.689	2.41187	97.11 (93.19, 101.19)	113.90 (106.94, 121.32)
						FDC	6259.17	698.31	1.00	8.412	2.52586		
				Alo (plasma)	25	Individual tablet	1615.86	108.23	1.74	21.273	15.59315	96.67 (95.26, 98.09)	82.77 (77.80, 88.05)
						FDC	1562.00	89.58	2.96	21.126	16.16844		
				Pio (serum)	45	Individual tablet	15862.68	1198.11	1.50	19.448	2.93851	102.69 (95.65, 110.24)	116.64 (101.78, 133.68)
						FDC	16288.77	1397.49	1.00	17.266	2.88807		

Alo=alogliptin, F=female, M=male, Pio=pioglitazone (b) (4)
(a) Ratios and CIs are expressed as percentages.

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Ritesh Jain
6/4/2009 03:57:16 PM
BIOPHARMACEUTICS

Wei Qiu
6/8/2009 02:41:54 PM
BIOPHARMACEUTICS

ONDQA (Biopharmaceutics) Review

NDA:	22-426
Submission Date:	09/19/08
Product:	SYR-322-4833 (alogliptin/pioglitazone) tablets, 12.5/15mg, 12.5/30mg, 12.5/45mg, 25/15mg, 25/30mg and 25/45mg mg
Type of Submission:	Original NDA
Sponsor:	Takeda
Reviewer:	Tapash K. Ghosh, Ph.D.

Background:

SYR-322-4833 Tablets are round, biconvex film-coated tablets produced in six dosage strengths; 12.5mg+15mg, 12.5mg+30mg, 12.5mg+45mg, 25mg+15mg, 25mg+30mg and 25mg+45mg of alogliptin and pioglitazone, respectively. All strengths of the drug product have the same diameter and weight. The six strengths are distinguished by film color, by printing ink color, and by dose-specific imprinted markings on one side of the tablet. A description of the appearance of SYR-322-4833 Tablets is provided below.

12.5mg+15mg:	Pale yellow, round, biconvex, film-coated tablet with both "A/P" and "12.5/15" printed on one side
12.5mg+30mg:	Pale peach, round, biconvex, film-coated tablet with both "A/P" and "12.5/30" printed on one side
12.5mg+45mg:	Pale red, round, biconvex, film-coated tablet with both "A/P" and "12.5/45" printed on one side
25mg+15mg:	Yellow, round, biconvex, film-coated tablet with both "A/P" and "25/15" printed on one side
25mg+30mg:	Peach, round, biconvex, film-coated tablet with both "A/P" and "25/30" printed on one side
25mg+45mg:	Red, round, biconvex, film-coated tablet with both "A/P" and "25/45" printed on one side

SYR-322-4833 (b) (4) tablets were (b) (4) evaluated in an *in vivo* bioequivalence study against the individual tablets of the corresponding dosage strengths. When the results did not show the bioequivalence of pioglitazone in the fixed dose combination (FDC) tablet compared to the corresponding individual tablets, the development focus was shifted to SYR-322-4833 (b) (4) tablets, which ultimately became the proposed commercial product.

The (b) (4) tablets were designed with the goal of achieving bioequivalence to the corresponding individual tablets (b) (4) Subsequently, the 2 bracketing dosage strengths of tablets containing alogliptin and pioglitazone (12.5 mg + 15 mg and 25 mg + 45 mg) were manufactured for clinical study using the SYR-322-4833 (b) (4) formulation. These 2 strengths were introduced for use in clinical Study 322OPI-101 to evaluate the bioequivalence of alogliptin and pioglitazone when administered as an FDC product and as individual tablets of the corresponding dosage strengths. In this pivotal BE study 322OPI-101, the bioequivalencies of alogliptin and pioglitazone when dosed orally as individual tablets and as the proposed commercial formulation of the FDC product (SYR-322-4833 (b) (4)) were determined in a open-label, randomized, 4-sequence, 4-period crossover study in 72 healthy adult (=18 years of age) subjects with the lowest (alogliptin 12.5 mg + pioglitazone 15 mg) and highest (alogliptin 25 mg + pioglitazone 45 mg) proposed dosage strengths of SYR-322-4833 (b) (4) To bridge these 2 doses with the 4 intermediate doses (12.5 mg + 30 mg, 12.5 mg + 45 mg, 25 mg + 15 mg and 25 mg + 30 mg) that were not evaluated in this study, a comparative dissolution analysis (SYR-322-4833 /00115) was performed for each dosage strength. The phase 3 formulation of alogliptin, which is bioequivalent to the proposed commercial formulation of alogliptin, and the commercial formulation of pioglitazone (ACTOS®) were used in this clinical study.

Based on the above mentioned comparative dissolution analysis (SYR-322-4833 /00115), the sponsor requested biowaivers for the 4 intermediate doses (12.5 mg + 30 mg, 12.5 mg + 45 mg, 25 mg + 15 mg and 25 mg + 30 mg).

Recommendation:

- The release of both alogliptin and pioglitazone were evaluated using the proposed dissolution method, which has demonstrated discriminatory ability between different SYR-322-4833 formulations. The successful comparisons of both alogliptin and pioglitazone dissolution from each of the 6 tablet strengths demonstrate the similarity of the formulations, and justify biowaivers for the strengths of SYR-322-4833 (b) (4) tablets not directly evaluated in the pivotal bioequivalence study.

- The sponsor's proposed operating conditions for routine dissolution testing of SYR-322-4833 tablets is not acceptable from "rpm" point of view. The Agency recommended dissolution condition is described below:

Medium: 900 mL of pH 2.2 Sörensen buffer (without deaeration)
Apparatus 2
Paddle rotation speed: 50 rpm

- The sponsor's proposed Q values for Alogliptin (Q of (b) (4) in 15 minutes) is acceptable at the rpm of 50 rpm.

- The sponsor's proposed Q values for Pioglitazone should be changed from Q = (b) (4) to Q = (b) (4) in 30 minutes at the rpm of 50 rpm.

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. . _____

Review

Composition:

The compositions of the 6 SYR-322-4833 (b) (4) tablet formulations are provided in Table 1.a.

Table 1.a Composition of SYR-322-4833 (b) (4) Tablets

Component	Quantity per Tablet (mg)					
	12.5 mg+15 mg	12.5 mg+30 mg	12.5 mg+45 mg	25 mg+15 mg	25 mg+30 mg	25 mg+45 mg
						(b) (4)
Alogliptin benzoate (As the free base)	17 (12.5)	17 (12.5)	17 (12.5)	34 (25)	34 (25)	34 (25)
Mannitol						(b) (4)
Cellulose, microcrystalline						
Hydroxypropylcellulose						
Croscarmellose sodium						
Magnesium stearate						
(b) (4)						
Pioglitazone hydrochloride (As the free base)	16.53 (15)	33.06 (30)	49.59 (45)	16.53 (15)	33.06 (30)	49.59 (45)
Lactose monohydrate						(b) (4)
(b) (4)						
Film-Coating				(b) (4)		
Hypromellose (b) (4)						(b) (4)
Talc						
Titanium dioxide						
Iron oxide yellow (b) (4)						
Iron oxide red (b) (4)						
(b) (4						
Printing Ink				(b) (4)		
Printing ink Red A1						(b) (4)
Printing ink Gray F1						
(b) (4)						

Biostudy:

The results of the pivotal biostudy (3220PI-101) as reported by the sponsor are presented in the following Tables.

Table 2.b Pharmacokinetic Parameters of Alogliptin 12.5 mg and Pioglitazone 15 mg When Administered as Individual Tablets and as SYR-322-4833 (b) (4)

Analyte Parameter (units)	n	LS Mean: SYR-322-4833 (b) (4) (12.5 mg + 15 mg) (T)	LS Mean: Alogliptin 12.5 mg + Pioglitazone 15 mg (R)	Ratio T/R·100 (90% CI) (a)
Alogliptin (Plasma)				
AUC(0-tlqc) (ng·hr/mL)	68	826.84	824.23	100.32 (99.00, 101.65)
AUC(0-inf) (ng·hr/mL)	66	904.72	904.17	100.06, (98.68, 101.46)
Cmax (ng/mL)	68	48.23	50.28	95.94 (91.83, 100.23)
Tmax (hr) (b,c)	68	3.00	2.99	N/A
Pioglitazone (Serum)				
AUC(0-tlqc) (ng·hr/mL)	68	5707.70	5774.19	98.85 (95.42, 102.40)
AUC(0-inf) (ng·hr/mL)	59	6399.01	6429.75	99.52 (96.58, 102.55)
Cmax (ng/mL)	68	612.22	626.25	97.76 (91.82, 104.08)
Tmax (hr) (b,d)	68	1.77	1.50	N/A

Table 2.c Pharmacokinetic Parameters of Alogliptin 25 mg and Pioglitazone 45 mg

Analyte Parameter (units)	n	LS Mean: SYR-322-4833 (b) (4) (25 mg + 45 mg) (T)	LS Mean: Alogliptin 25 mg + Pioglitazone 45 mg (R)	Ratio T/R·100 (90% CI) (a)
Alogliptin (Plasma)				
AUC(0-tlqc) (ng·hr/mL)	67	1582.33	1601.99	98.77 (97.58, 99.98)
AUC(0-inf) (ng·hr/mL)	66	1694.76	1719.46	98.56 (97.40, 99.74)
Cmax (ng/mL)	68	104.10	106.15	98.07 (93.33, 103.06)
Tmax (hr) (b,c)	68	2.50	2.98	N/A
Pioglitazone (Serum)				
AUC(0-tlqc) (ng·hr/mL)	67	14978.78	14369.87	104.24 (98.62, 110.18)
AUC(0-inf) (ng·hr/mL)	47	16789.67	15961.30	105.19 (98.19, 112.69)
Cmax (ng/mL)	68	1276.53	1303.92	97.90 (89.34, 107.28)
Tmax (hr) (b,d)	68	3.00	2.00	N/A

According to the sponsor, the proposed FDC (b) (4) tablets met the standards for bioequivalence to the reference alogliptin 12.5 mg and pioglitazone 15 mg and alogliptin 25 mg and pioglitazone 45 mg individual tablets. (*For details refer to clinical pharmacology review*).

2. Development of Dissolution Conditions

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Tapash Ghosh
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BIOPHARMACEUTICS

Patrick Marroum
6/5/2009 05:07:51 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-426**	**Brand Name**	**TBD**
OCPB Division (I, II, III)	**DCP II**	**Generic Name**	**Alogliptin/Pioglitazone Fixed Dose Combination Tablets**
Medical Division	**DMEP**	**Drug Class**	
OCPB Reviewer	**Ritesh Jain, Ph.D.**	**Indication(s)**	**Treatment of Type-2 Diabetes (T2DM).**
OCPB Team Leader	**Sally Choe, Ph.D.**	**Dosage Form**	**Tablet; 25/15, 25/30, 25/45, 12.5/15, 12.5/30, 12.5/45 mg/mg**
		Dosing Regimen	**25mg/15mg /day through 12.5mg/45mg/day**
Date of Submission	**09/19/2008**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**06/5/2009**	**Sponsor**	**Takeda Global Research & Development Center, Inc.**
PDUFA Due Date	**07/22/2009**	**Priority Classification**	**S**
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	**X**	**1**		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	**X**	**3**		
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**1**		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**5**		

Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?	**X**	Yes it is filable
Comments sent to firm ?		
QBR questions (key issues to be considered)	1) Was bioequivalence demonstrated between the proposed to-be-marketed formulation for the intended commercial manufacture and the pivotal clinical trial formulation? 2) What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal type? 3) Was formulation effect demonstrated for this fixed dose combination product?	
Other comments or information not included above	**DSI inspection is requested for the pivotal BE study 322OPI-101**	
Primary reviewer Signature and Date	**Ritesh Jain, Ph.D.**	
Secondary reviewer Signature and Date	**Sally Choe, Ph.D.**	

Background:

- This is a New Drug Application (NDA) submission for alogliptin/pioglitazone fixed dose combination tablets.
- The sponsor is proposing 6 different fixed dose combinations of alogliptin/pioglitazone. The doses are (alogliptin/pioglitazone) 25mg/15mg, 25mg/30mg, 25mg/45mg, 12.5mg/15mg, 12.5 mg/30mg, and 12.5mg/45mg.
- Alogliptin is an orally active, selective, and potent inhibitor of dipeptidyl peptidase-4 (DPP-4) that is being developed by TGRD as a novel antihyperglycemic agent.
- An NDA for alogliptin (original NDA 22-271) was submitted on December 27, 2007 and is under review.
- Pioglitazone (ACTOS®) is a peroxisome proliferator-activated receptor-gamma (PPARγ) agonist that is a member of the thiazolidinedione (TZD) class of oral antihyperglycemic agents and has been commercially available since 1999.

Biopharmaceutics Studies:

In this NDA, the sponsor submitted 5 biopharmaceutics related studies. In the clinical studies the sponsor used the phase 3 formulation of alogliptin, which is bioequivalent to the proposed commercial formulation of alogliptin (NDA 22-271) and the commercial formulation of pioglitazone (ACTOS®) individually. The sponsor conducted following biopharmaceutics studies with the proposed commercial fixed dose combination (FDC) tablet to bridge the information between to be marketed product and the individual products used in the clinical studies.

1) **A pilot relative bioavailability study with the highest and lowest strength of proposed commercial (FDC) tablet and individual tablets of alogliptin and pioglitazone. [Study-01-06-TL-322OPI-007]**
   - Open label, randomized, 4-period, 4-sequence, crossover, pilot study in 16 healthy adult subjects.
   - Small-scale batches of the highest and lowest dosage strength of FDC formulation **(SYR-322-4833 (b) (4))** were evaluated: alogliptin 12.5 mg + pioglitazone 15 mg and alogliptin 25 mg + pioglitazone 45 mg.
   - The relative bioavailability of alogliptin and pioglitazone were similar when dosed as SYR-322-4833 (b) (4) (FDC) as compared to when dosed individually at both dosage strengths (See Appendix 1).

2) **A pivotal bioequivalence study with the highest and lowest strength of proposed commercial (FDC) tablet and individual tablets of alogliptin and pioglitazone. [Study-322OPI-101]**
   - Open label, randomized, 4-sequence, 4-period crossover study in 72 healthy subjects
   - In this study the highest and lowest dosage strength of FDC formulation (**SYR-322-4833** (b) (4)) were evaluated: alogliptin 12.5 mg + pioglitazone 15 mg and alogliptin 25 mg + pioglitazone 45 mg.
   - The 90% CIs for the ratios of the LS means for AUC (0-tlqc), AUC (0-inf), and Cmax values of both alogliptin and pioglitazone were within the 80% to 125% range (APPENDIX 1).

- No statistically significant differences for the median Tmax values for either alogliptin or pioglitazone were observed between the SYR-322-4833 (b) (4) (12.5 + 15 mg) tablet, and the alogliptin 12.5 mg and pioglitazone 15 mg individual tablets.
- A statistically significant difference between the SYR-322-4833 (b) (4) (25 + 45 mg) tablet and the individual alogliptin 25 mg and pioglitazone 45 mg tablets was observed for the median T_{max} value of pioglitazone ($P<0.001$) but not alogliptin ($P=0.830$). According to sponsor this difference is not considered clinically significant because SYR-322-4833 is a chronically administered drug.

3) **A single dose food effect study on the proposed commercial formulation.[Study-01-06-TL-322OPI-006]**
   - This is a randomized, open-label, single-dose, 2-sequence, 2-period crossover study in 24 healthy adult subjects.
   - The 90% CIs for the ratios (fed/fasted) of the LS means for AUC(0-24), AUC(0-tlqc), AUC(0-inf), and Cmax of alogliptin and of pioglitazone were within the 80% to 125% range, indicating no effect of food on total or peak exposures in subjects who received SYR-322-4833 (b) (4) 25 mg + 45 mg (APPENDIX 1).
   - Median Tmax increased by approximately 2 hours when SYR-322-4833 (b) (4) 25 mg + 45 mg were administered under fed conditions compared with administration under fasted conditions. The difference in Tmax between the 2 treatments was statistically significant ($P<0.001$); however, the sponsor claims that this difference is not considered to be clinically relevant as this is a chronically administered drug.

4) **Sponsor also submitted two addition bioequivalence studies. These studies use the FDC tablets but not the proposed commercial FDC tablets. [Study-01-06-TL-322OPI-005(C), 322OPI-102(C)]**
   - Study-01-06-TL-322OPI-005 and study 322OPI-102 were randomized, open-label, 4-sequence, 4-period crossover BE study in 68 and 83 healthy subjects, respectively.
   - Two other different FDC formulations, SYR-322-4833 (b) (4) [study 01-06-TL-322OPI-005(C)] and SYR-322-4833 (b) (4) tablets [study 322OPI-102(C)], were used in these BE studies. These two formulations were different than the formulation used in pivotal BE study.
   - These two FDC formulations, 12.5 mg + 15 mg tablets and FDC 25mg + 45mg tablets, failed to meet the standards for bioequivalence to the alogliptin 12.5 mg and pioglitazone 15 mg and alogliptin 25 mg and pioglitazone 45 mg individual tablets (APPENDIX 1).

Internal Comments:

- In this NDA submission sponsor is proposing 6 fix dose combinations of alogliptin/ pioglitazone (12.5/15, 12.5/30, 12.5/45, 25/15, 25/30, 25/45 mg/mg). Bioequivalence studies were carried out only for highest (25mg/45mg) and the lowest (12.5mg/15mg) fixed dose strength combinations.
- According to sponsor the dose proportionality was established previously for alogliptin and pioglitazone covering the range of the proposed dosage strengths of SRY-322-4833 (b) (4) FDC tablets. Based on these results the sponsor is requesting biowaiver for 4 doses that are not evaluated in the in vivo study. This biowaiver request will be reviewed by ONDQA.
- DSI inspection is requested for the pivotal BE study **322OPI-101**. The site details are as follows:

Clinical Site:

Phase 1 Site (b) (4)
Responsibilities: Phase 1 clinical services (b) (4)
MDS Pharma Services
621 Rose Street
Lincoln, NE 68502
402-437-1158

Analytical Site:

Pharmacokinetic Assays

Site 1:
Responsibilities: Bioanalytical laboratory for alogliptin
(b) (4)

Site 2:
Responsibilities: Bioanalytical laboratory for pioglitazone
(b) (4)

APPENDIX 1

Appendix 2 Summary of Clinical Biopharmaceutic Studies

Study No. Country Objective Design	Drug Lot No.	No. Subjects Entered/ Completed	Mean Age (Range) (yr)	Analyte	Dose (mg)	Dosing	Pharmacokinetic Parameters						
							LS Mean		Median	Arithmetic Mean		Ratio T/R·100 (90% CI)	
							AUC(0-inf)) (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	CL/F (L/hr)	AUC(0-inf)	Cmax
322OPI-005 United States Bioequivalence Randomized, open-label, 4-sequence, 4-period crossover	Alo 12.5 mg 6E044 Pio 15 mg C12044 SYR-322-4833 (b) (4) (12.5 mg + 15 mg) Z6447031 Alo 25 mg 6E047 Pio 45 mg A12114 SYR-322-4833 (b) (4) (25 mg + 45 mg) Z6448011	68/62	32.2 (20-54)	Alo (plasma)	12.5	Individual tablet	840.76	52.07	2.00	19.688	15.07398	96.31 (94.94, 97.70)	84.16 (80.93, 87.51)
						FDC	809.73	43.82	2.49	20.076	15.67970		
				Pio (serum)	15	Individual tablet	6006.68	550.24	2.01	9.643	2.57340	104.54 (100.79, 108.44)	124.02 (114.45, 134.39)
						FDC	6279.65	682.41	1.00	7.740	2.47063		
				Alo (plasma)	25	Individual tablet	1642.13	116.37	2.00	18.437	15.41374	94.22 (92.96, 95.49)	85.31 (81.49, 89.30)
						FDC	1547.23	99.27	2.98	18.420	16.35181		
				Pio (serum)	45	Individual tablet	14361.00	1129.95	1.52	13.390	3.30294	77.63 (72.22, 83.43)	88.02 (80.00, 96.85)
						FDC	11147.96	994.60	1.02	12.369	4.50901		
322OPI-006 United States Food-effect Randomized, open-label, 2-sequence, 2-period, crossover	SYR-322-4833 (b) (4) (25 mg + 45 mg) Z644G027	24/23 16/15 M 8/8 F	28.4 (19-54)	Alo (plasma)	25	Fasted	1607.20	94.77	2.00	22.228	15.68149	101.43 (99.05, 103.87)	110.21 (101.61, 119.54)
						Fed	1630.19	104.44	3.00	21.607	15.44293		
				Pio (serum)	45	Fasted	15696.40	1478.31	2.00	21.635	3.12054	96.90 (87.05, 107.87)	103.60 (90.49, 118.61)
						Fed	15210.31	1531.59	4.00	14.040	2.99844		

Appendix 2 Summary of Clinical Biopharmaceutic Studies (continued)

Study No. Country Objective Design	Drug Lot No.	No. Subjects Entered/ Completed	Mean Age (Range) (yr)	Analyte	Dose (mg)	Dosing	Pharmacokinetic Parameters						
							LS Mean		Median	Arithmetic Mean		Ratio T/R·100 (90% CI)	
							AUC(0-inf)) (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	CL/F (L/hr)	AUC(0-inf)	Cmax
322OPI-007 United States Relative bioavailability Randomized, open-label, 4-sequence, 4-period crossover	Alo 12.5 mg 6E044 Pio 15 mg A12190 SYR-322-4833 (b) (4) (12.5 mg + 15 mg) Z6449011 Alo 25 mg 6E047 Pio 45 mg A12115 SYR-322-4833 (b) (4) (25 mg + 45 mg) Z644A011	16/16 12/12 M 4/4 F	28.8 (19-51)	Alo (plasma)	12.5	Individual tablet	943.69	61.35	1.50	19.004	13.38827	97.89 (96.06, 99.76)	94.66 (86.48, 103.62)
						FDC	923.79	58.07	3.00	19.559	13.66701		
				Pio (serum)	15	Individual tablet	7159.39	635.85	2.50	7.634	2.13678	93.44 (88.53, 98.62)	99.74 (84.13, 118.25)
						FDC	6689.46	634.21	1.53	6.677	2.29403		
				Alo (plasma)	25	Individual tablet	1811.87	122.77	2.00	18.430	13.96326	96.82 (93.66, 100.08)	99.92 (90.54, 110.28)
						FDC	1754.18	122.67	1.50	18.865	14.41238		
				Pio (serum)	45	Individual tablet	17787.78	1383.51	3.00	13.278	2.56445	102.53 (93.39, 112.58)	97.60 (75.86, 125.57)
						FDC	18238.57	1350.28	3.00	10.640	2.57047		
322OPI-101 United States Bioequivalence Randomized, open-label, 4-sequence, 4-period, crossover	Alo 12.5 mg 6J080 Pio 15 mg C13008 SYR-322-4833 (b) (4) (12.5 mg + 25 mg) Z644B027 Alo 25 mg 6J082 Pio 45 mg A12951 SYR-322-4833 (b) (4) (25 mg + 45 mg) Z644G027	72/66 46/43 M 26/23 F	33.2 (19-55)	Alo (plasma)	12.5	Individual tablet	904.17	50.28	2.99	22.922	14.05944	100.06 (98.68, 101.46)	95.94 (91.83, 100.23)
						FDC	904.72	48.23	3.00	22.631	14.05582		
				Pio (serum)	15	Individual tablet	6429.75	626.25	1.50	9.818	2.43504	99.52 (96.58, 102.55)	97.76 (91.82, 104.08)
						FDC	6399.01	612.22	1.77	9.450	2.43563		
				Alo (plasma)	25	Individual tablet	1719.46	106.15	2.98	21.415	14.74178	98.56 (97.40, 99.74)	98.07 (93.33, 103.06)
						FDC	1694.76	104.10	2.50	21.288	14.95689		
				Pio (serum)	45	Individual tablet	15961.30	1303.92	2.00	25.705	2.96712	105.19 (98.19, 112.69)	97.90 (89.34, 107.28)
						FDC	16789.67	1276.53	3.00	19.884	2.86841		

Appendix 2 Summary of Clinical Biopharmaceutic Studies (continued)

Study No. Country Objective Design	Drug Lot No.	No. Subjects Entered/ Completed	Mean Age (Range) (yr)	Analyte	Dose (mg)	Dosing	Pharmacokinetic Parameters						
							LS Mean		Median	Arithmetic Mean		Ratio T/R·100 (90% CI))	
							AUC(0-inf)) (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	CL/F (L/hr)	AUC(0-inf)	Cmax
322OPI-102	Alo 12.5 mg 6J080	83/51	35.6 (18-55)										
United States	Pio 15 mg A13263												
Bioequivalence	SYR-322-4833 (b) (4)			Alo (plasma)	12.5	Individual tablet	841.47	49.42	2.00	23.517	14.95244	97.08 (95.73, 98.45)	89.82 (85.47, 94.41)
Randomized, open-label, 4-sequence, 4-period crossover	(12.5 mg + 15 mg) Z644H011					FDC	816.94	44.39	2.01	22.769	15.40681		
	Alo 25 mg 6J082												
	Pio 45 mg C13281												
	SYR-322-4833 (b) (4) (25 mg + 45 mg) Z644J011			Pio (serum)	15	Individual tablet	6445.58	613.07	1.50	9.689	2.41187	97.11 (93.19, 101.19)	113.90 (106.94, 121.32)
						FDC	6259.17	698.31	1.00	8.412	2.52586		
				Alo (plasma)	25	Individual tablet	1615.86	108.23	1.74	21.273	15.59315	96.67 (95.26, 98.09)	82.77 (77.80, 88.05)
						FDC	1562.00	89.58	2.96	21.126	16.16844		
				Pio (serum)	45	Individual tablet	15862.68	1198.11	1.50	19.448	2.93851	102.69 (95.65, 110.24)	116.64 (101.78, 133.68)
						FDC	16288.77	1397.49	1.00	17.266	2.88807		

Alo=alogliptin, F=female, M=male, Pio=pioglitazone (b) (4)
(a) Ratios and CIs are expressed as percentages.

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/s/

Ritesh Jain
11/5/2008 10:13:07 AM
BIOPHARMACEUTICS

Sally Choe
11/5/2008 10:44:50 PM
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