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RESEARCH**

APPLICATION NUMBER:

203414Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

ONDQA BIOPHARMACEUTICS REVIEW ADDENDUM

| | |
|---|---|
| NDA#: | 203-414 |
| Submission Date: | November 22, 2011 |
| Brand Name: | ---- |
| Generic Name: | SYR-322MET (alogliptin/metformin HCl) |
| Formulation: | Fixed Dose Combination Tablets |
| Strength: | 12.5/500 mg and 12.5/1000 mg |
| Sponsor: | Takeda Global Research & Development Center |
| Biopharmaceutics Reviewer: | Houda Mahayni, Ph.D. |
| QbD Liaison and Secondary Signature: | Sandra Suarez Sharp, Ph.D. |
| Biopharmaceutics Lead (Acting): | Richard T. Lostritto, Ph.D. |
| Submission Type: | Original NDA |

INTRODUCTION

This is an addendum to the original Biopharmaceutics review for NDA 203-414 signed off in DARRTS on July 27, 2012, in which it recommended revisions to both the dissolution and disintegration acceptance criteria. ONDQA's CMC and Biopharmaceutics Teams met on July 31, 2012, to discuss the impact of the Biopharmaceutics comments on the QbD effort and the proposed design space. During the meeting it was decided to convey the following comments to the Applicant and to schedule a teleconference to discuss them. The comments were conveyed on August 1, 2012 and the TCON was held on August 2, 2012.

1. *The following dissolution criterion is recommended for both components of your proposed product:*

- $Q = \text{(b)(4)}$ in 15 min

This recommendation is based on the performance of all clinical and stability batches and on the discriminating power of the dissolution method (b)(4)

Revise the dissolution acceptance criteria for alogliptin and metformin accordingly and submit the updated specifications table for your drug product as soon as possible.

- *All disintegration results obtained on SYR-322MET biobatches support a disintegration acceptance criterion (b)(4). Therefore, we consider that your proposed disintegration acceptance criterion (b)(4) is permissive. However, in acknowledgment of all your efforts invested as part of the QbD implementation for your product, FDA is willing to apply a risk based approach and accept the proposed acceptance criterion for*

disintegration (b) (4) provided you commit to implement the following as part of your internal quality control system:

- o perform comparative dissolution testing using the f_2 factor (if feasible) (b) (4)

(b) (4)

This Addendum documents the discussion that took place at the teleconference and agreements reached which are summarized as follows:

- The Applicant accepted to revise the dissolution acceptance criterion to $Q =$ (b) (4) in 15 minutes and to submit a revised sheet of specifications reflecting these changes by August 6, 2012.
- FDA accepted the Applicant's proposal to use disintegration testing in lieu of dissolution testing as a release test for SYR-322MET tablets.
- The FDA took a risk-base approach on accepting the Applicant's proposed disintegration acceptance criterion (b) (4)

However, FDA recommended to the Applicant to consider initiating an investigation to determine the need for implementing, within their internal quality control system, dissolution testing at release for those batches which disintegration values are higher than (b) (4) min

REVIEWER'S COMMENTS

The discussion that took place during the teleconference included the following points:

1. The Applicant agreed to revise the dissolution acceptance criterion for both components (alogliptin and metformin HCl) to $Q =$ (b) (4) in 15 minutes and committed to update the dissolution acceptance criterion to reflect the agreed upon specification of $Q =$ (b) (4) in 15 minutes by August 6, 2012. For reference, Table 1 and Table 2 reflect the specification before revision for the two strengths proposed for marketing.

Table 1: Specification for SYR-322MET Tablets (12.5/500 mg)

| Test item | Acceptance criteria | Testing Requirement | Analytical procedure |
|---|---|---------------------|----------------------------------|
| Appearance | Pale yellow oblong film-coated tablets with "12.5/500" debossed on one side and "322M" debossed on the other side | Release / Stability | SYR-322MET-12178 |
| Identification | (b) (4) | | |
| A. HPLC Retention Time | | Release | SYR-322MET-12179 |
| B. Ultraviolet Spectrum Alogliptin | | Release | SYR-322MET-12180 |
| Metformin hydrochloride | | Release | |
| Disintegration* | | Release | USP <701> |
| Dissolution (%) Alogliptin | | Stability | SYR-322MET-12184 |
| Metformin hydrochloride | | Stability | |
| Related Substances Alogliptin Total Any individual | | Release / Stability | SYR-322MET-12181 |
| Metformin hydrochloride Total (b) (4) | | Release / Stability | SYR-322MET-12182 |
| Others (Individual) | | | |
| Content Uniformity Alogliptin | | Release | SYR-322MET-12183 |
| Metformin hydrochloride | | Release | |
| Assay (%) Alogliptin | | Release / Stability | SYR-322MET-12185 |
| Metformin hydrochloride | | Release / Stability | |
| (b) (4) | | | |

Table 2: Specification for SYR-322MET Tablets (12.5/1000 mg)

| Test item | Acceptance criteria | Testing Requirement | Analytical procedure |
|---|--|---------------------|----------------------------------|
| Appearance | Pale yellow oblong film-coated tablets with "12.5/1000" debossed on one side and "322M" debossed on the other side | Release / Stability | SYR-322MET-12178 |
| Identification | (b) (4) | | |
| A. HPLC Retention Time | | Release | SYR-322MET-12179 |
| B. Ultraviolet Spectrum Alogliptin | | Release | SYR-322MET-12180 |
| Metformin hydrochloride | | Release | |
| Disintegration* | | Release | USP <701> |
| Dissolution (%) Alogliptin | (b) (4) | Stability | SYR-322MET-12184 |
| Metformin hydrochloride | | Stability | |
| Related Substances Alogliptin Total Any individual | | Release / Stability | SYR-322MET-12181 |
| Metformin hydrochloride Total | | Release / Stability | SYR-322MET-12182 |
| Others (Individual) | | | |
| Content Uniformity Alogliptin | (b) (4) | Release | SYR-322MET-12183 |
| Metformin hydrochloride | | Release | |
| Assay (%) Alogliptin | | Release / Stability | SYR-322MET-12185 |
| Metformin hydrochloride | Release / Stability | | |

(b) (4)

2. Summary of discussion points related to disintegration

○ The FDA made the following statements:

- The rationale for recommending to *perform comparative dissolution testing using the f_2 factor (if feasible)* (b) (4)

is as follows:

(b) (4)

○ The Applicant made the following points:

(b) (4)

- The proposed disintegration acceptance criterion (b) (4) is not permissive.
- Table 84 shows (b) (4) both development scale and full scale batches.
- Table 88 and 89 shows the correlation is maintained in the registration stability batches.
- Although there was not a good correlation between disintegration and dissolution (b) (4) all the batches tested with disintegration values (b) (4) met the dissolution criterion of $Q = (b) (4)$ at 15 min.

Table 84

(b) (4)

(b) (4)



Table 88

(b) (4)

A large rectangular area is completely redacted with a solid grey fill, obscuring the content of Table 88.

Table 89

(b) (4)

A large rectangular area is completely redacted with a solid grey fill, obscuring the content of Table 89.

Table 84, Table 88, and Table 89 are copied from Section 3.2.P.2.3 (Pharmaceutical Development: Manufacturing Process Development, pages 93 and 97 respectively).

FDA took a risk-base approach on accepting the Applicant's proposed disintegration acceptance criterion

(b) (4)

However, if this acceptance criterion is not met for some batches (e.g. upon stability), FDA requested the Applicant to initiate an investigation within their internal quality control system.

RECOMMENDATION

Based on the review of the overall Biopharmaceutics information provided in this NDA submission* and the discussion and agreement reached during the teleconference held on August 2, 2012, between FDA and Takeda's representatives, NDA 203-414 for SYR-322MET (alogliptin/metformin HCl) Fixed Dose Combination Tablets is recommended for APPROVAL from the Biopharmaceutics perspective.

**Refer to the Original Biopharmaceutics review in DARRTS for NDA 203-414 by Dr. Houda Mahayni, dated July 27, 2012.*

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cc: DARRTS CC List: RLostritto; ADorantes

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

/s/

HOUDA MAHAYNI
08/06/2012

SANDRA SUAREZ
08/06/2012

CLINICAL PHARMACOLOGY REVIEW

| | |
|-------------------------------|---|
| NDA | 203414 |
| Submission Date: | November 22, 2011 |
| Brand Name: | Kazano |
| Generic Name: | Alogliptin benzoate and metformin hydrochloride fixed dose combination |
| Formulation/Strength: | Tablet 12.5 mg/500 mg, 12.5 mg/1000 mg |
| OCP Reviewer: | Zhihong Li, Ph.D. |
| OCP Team Leader: | Immo Zadezensky, Ph.D. (acting) |
| OCP Division: | Division of Clinical Pharmacology 2 |
| OND Division: | Division of Metabolism and Endocrinology Products |
| Sponsor: | Takeda Global R & D Center, Inc. |
| Submission Type; Code: | 505(b)(2), standard review |
| Dosing regimen: | BID with food |
| Indication: | As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. |

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1 EXECUTIVE SUMMARY

Takeda Global Research & Development Center, Inc. (hereafter Takeda/the sponsor) submitted a New Drug Application (NDA) 203414 for SYR-322MET (Alogliptin/Metformin fixed dose combination) tablets, 12.5 mg/500 mg and 12.5 mg/1000 mg for the treatment of Type 2 Diabetes (T2DM). The proposed indication is “as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus”. The active components of SYR-322MET are alogliptin and metformin. Alogliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor developed by Takeda as an antihyperglycemic agent. A New Drug Application (NDA) for alogliptin (NDA 22-271) is currently under review by the Agency. Metformin is a commercially available and approved biguanide that is indicated as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

This application is submitted by the sponsor as a 505(b)(2) NDA. The sponsor is referring to Glucophage (NDA 20357) by Bristol-Myers Squibb Company.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the NDA 203414 for SYR-322MET submitted on November 22, 2011. The clinical pharmacology information submitted under this NDA is acceptable. The results of the Office of Scientific Investigation (OSI) inspection on pivotal bioequivalence (BE) trial are acceptable.

1.2 PHASE IV COMMITMENTS

None.

1.3 CLINICAL PHARMACOLOGY SUMMARY

The clinical development of SYR-322MET includes 3 phase 3 studies and 4 phase 1 studies. The phase 3 studies included two 26-week studies designed to assess the efficacy and safety of alogliptin in combination with metformin for the treatment of T2DM (MET-302 and 322-008) and a 52-week study designed to assess the efficacy and safety of alogliptin in combination with metformin and pioglitazone for the treatment of T2DM (OPI-004). The phase 1 studies included:

- 1 bioequivalence study (MET-101),
- 1 food-effect study (MET-102),
- 1 drug-interaction study with alogliptin and metformin (322-005), and
- 1 pharmacokinetic study that assessed QD versus BID dosing (322-101).

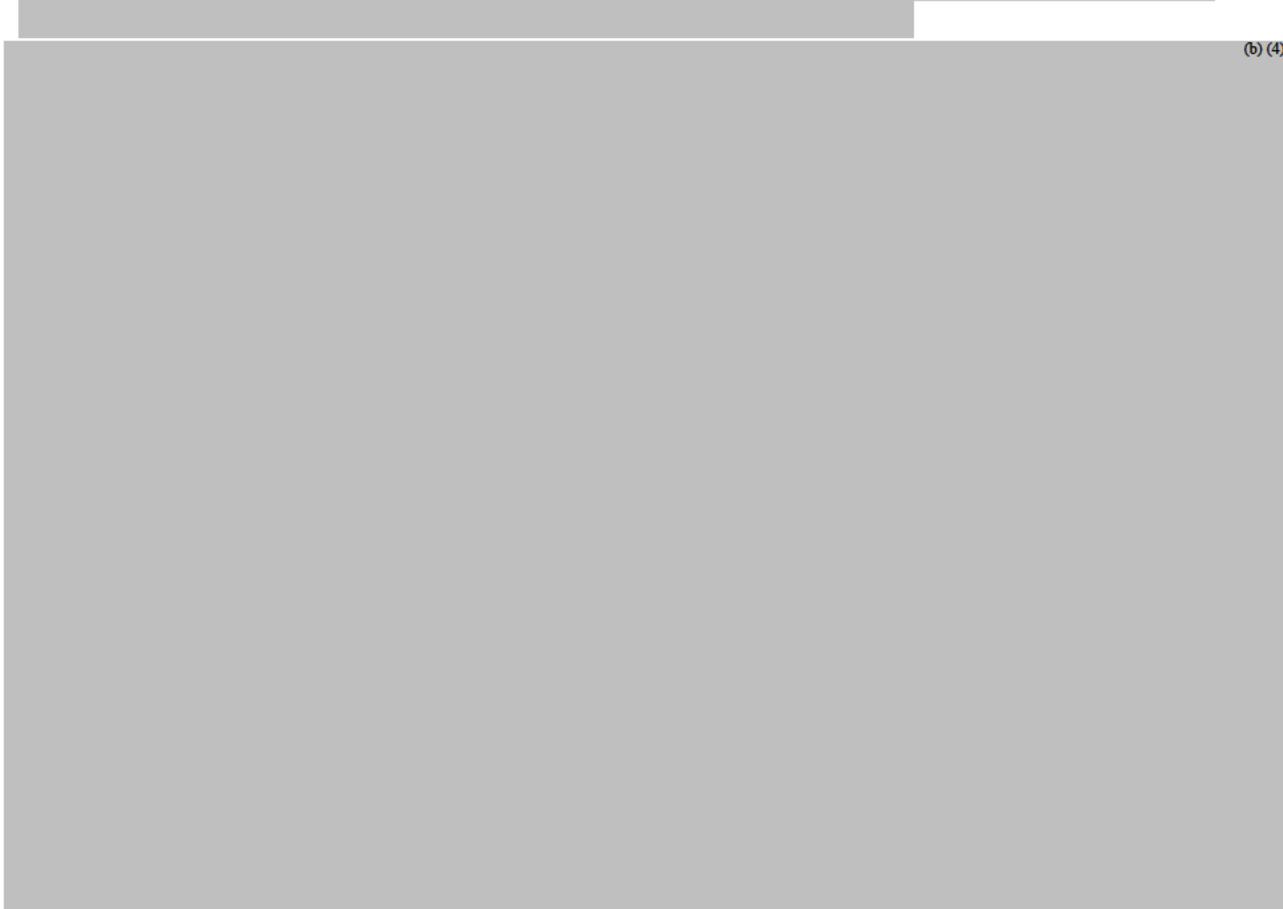
Bioequivalence (MET-101):

 (b) (4)
commercial formulation of the 2 proposed dosage strengths of SYR-322MET (12.5 mg + 500 mg and 12.5 mg + 1000 mg), met the standards for bioequivalence to coadministered individual alogliptin and metformin hydrochloride (HCl) tablets in Study MET-101. The summary of the statistical evaluations are provided in Tables 1 to 4. At the request of the Division of Metabolism

and Endocrinology Products (DMEP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspections of the clinical and analytical portions of study SYR-322MET_101. Following the inspections, DBGC reviewers recommend that the data from clinical and analytical portions of study SYR- 322MET_101 can be accepted for further agency review.

Table 1

(b) (4)



(b) (4)

Table 2

(b) (4)

(b) (4)

Table 3 Pharmacokinetic Parameters of Alogliptin 12.5 mg and Metformin 500 mg after Administration as Individual Tablets and as Combination Tablets

| Analyte Parameter (units) | Arithmetic Mean (%CV) | | LS Mean | | |
|---------------------------------|-------------------------------|------------------------------------|-------------------------------|------------------------------------|---------------------------------|
| | Treatment E N=47 (Test) | Treatment F N=45 (Reference) | Treatment E N=47 (Test) | Treatment F N=45 (Reference) | Ratio (T/R)·100 (90% CI) (a) |
| Alogliptin (Plasma) | | | | | |
| AUC(0-tlqc) (ng·hr/mL) | 888.9 (15.02) | 900.0 (14.30) | 873.2 | 886.6 | 98.50 (96.57, 100.46) |
| AUC(0-inf) (ng·hr/mL) | 947.9 (15.35) | 962.4 (14.92) | 931.9 | 947.6 | 98.34 (96.38, 100.35) |
| Cmax (ng/mL) | 74.719 (21.84) | 76.620 (29.92) | 72.796 | 73.828 | 98.60 (93.27, 104.24) |
| Tmax (hr) (b) | 3.00 (1.00-4.05) | 3.00 (1.00-6.00) | 3.000 | 3.000 | -- |
| Metformin (Plasma) | | | | | |
| AUC(0-tlqc) (ng·hr/mL) | 8229.4 (24.10) | 8329.3 (25.64) | 7951.6 | 7943.0 | 100.11 (96.03, 104.36) |
| AUC(0-inf) (ng·hr/mL) (c) | 8453.3 (24.42) | 8542.1 (23.37) | 8163.0 | 8298.9 | 98.36 (94.40, 102.50) |
| Cmax (ng/mL) | 1241.298 (26.64) | 1249.200 (27.80) | 1194.732 | 1182.679 | 101.02 (95.98, 106.33) |
| Tmax (hr) (b) | 2.00 (0.50-4.05) | 2.00 (1.00-4.02) | 2.00 | 2.00 | -- |

%CV=percent coefficient of variation.

E = 1 SYR-322MET FDC (12.5 mg + 500 mg) tablet (test treatment).

F = 1 alogliptin 12.5 mg tablet administered with 1 metformin 500 mg tablet (reference treatment).
 AUC(0-tlqc): AUC from time 0 to last quantifiable concentration, or AUC(0-last).

(a) Ratios and CIs are presented as percentages.

(b) Tmax is reported as median (minimum, maximum).

(c) N=43 for Treatment E and N=39 for Treatment F.

Table 4 Pharmacokinetic Parameters of Alogliptin 12.5 mg and Metformin 1000 mg after Administration as Individual Tablets and as a Combination Tablet

| Analyte Parameter (units) | Arithmetic Mean (%CV) | | LS Mean | | Ratio (T/R)-100 (90% CI) (a) |
|---------------------------------|-------------------------------|------------------------------------|-------------------------------|------------------------------------|---------------------------------|
| | Treatment G N=44 (Test) | Treatment H N=46 (Reference) | Treatment G N=44 (Test) | Treatment H N=46 (Reference) | |
| Alogliptin (Plasma) | | | | | |
| AUC(0-tlqc) (ng·hr/mL) | 862.8 (15.26) | 854.1 (16.99) | 851.1 | 840.2 | 101.29 (99.29, 103.33) |
| AUC(0-inf) (ng·hr/mL) | 928.5 (15.75) | 924.0 (17.31) | 914.1 | 907.8 | 100.69 (98.66, 102.77) |
| Cmax (ng/mL) | 67.984 (25.75) | 66.357 (23.26) | 65.801 | 64.838 | 101.49 (95.94, 107.35) |
| Tmax (hr) (b) | 2.00 (1.00-6.03) | 2.00 (1.00-6.00) | 2.00 | 2.00 | -- |
| Metformin (Plasma) | | | | | |
| AUC(0-tlqc) (ng·hr/mL) | 12963.7 (26.25) | 13521.2 (25.24) | 12253.1 | 12813.4 | 95.63 (91.69, 99.73) |
| AUC(0-inf) (ng·hr/mL) (c) | 13182.7 (25.25) | 14022.0 (25.26) | 12556.8 | 13253.9 | 94.74 (90.71, 98.95) |
| Cmax (ng/mL) | 2014.318 (25.41) | 2121.304 (26.32) | 1906.439 | 2004.868 | 95.09 (90.29, 100.14) |
| Tmax (hr) (b) | 2.00 (1.00-4.00) | 2.00 (1.00-3.02) | 2.00 | 2.00 | -- |

G = 1 SYR-322MET FDC (12.5 mg + 1000 mg) tablet (test treatment).

H = 1 alogliptin 12.5 mg tablet administered with 1 metformin 1000 mg tablet (reference treatment).

AUC(0-tlqc): AUC from time 0 to last quantifiable concentration, or AUC(0-last).

(a) Ratios and CIs are presented as percentages.

(b) Tmax is reported as median (minimum, maximum).

(c) N=35 for Treatment G and N=40 for Treatment H.

Food Effect (MET-102):

As shown in Table 5, food did not affect total exposure (as AUC(0-last) and AUC(0-inf)) to either alogliptin or metformin when administered as the highest proposed dosage strength (12.5 mg + 1000 mg) of the commercial formulation of SYR-322MET (MET-102). Food also did not have any clinically meaningful effect on peak exposure to alogliptin (a 13% decrease was observed, but the lower bound of the 90% CI of the LS mean for Cmax was only slightly below 80% [79.90%]) nor did it have a statistically significant effect (P=0.263) on Tmax of alogliptin when it was administered as SYR-322MET; however, compared with administration of SYR-322MET without food, peak exposure to metformin decreased 28% and Tmax of metformin was delayed by 1.5 hours when SYR-322MET was administered with food. The 90% CI for the ratio of the LS mean for Cmax of metformin that was associated with this decrease in peak exposure was below the 80% to 125% range (66.53%, 77.15%), and the change in Tmax was statistically significant (P<0.001).

Table 5 Plasma Pharmacokinetic Parameters of Alogliptin and Metformin Following Administration of an SYR-322MET 12.5 mg + 1000 mg Tablet under Fed and Fasted Conditions

| Analyte Parameter (units) | N (T) | N (R) | Geometric Means | | Ratio T/R-100 (90% CI) (a) |
|------------------------------|----------|----------|--|---|-------------------------------|
| | | | SYR-322MET 12.5 mg + 1000 mg Fed (T) | SYR-322MET 12.5 mg + 1000 mg Fasted (R) | |
| Alogliptin | | | | | |
| AUC(0-tlqc) (ng·hr/mL) | 24 | 24 | 810.49 | 832.32 | 97.38 (92.27, 102.77) |
| AUC(0-inf) (ng·hr/mL) | 24 | 23 | 878.02 | 917.01 | 95.75 (91.52, 100.18) |
| Cmax (ng/mL) | 24 | 24 | 56.16 | 64.67 | 86.85 (79.90, 94.39) |
| Tmax (hr) (b,c) | 24 | 24 | 2.75 | 2.50 | N/A |
| Metformin | | | | | |
| AUC(0-tlqc) (ng·hr/mL) | 24 | 24 | 12573.39 | 13624.16 | 92.29 (85.64, 99.45) |
| AUC(0-inf) (ng·hr/mL) | 22 | 23 | 12637.16 | 13798.21 | 91.59 (84.63, 99.12) |
| Cmax (ng/mL) | 24 | 24 | 1509.23 | 2106.59 | 71.64 (66.53, 77.15) |
| Tmax (hr) (b,d) | 24 | 24 | 4.00 | 2.50 | N/A |

N/A=not applicable, T=test treatment, R=reference treatment.

AUC(0-tlqc): AUC from time 0 to last quantifiable concentration, or AUC(0-last).

(a) Ratios and CIs are presented as percentages.

(b) Tmax is presented as the median.

(c) p=0.263.

(d) p<0.001.

The results for alogliptin are consistent with the results of food-effect studies with alogliptin monotherapy tablets (single doses of 12.5 to 100 mg) wherein food had no effect on exposure of alogliptin (alogliptin NDA 22-271, Study 322-026). The labeling for metformin states that peak and total exposure decreased 40% and 25%, respectively, and Tmax was delayed 35 minutes when a single 850 mg dose of metformin HCl was administered with food. Although food appears to decrease and delay absorption of metformin, the prescribing information for metformin recommends that metformin be dosed with food to reduce gastrointestinal side-effects. Therefore, alogliptin and metformin were dosed with food in the pivotal phase 3 study (MET-302), and it will be recommended that SYR-322MET be administered with food.

Dosing Regimen (322-101):

QD doses of alogliptin were used in the pivotal monotherapy studies (NDA 22-271); the prescribing information for metformin recommends that metformin be administered in divided doses. Therefore, SYR-322MET was developed for BID dosing and Study 322-101 was conducted to evaluate the pharmacokinetics and pharmacodynamics of alogliptin when dosed BID compared with QD dosing. Both daily exposure (AUC(0-24)) of alogliptin and DPP-4 inhibition (as AUEC(0-24), E0, and E24) were similar when alogliptin was dosed BID and QD. In addition, in the phase 3 study MET-302, alogliptin 12.5 mg BID dosing demonstrated similar reductions in HbA1c compared to alogliptin 25 mg QD (see Statistics review dated 7/17/2012 in DARRTS for details), thus supporting the rationale for BID dosing. Based on these results, alogliptin and metformin were administered BID in the phase 3 study (MET-302), and BID dosing is acceptable for SYR-322MET.

Study 322-005 was reviewed in NDA 22-271, no clinical significant drug-drug interaction was

observed when alogliptin and metformin were coadministered. For details, see NDA 22-271 clinical pharmacology review in DARRTS dated 1/18/2012 and 3/7/2012.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Drug substance: alogliptin benzoate and metformin hydrochloride

SYR-322MET is a fixed-dose combination (FDC) product; the active components of SYR-322MET are alogliptin benzoate (SYR-322) and metformin hydrochloride.

The chemical structures of alogliptin and metformin are illustrated in Figure 1.

Figure 1 Chemical Structures of Alogliptin and Metformin

| | Structure | Molecular Formula | Molecular Weight (free base) |
|-------------------------|-----------|--------------------------------------|------------------------------|
| Alogliptin benzoate | | $C_{18}H_{21}N_5O_2 \cdot C_7H_6O_2$ | 339.39 |
| Metformin hydrochloride | | $C_4H_{11}N_5 \cdot HCl$ | 165.62 |

Alogliptin benzoate is a non-hygroscopic white to off-white crystalline solid. The compound is sparingly soluble in water and in aqueous buffers ranging from pH 3 to 11. ^{(b) (4)}

Metformin hydrochloride is a hygroscopic white crystalline powder. It is freely soluble in water, slightly soluble in alcohol, and practically insoluble in acetone, ether, and chloroform. ^{(b) (4)}

Drug product: SYR-322MET tablets

SYR-322MET tablets are oblong, (b) (4) film-coated tablets (b) (4) (b) (4) 12.5mg+500mg, and 12.5mg+1000mg of alogliptin and metformin hydrochloride, respectively. All (b) (4) were developed as potential commercial formulations (b) (4) distinguished by size, film color, and debossed markings.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Alogliptin is a potent, selective inhibitor of dipeptidyl peptidase-4 (DPP-4) activity that has been developed as a treatment for T2DM. DPP-4 is the primary enzyme involved in the degradation of at least 2 incretin hormones released from the gut in response to nutrient ingestion: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Incretin hormones exert important effects on pancreatic islet β -cells to stimulate glucose-dependent insulin secretion and regulate β -cell proliferation and cytoprotection. Inhibition of DPP-4 activity thereby augments glucose-stimulated insulin secretion, resulting in reductions in glycemia. Alogliptin does not inhibit other DPPs or related proteases.

Metformin hydrochloride is a member of the biguanide class of antihyperglycemic agents, improves glucose tolerance in patients with T2DM by lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

2.1.3 What are the proposed dosage and route of administration?

Two SYR-322MET doses are available: 12.5 mg alogliptin/500 mg metformin HCl and 12.5 mg alogliptin/1000 mg metformin HCl.

SYR-322MET should be taken twice daily with food with gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin.

Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 25 mg alogliptin and 2000 mg metformin HCl.

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 clinical development of SYR-322MET includes 3 phase 3 studies and 4 phase 1 studies. The phase 3 studies included two 26-week studies designed to assess the efficacy and safety of alogliptin in combination with metformin for the treatment of T2DM (MET-302 and 322-008) and a 52-week study designed to assess the efficacy and safety of alogliptin in combination with metformin and pioglitazone for the treatment of T2DM (OPI-004). The phase 1 studies included 1 bioequivalence study (MET-101), 1 food-effect study (MET-102), 1 drug-interaction study with alogliptin and metformin (322-005), and 1 pharmacokinetic study that assessed QD versus BID dosing (322-101). The key design features of these studies were summarized in Table 6.

Table 6 Design Features of the Clinical Pharmacology and Clinical Studies

| Study No. (abbreviation) No. of Centers–Country Study Start-End Dates | Study Design Primary Objective (Endpoint) | Population (randomized) (a) Gender (n[%]) Race (n[%]) (b) Mean Age (min-max) | Treatment Duration | Treatment (dosed/completed) (c) |
|---|--|--|---|--|
| 5.3.1.1 Bioavailability Study Reports | | | | |
| SYR-322MET_102 (MET-102) 1-US 07Jan10–12Feb10 | Phase 1, open-label, randomized, single site, 2- period crossover Food effect | 24 healthy subjects 13 (54.2%) Men, 11 (45.8%) Women 22 (91.7%) W, 2 (8.3%) B 35.2 (20-53) years | 1 day in each period with a 7-day washout | FDC 12.5/1000 mg BID (24/24) fasted FDC 25/1000 mg BID (24/24) fed Total (24/24) |
| 5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports | | | | |
| SYR-322MET_101 (MET-101) 1-US 05May09–15Jul09 | Phase 1, open-label, randomized, 2-cohort, single- center, 4-sequence, 4-period crossover Bioequivalence | 96 healthy subjects <u>Cohort 1:</u> 27 (56.3%) Men, 21 (43.8%) Women 35 (72.9%) W, 8 (16.7%) B, 4 (8.3%) A, 1 (2.1%) NH or OPI 30.2 (19-54) years <u>Cohort 2:</u> 22 (45.8%) Men, 26 (54.2%) Women 36 (75.0%) W, 8 (16.7%) B, 3 (6.3%) NH or OPI, 1 (2.1%) AI or AN 27.9 (19-51) years | 4 single doses separated by a 7-day washout | <u>Cohort 1:</u> FDC 6.25/500 mg BID ALO 6.25 mg+MET 500 mg BID FDC 6.25/1000 mg BID ALO 6.25 mg+MET 1000 mg BID Total (48/45) <u>Cohort 2:</u> FDC 12.5/500 mg BID ALO 12.5 mg+MET 500 mg BID FDC 12.5/1000 mg BID ALO 12.5 mg+MET 1000 mg BID Total (48/42) |
| 5.3.3.1 Healthy Subject Pharmacokinetic and Initial Tolerability Study Reports | | | | |
| SYR-322-101 (322-101) 1-US 27Apr07–09Jun07 | Phase 1 open-label, multiple- dose, randomized, 2-period crossover PK of QD vs BID dosing | 28 healthy subjects 20 (71.4%) Men, 8 (28.6%) Women 8 (28.6%) W, 2 (7.1%) MR, 20 (71.4%) B, 1 (3.6%) AI or AN 1 (3.6%) NH or OPI 31.7 (19-54) years | 7 days in each period with a 7-day washout | ALO 12.5 mg BID and ALO 25 mg QD (28/24) |

| Study No. (abbreviation) No. of Centers–Country Study Start-End Dates | Study Design Primary Objective (Endpoint) | Population (randomized) (a) Gender (n[%]) Race (n[%]) (b) Mean Age (min-max) | Treatment Duration | Treatment (dosed/completed) (c) |
|---|--|--|---|---|
| 5.3.3.4 Extrinsic Factor Pharmacokinetic Study Reports | | | | |
| SYR-322-005 (322-005) 1-US 07Apr05–01Jun05 | Phase 1, randomized, open-label, 2-phase, single-dose (2-period–crossover), and multiple-dose (3-period crossover) Effect of food on PK and DDI: MET and cimetidine | 36 healthy subjects 20 (55.6%) Men, 16 (44.4%) Women 31 (86.1%) W, 4 (11.1%) B, 1 (2.8%) AI 30.8 (19-47) years | 1 day in each period for food effect with a 96-hour washout; 6 days in each period for DDI with a 96-hour washout | <u>Food effect phase</u> ALO 100 mg fasted (36/36) ALO 100 mg fed (36/36) <u>DDI phase (MET arm)</u> ALO 100 mg QD, MET 1000 mg BID, and ALO 100 mg QD + MET 1000 mg BID (17/16) <u>DDI phase (cimetidine arm)</u> ALO 100 mg QD, cimetidine 400 mg QD, and ALO 100 mg QD + cimetidine 400 mg QD (18/18) Total (36/34) |
| 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication | | | | |
| SYR-322MET_302 (MET-302) 219-14 countries 16Nov09-30Jun11 | Phase 3, multicenter, randomized, double-blind, placebo-controlled Efficacy (HbA1c) and safety | 784 subjects with T2DM 374 (47.7%) Men, 410 (52.3%) Women 561 (71.6%) W, 143 (18.2%) A, 37 (4.7%) B, 41 (5.2%) AI or AN, 1 (0.1%) NH or OPI, 1 (0.1%) M 53.5 (22-80) years | 26 weeks | Placebo (106/74) A12.5 BID (110/71) A25 QD (112/89) M500 BID (109/94) M1000 BID (111/95) A12.5+M500 BID (106/92) A12.5 +M1000 BID (114/94) Total (768/609) (d) |
| SYR-322-MET-008 (322-008) 115-15 countries 10Mar06–12Jun07 | Phase 3, randomized, double-blinded, placebo-controlled, 3-treatment arm design Efficacy (HbA1c) and safety | 527 subjects with T2DM being treated with MET alone 265 (50.3%) Men, 262 (49.7%) Women 408 (77.4%) W, 49 (9.3%) O, 42 (8.0%) A, 24 (4.6%) B, 3 (0.6%) AI or AN, 1 (0.2%) NH or OPI 54.7 (22-80) years | 26 weeks | MET+ALO 12.5 mg (213/176) MET+ALO 25 mg (207/165) MET+PBO (104/72) Total (524/413) |
| 01-06-TL-322OPI-004 (OPI-004) 235-17 countries 30Jan07–05Jun09 | Phase 3, randomized, multicenter, double-blinded, 2-treatment arm Efficacy (HbA1c) and safety | 803 subjects with T2DM and inadequate glycemic control on MET (≥1500 mg or MTD) and PIO 30 mg 389 (48.4%) Women, 414 (51.6%) Men 498 (62.0%) W, 157 (19.6%) A, 77 (9.6%) B, 67 (8.3%) O, 2 (0.2%) NH or OPI, 2 (0.2%) AI or AN 55.1 (25-80) years | 52 weeks | MET+ALO 25+PIO 30 mg (404/283) MET+PIO 45 mg (399/243) Total (803/526) |

2.2.2 What is the relative bioavailability of SYR-322MET compared to the individual components?

See Individual Study Review on study SYR-322MET_101 for details.

(b) (4)
commercial formulation of the 2 proposed dosage strengths of SYR-322MET (12.5 mg + 500 mg and 12.5 mg + 1000 mg), met the standards for bioequivalence to coadministered individual alogliptin and metformin hydrochloride (HCl) tablets.

2.2.3 What is the effect of food on the proposed fixed dose combination?

See Individual Study Review on study SYR-322MET_102 for details.

Food did not affect total exposure (as AUC(0-last) and AUC(0-inf)) to either alogliptin or metformin when administered as the highest proposed dosage strength (12.5 mg + 1000 mg) of the commercial formulation of SYR-322MET (MET-102). Food also did not have any clinically meaningful effect on peak exposure to alogliptin (a 13% decrease was observed, but the lower bound of the 90% CI of the LS mean for C_{max} was only slightly below 80% [79.90%]) nor did it have a statistically significant effect (P=0.263) on T_{max} of alogliptin when it was administered as SYR-322MET; however, compared with administration of SYR-322MET without food, peak exposure to metformin decreased 28% and T_{max} of metformin was delayed by 1.5 hours when SYR-322MET was administered with food. The 90% CI for the ratio of the LS mean for C_{max} of metformin that was associated with this decrease in peak exposure was below the 80% to 125% range (66.53%, 77.15%), and the change in T_{max} was statistically significant (P<0.001).

The results for alogliptin are consistent with the results of food-effect studies with alogliptin monotherapy tablets (single doses of 12.5 to 100 mg) wherein food had no effect on exposure to alogliptin (alogliptin NDA 22-271, Study 322-026). The labeling for metformin states that peak and total exposure decreased 40% and 25%, respectively, and T_{max} was delayed 35 minutes when a single 850 mg dose of metformin HCl was administered with food. Although food appears to decrease and delay absorption of metformin, the prescribing information for metformin recommends that metformin be dosed with food to reduce gastrointestinal side-effects. Therefore, alogliptin and metformin were dosed with food in the pivotal phase 3 study (MET-302), and it will be recommended that SYR-322MET be administered with food.

2.2.4 Is the dosing regimen supported by the PK study?

See Individual Study Review on study SYR-322_101 and study SYR-322MET_302 for details.

QD doses of alogliptin were used in the pivotal monotherapy studies (NDA 22-271); the prescribing information for metformin recommends that metformin be administered in divided doses. Therefore, SYR-322MET was developed for BID dosing and Study 322-101 was conducted to evaluate the pharmacokinetics and pharmacodynamics of alogliptin when dosed BID compared with QD dosing. In this study, both daily exposure (AUC(0-24)) to alogliptin and DPP-4 inhibition (as AUEC(0-24), E0, and E24) were similar when alogliptin was dosed BID

and QD. In addition, in the phase 3 study MET-302, alogliptin 12.5 mg BID dosing demonstrated similar reductions in HbA1c compared to alogliptin 25 mg QD, thus supporting the rationale for BID dosing (see Statistics review dated 7/17/2012 in DARRTS for details). Based on these results, alogliptin and metformin were administered BID in the phase 3 study (MET_302), and BID dosing is acceptable for SYR-322MET.

2.3 INTRINSIC/EXTRINSIC FACTORS

The detailed intrinsic/extrinsic factors information of alogliptin can be founded in NDA 22-271 which was reviewed separately (Clinical Pharmacology review dated 1/18/2012 and 3/7/2012 in DARRTS). Metformin intrinsic/extrinsic factors information can be found in the prescribing information.

2.4 ANALYTICAL SECTION

2.4.1 Are the analytical methods appropriately validated?

At the request of the Division of Metabolism and Endocrinology Products (DMEP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspections of the clinical and analytical portions of study SYR-322MET_101. Following the inspections, DBGC reviewers recommend that the data from clinical and analytical portions of study SYR- 322MET_101 can be accepted for further agency review.

Bioanalytical Method for Alogliptin and M-I in Human Plasma (Method LCMS 307.4 version 1.00, 1.01, 1.02, 1.03, and 1.04)

A liquid chromatography with tandem mass spectrometry (LC/MS/MS) method (LCMS307.4 v1.00 method) for the quantification of alogliptin and its metabolite M-I (*N*-desmethyl alogliptin) in human K3EDTA plasma was validated (b) (4). The QC statistics for the Method LCMS307.4 v1.00 validation are presented in Table 7.

Table 7 QC Statistics for Method LCMS307.4 v1.00

| Analyte | Accuracy (a) | Precision (%CV) |
|------------|----------------|-----------------|
| Alogliptin | -1.79 to 3.13 | 4.53 to 9.26 |
| M-I | -0.134 to 8.04 | 4.73 to 12.9 |

(a) Expressed as % difference relative to theoretical concentrations.

The validation report was amended to include long-term frozen storage stability data (LCMS307.4 addendum 1). The method was further modified to truncate the standard curve range to an LLOQ of 1.00 ng/mL and 0.100 ng/mL for alogliptin and M-I, respectively; and an upper limit of quantitation (ULOQ) of 250 ng/mL and 25.0 ng/mL for alogliptin and M-I, respectively. The matrix additive was also changed to dipotassium EDTA (LCMS307.4 v1.04 method). This method was used to support Studies 322MET_101, 322MET_102 and 322_101. The revalidation data are located in Addendum 2 (LCMS307.4 addendum 2).

The QC statistics for the Method LCMS307.4 v1.04 validation are presented in Table 8.

Table 8 QC Statistics for Method LCMS307.4 v1.04

| Analyte | Accuracy (a) | Precision (%CV) |
|------------|---------------|-----------------|
| Alogliptin | -1.94 to 2.88 | 0.457 to 3.96 |
| M-I | -13.7 to 1.83 | 1.36 to 5.74 |

(a) Expressed as % difference relative to theoretical concentrations.

Bioanalytical Method for Alogliptin and M-I in Human Urine (Method LCMS 307.6 version 1.00, 1.01, and 1.02)

An LC/MS/MS method (LCMS307.6 v1.00 method) for the quantification of alogliptin and its metabolite M-I in human urine was validated (b)(4). The QC statistics for the LCMS307.6 v1.00 validation are presented in Table 9.

Table 9 QC Statistics for Method LCMS307.6 v1.00

| Analyte | Accuracy (a) | Precision (%CV) |
|------------|---------------|-----------------|
| Alogliptin | -6.22 to 1.79 | 2.60 to 5.37 |
| M-I | -3.32 to 2.36 | 2.33 to 6.79 |

(a) Expressed as % difference relative to theoretical concentrations.

Bioanalytical Method for Metformin in Human Plasma (Method LCMS 153 V 1.00)

An LC/MS/MS method (Method LCMS 153.5 V 1.00) for the quantification of metformin in human K2EDTA plasma was validated (b)(4). The QC statistics for the LCMS153.5 validation are presented in Table 10.

Table 10 QC Statistics for Method LCMS 153.5 V 1.00

| Analyte | Accuracy (a) | Precision (%CV) |
|-----------|---------------|-----------------|
| Metformin | -3.37 to 2.47 | 3.03 to 6.02 |

(a) Expressed as % difference relative to theoretical concentrations.

A partial validation was conducted (b)(4) to support the use of heparin as the anticoagulant (LCMS 153). This method, LCMS 153 V 1.00, was used to support Studies 322MET_101 and 322MET_102. The QC statistics for the LCMS153 validation are presented in Table 11.

Table 11 QC Statistics for Method LCMS 153 V 1.00

| Analyte | Accuracy (a) | Precision (%CV) |
|-----------|---------------|-----------------|
| Metformin | -3.26 to 3.74 | 3.95 to 9.69 |

(a) Expressed as % difference relative to theoretical concentrations.

3 DETAILED LABELING RECOMMENDATIONS

A decision on the approval for NDA 22-271 for alogliptin is pending at the time of this review.

Thus, no detailed labeling discussion will be included in this review for the FDC. A separate memo will be drafted once a final decision for NDA 22-271 is reached.

4 APPENDICES

4.1 INDIVIDUAL STUDY REVIEW

4.1.1 SYR-322MET_101: An Open-Label, Randomized, 2-Cohort, 4-Sequence, 4-Period Crossover Study to Determine the Bioequivalence of Alogliptin 6.25 mg and 12.5 mg and Metformin 500 mg and 1000 mg When Administered as Individual Tablets and as a Fixed-Dose Combination Tablet

Objectives:

Primary Objective: The primary objective of this study was to determine the bioequivalence of alogliptin and immediate-release metformin when administered as individual tablets and as an FDC product.

The following 4 doses of the FDC product will be evaluated:

- Alogliptin 6.25 mg + metformin 500 mg.
- Alogliptin 6.25 mg + metformin 1000 mg.
- Alogliptin 12.5 mg + metformin 500 mg.
- Alogliptin 12.5 mg + metformin 1000 mg.

Secondary Objective: The secondary objective of this study was to evaluate the safety and tolerability of alogliptin and metformin when administered as individual tablets and as an FDC product.

Study design:

This was a single-center, open-label, randomized, 2-cohort, 4-sequence, 4-period crossover study. A schematic of study design is shown in Figure 2.

Ninety-six healthy male or female subjects, aged 18 to 55, inclusive, were planned for enrollment. Subjects were randomized in the order in which they are enrolled into the study. The first 48 eligible subjects were assigned to Cohort 1. Once Cohort 1 was completely enrolled, the following eligible 48 subjects were assigned to Cohort 2. Within each Cohort, subjects were equally randomized to 1 of 4 treatment sequences in a 1:1:1:1 ratio. A washout interval of 7 days (beginning immediately after dosing on Day 1 of Periods 1-3) separated the doses of each study period, which is >5 half-lives of alogliptin or metformin.

Figure 2 Schematic of Study Design

| Pretreatment Period(a) | | Randomization | Treatment Period 1(a) | | Treatment Period 2(a) | | Treatment Period 3(a) | | Treatment Period 4(a) | | |
|--------------------------|------------------------|---------------|-----------------------|----------|-----------------------|----------|-----------------------|----------|-----------------------|----------|----------------------|
| Screening Days -28 to -2 | Check-in Day -1 | | Day 1 Dosing | Days 2-7 | Day 1 Dosing | Days 2-7 | Day 1 Dosing | Days 2-7 | Day 1 Dosing | Days 2-3 | Final Visit/ET Day 4 |
| Cohort 1 (n=48) | Sequence I (n=12) | A | WO | D | WO | B | WO | C | WO | | |
| | Sequence II (n=12) | B | | A | | C | | D | | | |
| | Sequence III (n=12) | C | | B | | D | | A | | | |
| | Sequence IV (n=12) | D | | C | | A | | B | | | |
| Cohort 2 (n=48) | Sequence I (n=12) | E | WO | H | WO | F | WO | G | WO | | |
| | Sequence II (n=12) | F | | E | | G | | H | | | |
| | Sequence III (n=12) | G | | F | | H | | E | | | |
| | Sequence IV (n=12) | H | | G | | E | | F | | | |

A = 1 SYR-322MET FDC (6.25 mg + 500 mg) tablet (test treatment).

B = 1 alogliptin 6.25 mg tablet administered with 1 metformin 500 mg tablet (reference treatment).

C = 1 SYR-322MET FDC (6.25 mg + 1000 mg) tablet (test treatment).

D = 1 alogliptin 6.25 mg tablet administered with 1 metformin 1000 mg tablet (reference treatment).

E = 1 SYR-322MET FDC (12.5 mg + 500 mg) tablet (test treatment).

F = 1 alogliptin 12.5 mg tablet administered with 1 metformin 500 mg tablet (reference treatment).

G = 1 SYR-322MET FDC (12.5 mg + 1000 mg) tablet (test treatment).

H = 1 alogliptin 12.5 mg tablet administered with 1 metformin 1000 mg tablet (reference treatment).

WO = washout.

(a) Subjects were admitted to the clinic on Day -1 of Treatment Period 1 only and Day 7 for Periods 1-3 and were discharged from the clinic on Day 4 after the completion of all scheduled procedures.

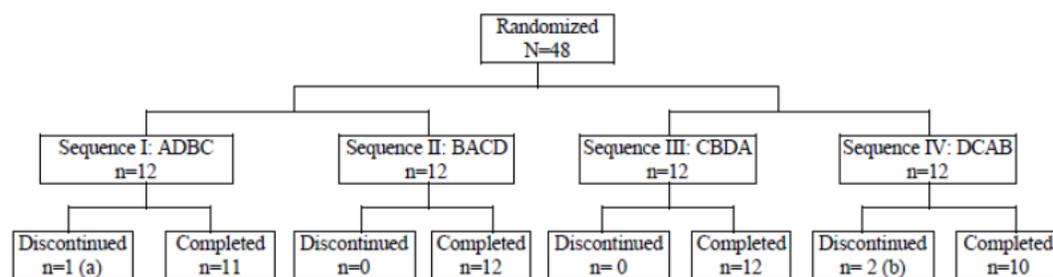
PK evaluations:

PK blood samples (3 mL for alogliptin and 4 mL for metformin) were collected starting on Day 1 within 15 minutes 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 period.

Disposition of Subjects

In Cohort 1, 45 subjects completed the study and 3 subjects prematurely discontinued study drug (1 for an adverse event and 2 due to “other” reasons). The disposition of subjects by sequence group is shown in Figure 3 for Cohort 1.

Figure 3 Disposition of Subjects: Cohort 1



A = 1 SYR-322MET FDC (6.25 mg + 500 mg) tablet (test treatment).

B = 1 alogliptin 6.25 mg tablet administered with 1 metformin 500 mg tablet (reference treatment).

C = 1 SYR-322MET FDC (6.25 mg + 1000 mg) tablet (test treatment).

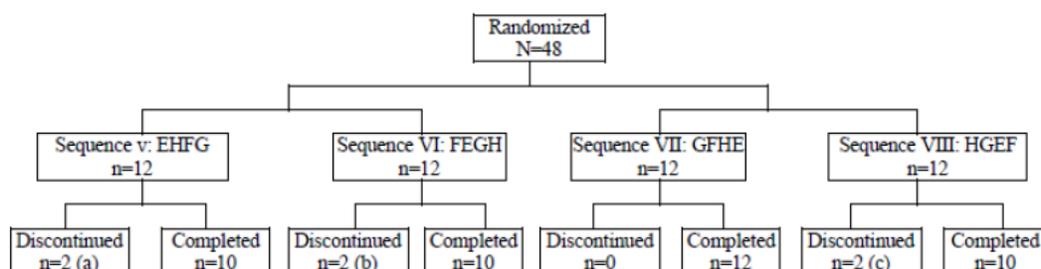
D = 1 alogliptin 6.25 mg tablet administered with 1 metformin 1000 mg tablet (reference treatment).

(a) Reason for discontinuation was “other” (principal investigator’s discretion).

(b) Reasons for discontinuation were adverse event and “other” (principal investigator’s discretion).

In Cohort 2, 42 subjects completed the study and 6 subjects prematurely discontinued study drug (1 for an adverse event, 3 due to a major protocol violation, 1 for “other” reasons, and 1 voluntary withdrew). The disposition of subjects by sequence group is shown in Figure 4 for Cohort 2.

Figure 4 Disposition of Subjects: Cohort 2



E = 1 SYR-322MET FDC (12.5 mg + 500 mg) tablet (test treatment).

F = 1 alogliptin 12.5 mg tablet administered with 1 metformin 500 mg tablet (reference treatment).

G = 1 SYR-322MET FDC (12.5 mg + 1000 mg) tablet (test treatment).

H = 1 alogliptin 12.5 mg tablet administered with 1 metformin 1000 mg tablet (reference treatment).

(a) Reasons for discontinuation were major protocol deviations (2 subjects).

(b) Reasons for discontinuation were major protocol deviation and adverse event.

(c) Reasons for discontinuation were voluntary withdrawal and “other” (principal investigator’s discretion).

Study results:

(b) (4)

Figure 5

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Table 12

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Figure 6

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Table 13

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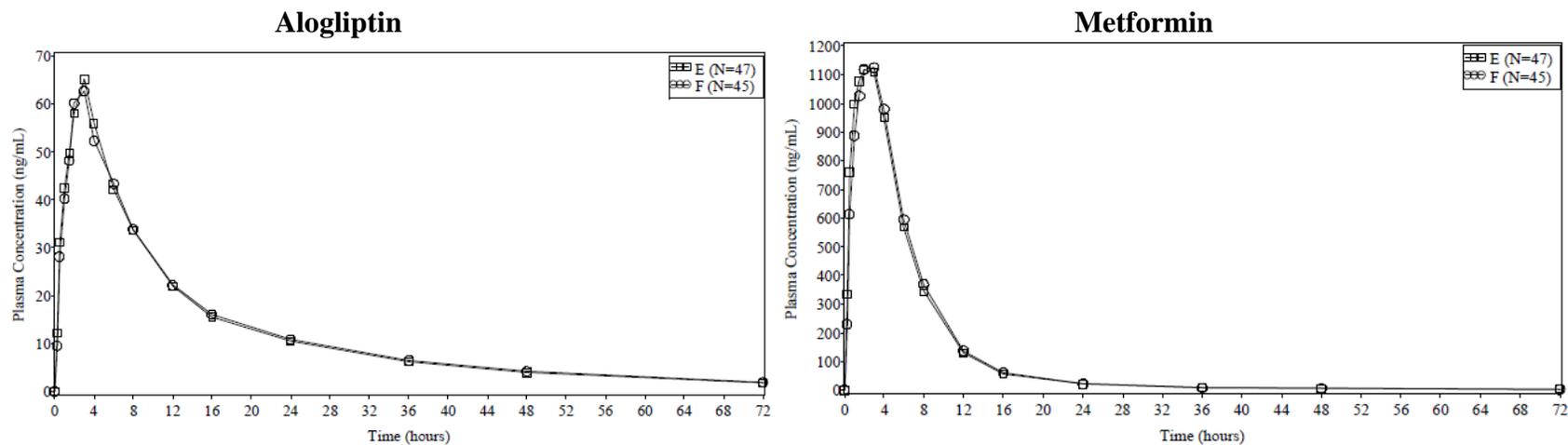
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Mean plasma concentrations of alogliptin and metformin following administration of an SYR-322MET 12.5 mg + 500 mg tablet and individual alogliptin 12.5 mg and metformin HCl 500 mg tablets are presented in Figure 7. Plasma pharmacokinetic parameters of alogliptin and metformin following administration of an SYR-322MET 12.5 mg + 500 mg tablet and individual alogliptin 12.5 mg and metformin HCl 500 mg tablets and are presented in Table 14.

Figure 7 Mean Plasma Concentrations of Alogliptin and Metformin vs Time Following Administration of an SYR-322MET 12.5 mg + 500 mg Tablet and Individual Alogliptin 12.5 mg and Metformin HCl 500 mg Tablets



E = 1 SYR-322MET FDC (12.5 mg + 500 mg) tablet (test treatment).

F = 1 alogliptin 12.5 mg tablet administered with 1 metformin 500 mg tablet (reference treatment).

Table 14 Pharmacokinetic Parameters of Alogliptin 12.5 mg and Metformin 500 mg after Administration as Individual Tablets and as Combination Tablets

| Analyte Parameter (units) | Arithmetic Mean (%CV) | | LS Mean | | |
|---------------------------------|-------------------------------|------------------------------------|-------------------------------|------------------------------------|---------------------------------|
| | Treatment E N=47 (Test) | Treatment F N=45 (Reference) | Treatment E N=47 (Test) | Treatment F N=45 (Reference) | Ratio (T/R)·100 (90% CI) (a) |
| Alogliptin (Plasma) | | | | | |
| AUC(0-tlqc) (ng·hr/mL) | 888.9 (15.02) | 900.0 (14.30) | 873.2 | 886.6 | 98.50 (96.57, 100.46) |
| AUC(0-inf) (ng·hr/mL) | 947.9 (15.35) | 962.4 (14.92) | 931.9 | 947.6 | 98.34 (96.38, 100.35) |
| Cmax (ng/mL) | 74.719 (21.84) | 76.620 (29.92) | 72.796 | 73.828 | 98.60 (93.27, 104.24) |
| Tmax (hr) (b) | 3.00 (1.00-4.05) | 3.00 (1.00-6.00) | 3.000 | 3.000 | -- |
| Metformin (Plasma) | | | | | |
| AUC(0-tlqc) (ng·hr/mL) | 8229.4 (24.10) | 8329.3 (25.64) | 7951.6 | 7943.0 | 100.11 (96.03, 104.36) |
| AUC(0-inf) (ng·hr/mL) (c) | 8453.3 (24.42) | 8542.1 (23.37) | 8163.0 | 8298.9 | 98.36 (94.40, 102.50) |
| Cmax (ng/mL) | 1241.298 (26.64) | 1249.200 (27.80) | 1194.732 | 1182.679 | 101.02 (95.98, 106.33) |
| Tmax (hr) (b) | 2.00 (0.50-4.05) | 2.00 (1.00-4.02) | 2.00 | 2.00 | -- |

%CV=percent coefficient of variation.

E = 1 SYR-322MET FDC (12.5 mg + 500 mg) tablet (test treatment).

F = 1 alogliptin 12.5 mg tablet administered with 1 metformin 500 mg tablet (reference treatment).

AUC(0-tlqc): AUC from time 0 to last quantifiable concentration, or AUC(0-last).

(a) Ratios and CIs are presented as percentages.

(b) Tmax is reported as median (minimum, maximum).

(c) N=43 for Treatment E and N=39 for Treatment F.

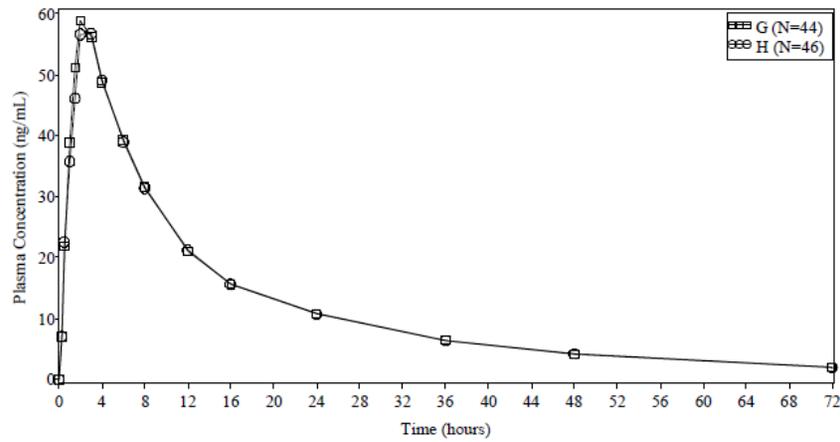
The 90% CIs for the ratios of the LS means for the AUC(0-last), AUC(0-inf), and Cmax values of both alogliptin and metformin were within the 80% to 125% bioequivalence range. Therefore, the SYR-322MET 12.5 mg + 500 mg tablet met the standards for bioequivalence to the individual alogliptin 12.5 mg and metformin 500 mg tablets.

No statistically significant differences in the median Tmax values for either alogliptin or metformin were observed between the SYR-322MET 12.5 mg + 500 mg tablet and the individual alogliptin 12.5 mg and metformin 500 mg tablets.

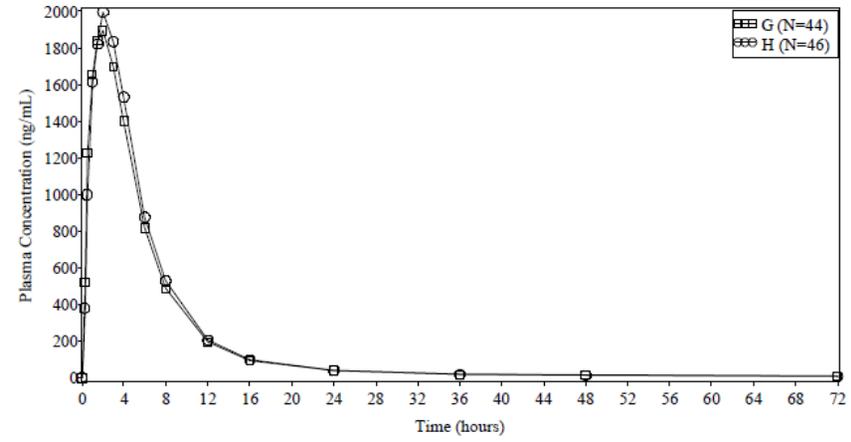
Mean plasma concentrations of alogliptin and metformin following administration of an SYR-322MET 12.5 mg + 1000 mg tablet and individual alogliptin 12.5 mg and metformin HCl 1000 mg tablets are presented in Figure 8. Plasma pharmacokinetic parameters of alogliptin and metformin following administration of an SYR-322MET 12.5 mg + 1000 mg tablet and individual alogliptin 12.5 mg and metformin 1000 mg HCl tablets are presented in Table 15.

Figure 8 Mean Plasma Concentrations of Alogliptin and Metformin vs Time Following Administration of an SYR-322MET 12.5 mg + 1000 mg Tablet and Individual Alogliptin 12.5 mg and Metformin HCl 1000 mg Tablets

Alogliptin



Metformin



G = 1 SYR-322MET FDC (12.5 mg + 1000 mg) tablet (test treatment).

H = 1 alogliptin 12.5 mg tablet administered with 1 metformin 1000 mg tablet (reference treatment).

Table 15 Pharmacokinetic Parameters of Alogliptin 12.5 mg and Metformin 1000 mg after Administration as Individual Tablets and as a Combination Tablet

| Analyte Parameter (units) | Arithmetic Mean (%CV) | | LS Mean | | |
|---------------------------------|-------------------------------|------------------------------------|-------------------------------|------------------------------------|---------------------------------|
| | Treatment G N=44 (Test) | Treatment H N=46 (Reference) | Treatment G N=44 (Test) | Treatment H N=46 (Reference) | Ratio (T/R)·100 (90% CI) (a) |
| Alogliptin (Plasma) | | | | | |
| AUC(0-tlqc) (ng·hr/mL) | 862.8 (15.26) | 854.1 (16.99) | 851.1 | 840.2 | 101.29 (99.29, 103.33) |
| AUC(0-inf) (ng·hr/mL) | 928.5 (15.75) | 924.0 (17.31) | 914.1 | 907.8 | 100.69 (98.66, 102.77) |
| Cmax (ng/mL) | 67.984 (25.75) | 66.357 (23.26) | 65.801 | 64.838 | 101.49 (95.94, 107.35) |
| Tmax (hr) (b) | 2.00 (1.00-6.03) | 2.00 (1.00-6.00) | 2.00 | 2.00 | -- |
| Metformin (Plasma) | | | | | |
| AUC(0-tlqc) (ng·hr/mL) | 12963.7 (26.25) | 13521.2 (25.24) | 12253.1 | 12813.4 | 95.63 (91.69, 99.73) |
| AUC(0-inf) (ng·hr/mL) (c) | 13182.7 (25.25) | 14022.0 (25.26) | 12556.8 | 13253.9 | 94.74 (90.71, 98.95) |
| Cmax (ng/mL) | 2014.318 (25.41) | 2121.304 (26.32) | 1906.439 | 2004.868 | 95.09 (90.29, 100.14) |
| Tmax (hr) (b) | 2.00 (1.00-4.00) | 2.00 (1.00-3.02) | 2.00 | 2.00 | -- |

G = 1 SYR-322MET FDC (12.5 mg + 1000 mg) tablet (test treatment).

H = 1 alogliptin 12.5 mg tablet administered with 1 metformin 1000 mg tablet (reference treatment).

AUC(0-tlqc): AUC from time 0 to last quantifiable concentration, or AUC(0-last).

(a) Ratios and CIs are presented as percentages.

(b) Tmax is reported as median (minimum, maximum).

(c) N=35 for Treatment G and N=40 for Treatment H.

The 90% CIs for the ratios of the LS means for the AUC(0-last), AUC(0-inf), and Cmax values of both alogliptin and metformin were within the 80% to 125% bioequivalence range. Therefore, the SYR-322MET 12.5 mg + 1000 mg tablet met the standards for bioequivalence to the individual alogliptin 12.5 mg and metformin HCl 1000 mg tablets.

No statistically significant differences in the median Tmax values for either alogliptin or metformin were observed between the SYR-322MET 12.5 mg + 1000 mg tablet and the individual alogliptin 12.5 mg and metformin HCl 1000 mg tablets.

4.1.2 SYR-322MET_102: A Phase 1, Open-Label, Randomized, Crossover Study to Determine the Effects of Food on the Pharmacokinetics of a Fixed-Dose Combination of SYR-322 and Metformin Hydrochloride in Healthy Adult Subjects

Objectives:

The primary objective of this study was to determine the effect of food on the pharmacokinetics of a single oral dose of SYR-322MET FDC tablet in healthy adult subjects.

Study design:

This was a phase 1, open label, randomized, single site, 2-period crossover study. A schematic of the study design is displayed in Figure 9.

Twenty-four healthy male and female subjects aged 18 to 55 years, inclusive, were planned for enrollment. Subjects were assigned randomly to 1 of 2 treatment sequences (12 subjects per sequence). The study consisted of Screening (Day -28 to Day -2), Check-in (Day -1), and 2 crossover periods during which subjects received a single dose of SYR-322MET 12.5 mg + 1000 mg in the fasted state (reference treatment) or a single dose of SYR-322MET 12.5 mg + 1000 mg in the fed state (test treatment). There was a washout interval of at least 7 days between periods and a pharmacokinetic evaluation of 72 hours following dosing in each period.

For all subjects on Day -1 of each period, a standardized dinner and snack were served. All subjects were then required to fast from approximately 2200 hours on Day -1 of each period until the scheduled breakfast on Day 1 (fed regimen) or until lunch (fasted regimen). Subjects in the fed regimen received study drug immediately after completing the standard high-fat breakfast on Day 1. The standard high-fat breakfast consisted of 2 eggs fried in 2 teaspoons butter, 2 strips of bacon, 2 slices white toast with 2 teaspoons butter, 4 ounces of hash brown potatoes cooked with 2 teaspoons butter, and 8 fluid ounces of whole milk. Lunch was served approximately 4 hours postdose, dinner was served approximately 9 hours postdose, and a snack was served approximately 13 hours postdose. Water was allowed as desired except from 1 hour before through 1 hour after study drug administration. Only 240 mL of water was allowed during dosing.

Figure 9 Schematic of Study Design

| Sequence | Period 1 | Period 2 |
|----------|---------------------------------------|---------------------------------------|
| AB | SYR-322MET 12.5 mg + 1000 mg (fasted) | SYR-322MET 12.5 mg + 1000 mg (fed) |
| BA | SYR-322MET 12.5 mg + 1000 mg (fed) | SYR-322MET 12.5 mg + 1000 mg (fasted) |

Regimen A=SYR-322MET 12.5 mg + 1000 mg under fasted conditions (reference treatment).

Regimen B=SYR-322MET 12.5 mg + 1000 mg after a high-fat meal (test treatment).

PK evaluations:

Alogliptin and metformin pharmacokinetic blood samples were collected at 0-hour predose (no earlier than 30 minutes predose) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hours postdose of both periods.

The following pharmacokinetic parameters were calculated using noncompartmental methods:

AUC(0-last) Area under the serum concentration-time curve from 0 to the last quantifiable concentration calculated using the linear trapezoidal rule.

AUC(0-inf) Area under the plasma concentration-time curve from 0 to infinity calculated as $AUC(0-inf)=AUC(0-last) + lqc/\lambda_z$, where tlast is the time of last quantifiable concentration and lqc is the last quantifiable concentration.

Cmax Maximum observed plasma concentration.

Tmax Time of the maximum plasma concentration.

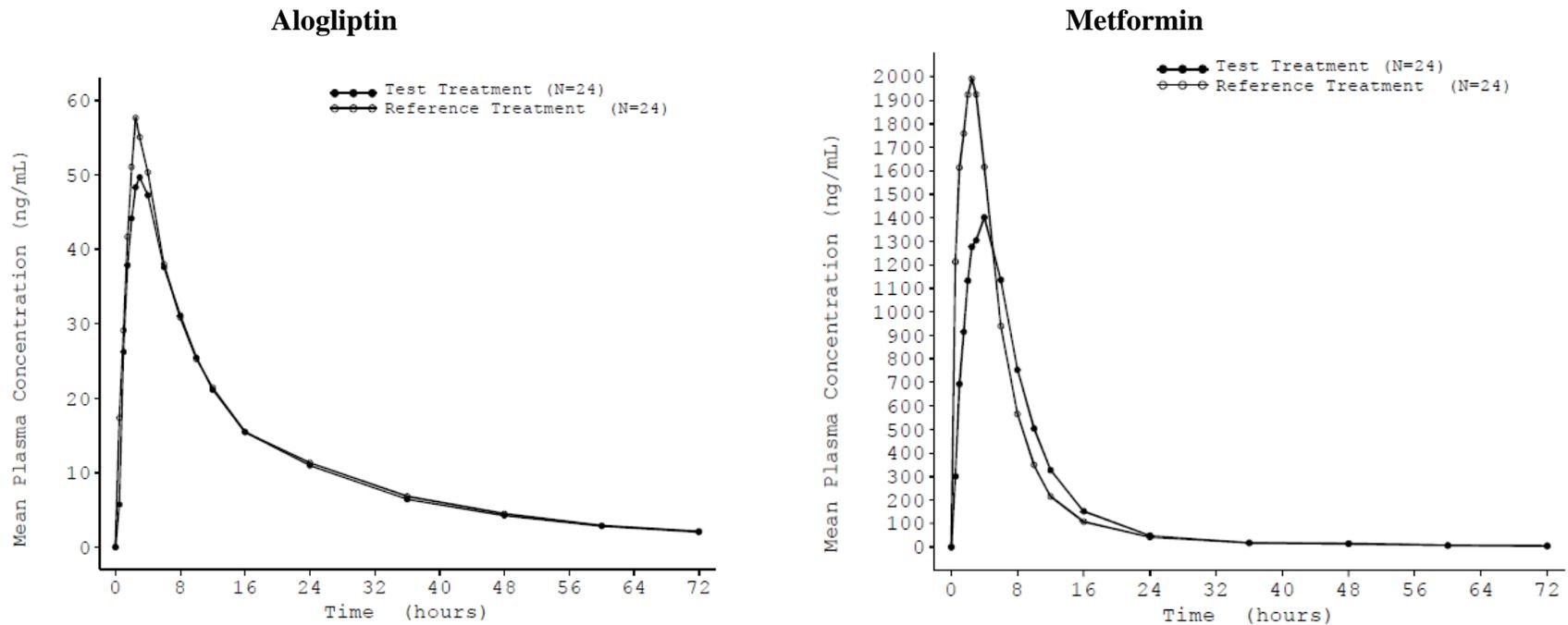
| | |
|-------------|--|
| λ_z | Elimination rate constant, where λ_z is the negative of the slope of the linear regression of the natural logarithm concentration versus time profile during the terminal phase. |
| T1/2 | The terminal elimination half-life, where $T1/2 = \ln(2) / \lambda_z$. |
| CL/F | Apparent oral clearance, where $CL/F = \text{Dose} / \text{AUC}(0\text{-}\infty)$. |
| Vz/F | Apparent volume of distribution, calculated as $V_z/F = (CL/F) / \lambda_z$. |

Study results:

All 24 subjects who completed at least 1 treatment and had no major protocol deviation were included in the pharmacokinetic and statistical analyses. No subject was excluded from the pharmacokinetic analysis.

Mean plasma concentrations of alogliptin and metformin following administration of an SYR-322MET 12.5 mg + 1000 mg tablet under fed and fasted conditions are presented in Figure 10. Plasma pharmacokinetic parameters of alogliptin and metformin following administration of an SYR-322MET 12.5 mg + 1000 mg tablet under fed and fasted conditions are presented in Table 16.

Figure 10 Mean Plasma Concentrations of Alogliptin and Metformin vs Time Following Administration of an SYR-322MET 12.5 mg + 1000 mg Tablet under Fed and Fasted Conditions



Test Treatment=SYR-322MET 12.5 mg + 1000 mg tablet under fed conditions.
Reference Treatment=SYR-322MET 12.5 mg + 1000 mg tablet under fasted conditions.

Table 16 Plasma Pharmacokinetic Parameters of Alogliptin and Metformin Following Administration of an SYR-322MET 12.5 mg + 1000 mg Tablet under Fed and Fasted Conditions

| Analyte Parameter (units) | N (T) | N (R) | Geometric Means | | Ratio T/R-100 (90% CI) (a) |
|------------------------------|----------|----------|--|---|-------------------------------|
| | | | SYR-322MET 12.5 mg + 1000 mg Fed (T) | SYR-322MET 12.5 mg + 1000 mg Fasted (R) | |
| Alogliptin | | | | | |
| AUC(0-tlqc) (ng·hr/mL) | 24 | 24 | 810.49 | 832.32 | 97.38 (92.27, 102.77) |
| AUC(0-inf) (ng·hr/mL) | 24 | 23 | 878.02 | 917.01 | 95.75 (91.52, 100.18) |
| Cmax (ng/mL) | 24 | 24 | 56.16 | 64.67 | 86.85 (79.90, 94.39) |
| Tmax (hr) (b,c) | 24 | 24 | 2.75 | 2.50 | N/A |
| Metformin | | | | | |
| AUC(0-tlqc) (ng·hr/mL) | 24 | 24 | 12573.39 | 13624.16 | 92.29 (85.64, 99.45) |
| AUC(0-inf) (ng·hr/mL) | 22 | 23 | 12637.16 | 13798.21 | 91.59 (84.63, 99.12) |
| Cmax (ng/mL) | 24 | 24 | 1509.23 | 2106.59 | 71.64 (66.53, 77.15) |
| Tmax (hr) (b,d) | 24 | 24 | 4.00 | 2.50 | N/A |

N/A=not applicable, T=test treatment, R=reference treatment.

AUC(0-tlqc): AUC from time 0 to last quantifiable concentration, or AUC(0-last).

(a) Ratios and CIs are presented as percentages.

(b) Tmax is presented as the median.

(c) p=0.263.

(d) p<0.001.

The 90% CIs for the ratios of the LS means for the AUC(0-last) and AUC(0-inf) values of alogliptin and metformin were within the 80% to 125% range following administration of an SYR-322MET 12.5 mg + 1000 mg tablet under fed and fasted conditions. The Cmax of alogliptin was 13% lower under fed conditions, and the lower bound of the 90% CI for the ratio of the LS mean for the Cmax of alogliptin was slightly below 80%. The Cmax of metformin was approximately 28% lower under fed conditions than under fasting conditions, and the 90% CI of the ratio of the LS mean for the Cmax of metformin was below the 80% to 120% range.

No statistically significant difference in the median Tmax for alogliptin was observed between fed and fasted administration of an SYR-322MET 12.5 mg + 1000 mg tablet; however, the median Tmax for metformin was 1.5 hours longer under fed conditions than under fasted conditions, and this difference in the Tmax of metformin was statistically significant (p<0.001).

These results are consistent with the alogliptin food effect study (NDA 22-271), which showed that administration of alogliptin with food had no effect on the total or peak exposure of alogliptin. The food effect observed for metformin is consistent with what has been reported for metformin. According to the prescribing information, food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower Cmax, a 25% lower AUC, and a 35-minute prolongation of Tmax following administration of a single metformin 850 mg tablet with food.

4.1.3 SYR-322_101: An Open-Label, Multiple-Dose, Randomized, Crossover Study to Determine the Pharmacokinetics and Pharmacodynamics of SYR-322 Twice Daily versus Once-Daily Dosing in Healthy Male and Female Subjects

Objectives:

Primary:

The primary objective of this study was to evaluate the pharmacokinetic profile of 12.5 mg twice daily (BID) vs 25 mg once-daily (QD) dosing of alogliptin.

Secondary:

The secondary objective of this study was to assess the pharmacodynamic effect (dipeptidyl peptidase-4 [DPP-4] inhibition), safety, and tolerability of BID vs QD dosing of alogliptin.

Study design:

This was a phase 1, single-center, open-label, randomized, 2-period crossover study to evaluate multiple-dose pharmacokinetics and pharmacodynamic effects of alogliptin following 12.5 mg BID and 25 mg QD dosing of alogliptin for 7 days.

Subjects were assigned randomly to 1 of 2 sequences (14 subjects per sequence) and received multiple oral doses of alogliptin 25 mg QD and multiple oral doses of alogliptin 12.5 mg BID (every 12 hours) for a total of 7 dosing days per treatment period. A washout interval of 7 days (beginning immediately after dosing on Day 7) separated the 2 treatment periods. A schematic of the study design is included as Figure 11.

Figure 11 Schematic of Study Design

| Pretreatment | | Treatment Period (a) | | | |
|----------------|-------------------|------------------------|--------------|--------------------|------------------|
| Screening | Baseline/Check-in | 1 | | 2 | |
| Days -28 to -2 | Day -1 | Days 1 to 7 Dosing (b) | Days 8 to 14 | Days 1 to 7 Dosing | Day 8 Study Exit |
| | | A (N=14) | Washout | B | |
| | | B (N=14) | | A | |

(a) Samples for pharmacokinetic analyses were collected on Days 1 and 5 to 7.

(b) Subjects were randomized immediately prior to dosing on Day 1.

A=alogliptin 25 mg QD=reference treatment.

B=alogliptin 12.5 mg BID=test treatment.

Subjects were required to fast overnight (at least 8 hours) prior to the daily morning dose beginning on the evening of Day -1 of each Treatment Period and for 1 hour following dosing. Subjects randomized to the BID dosing regimen were required to fast for 2 hours prior to the evening dose and for 1 hour following the evening dose. Subjects were given a standardized light breakfast approximately 1 hour following the morning dose each day. The BID evening dose was administered approximately 12 hours following the morning dose. All subjects were given an optional evening snack approximately 1 hour following the evening BID dose.

PK evaluations:

Blood samples for plasma alogliptin assays and DPP-4 inhibition were collected according to the schedule in Table 17 and Table 18.

Table 17 Pharmacokinetic Blood Sampling Schedule for Alogliptin

| Treatment | Study Day | Scheduled Time |
|-------------|------------------|--|
| 25 mg QD | Days 1, 5, and 6 | Within 30 minutes prior to dose. |
| | Day 7 | Within 30 minutes prior to dose, and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 hours postdose. |
| 12.5 mg BID | Days 1, 5, and 6 | Within 30 minutes prior to morning dose. |
| | Day 7 | Within 30 minutes prior to morning dose and within 15 minutes prior to evening dose, and 0.5, 1, 2, 3, 4, 6, 8, 12, 12.5, 13, 14, 15, 16, 18, 20, and 24 hours postdose. |

Table 18 Pharmacodynamic Blood Sampling Schedule for Alogliptin

| Treatment | Study Day | Scheduled Time |
|-------------|-----------|--|
| 25 mg QD | Day 1 | Within 30 minutes prior to dose. |
| | Day 7 | Within 30 minutes prior to dose, and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 hours postdose. |
| 12.5 mg BID | Day 1 | Within 30 minutes prior to morning dose. |
| | Day 7 | Within 30 minutes prior to morning dose and within 15 minutes prior to the evening dose, and 0.5, 1, 2, 3, 4, 6, 8, 12, 12.5, 13, 14, 15, 16, 18, 20, and 24 hours postdose. |

The following pharmacokinetic parameters were derived from plasma concentration-time profiles for all evaluable subjects:

| | |
|---------------------|---|
| AUC(0-tau) | Area under the plasma concentration-time curve (AUC) from time 0 to time tau, calculated by the linear trapezoidal method; where time 0 is 0 (AM) and time tau is 24 (PM) for alogliptin QD, and time 0 is both 0 (AM) and 12 (PM) and time tau is both 12 (AM) and 24 (PM) for alogliptin BID. |
| AUC(0-24) | AUC from time 0 to 24 hours, calculated by the linear trapezoidal method. |
| C _{max} | Maximum observed plasma concentration. |
| T _{max} | Time to reach C _{max} . |
| C _{trough} | Observed predose (trough) plasma concentration. |
| C _{min} | Minimum observed plasma concentration on Day 7. |
| Swing (%) | The percent swing defined as $100 \times ([C_{\max} - C_{\min}]/C_{\min})$. |
| Fluctuation | The percent fluctuation defined as $100 \times ([C_{\max} - C_{\min}]/C_{\text{avg}})$. |
| C _{avg} | Average plasma concentration during dosing interval, calculated as $AUC/(0\text{-tau})/\text{tau}$. |

The AUC(0-24) was defined as AUC(0-12) + AUC(12-24) for alogliptin BID, and AUC(0-24) for alogliptin QD.

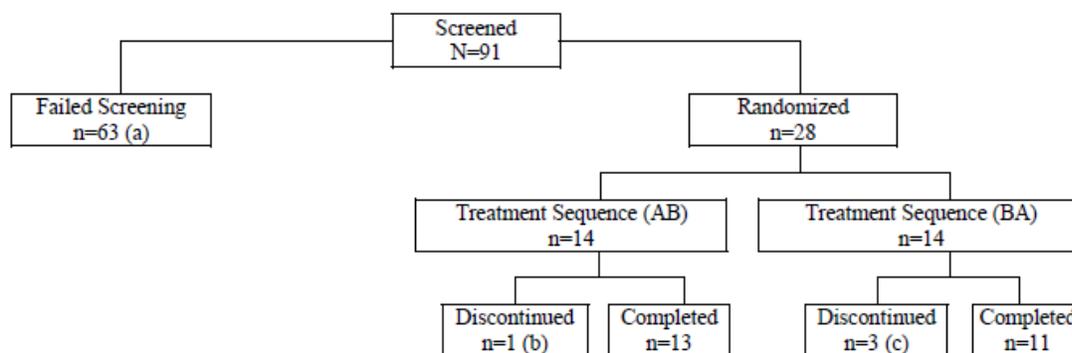
Pharmacodynamic effects were measured by DPP-4 inhibition. The following parameters were

calculated:

- AUEC(0-24) Area under the pharmacodynamic effect curve from time 0 to 24 hours.
AUEC(0-tau) Area under the pharmacodynamic effect curve from time 0 to time tau, where tau=12 for BID or tau=24 for QD.
Emax Maximum observed pharmacodynamic effect.
Tmax Time to reach Emax.
E0 Observed effect at time 0 for BID and QD dosing regimens.
E12 Observed effect at 12 hours postdose for BID dosing regimen.
E24 Observed effect at 24 hours postdose for BID and QD dosing regimens.

The disposition of subjects is shown in Figure 12.

Figure 12 Disposition of Subjects



Treatment A=alogliptin 25 mg QD=reference treatment, Treatment B=alogliptin 12.5 mg BID=test treatment.

(a) Reasons for screen failure were failure to meet entrance criteria (42 subjects), “other” (11 subjects), and voluntary withdrawal (10 subjects).

(b) Reason for discontinuation was adverse event (1 subject).

(c) Reasons for discontinuation were voluntary withdrawal (1 subject) and “other” (2 subjects).

Study results:

Mean plasma concentrations of alogliptin following administration of alogliptin 12.5 mg BID and 25 mg QD for 7 days are presented in Figure 13. Plasma and urine pharmacokinetic parameters of alogliptin following administration of alogliptin 12.5 mg BID and 25 mg QD for 7 days are presented in Table 19.

Figure 13 Mean Plasma Concentrations of Alogliptin vs Time Following Administration of Alogliptin 12.5 mg BID and 25 mg QD for 7 Days

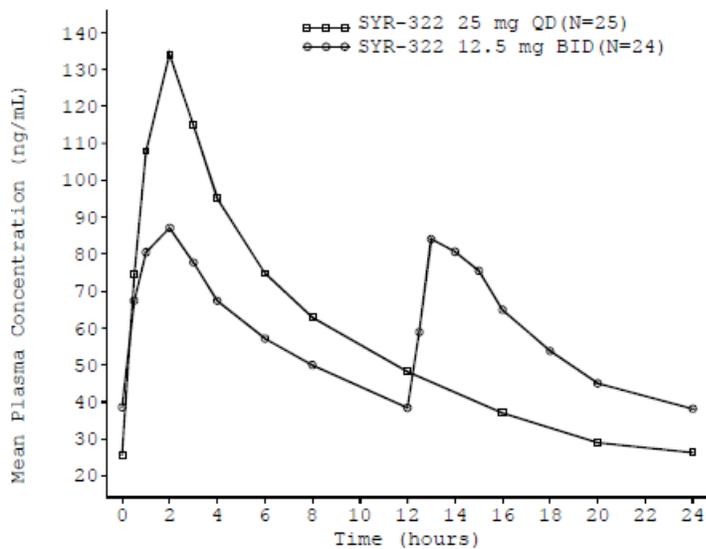


Table 19 Plasma and Urine Pharmacokinetic Parameters of Alogliptin Following Administration of Alogliptin 12.5 mg BID and 25 mg QD for 7 Days

| Matrix Alogliptin Parameter (units) | N (T) | N (R) | Arithmetic Mean (%CV) | | LS Mean | | |
|---|----------|----------|-------------------------------|----------------------------|-------------------------------|----------------------------|---------------------------------|
| | | | Alogliptin 12.5 mg BID (T) | Alogliptin 25 mg QD (R) | Alogliptin 12.5 mg BID (T) | Alogliptin 25 mg QD (R) | Ratio (T/R)-100 (90% CI) (a) |
| Plasma | | | | | | | |
| AUC(0-24) (ng-hr/mL) | 24 | 25 | 1383.58 (14.386) | 1362.22 (17.877) | 1378.54 | 1339.21 | 102.94 (97.57, 108.60) |
| AUC(0-12) (ng-hr/mL) (b) | 24 | N/A | 706.69 (15.364) | N/A | 698.77 | N/A | 95.88 (93.39, 98.44) |
| AUC(12-24) (ng-hr/mL) (b) | 24 | N/A | 676.89 (14.482) | N/A | 670.01 | N/A | |
| Cmax (ng/mL) (c) | 24 | 25 | 92.65 (22.668) | 144.26 (24.812) | 91.02 | 139.23 | 65.38 (59.17, 72.24) |
| Tmax (hr) (c,d,e) | 25 | 25 | 1.98 (0.983, 3.017) | 1.98 (0.517, 2.983) | N/A | N/A | N/A |
| Urine | | | | | | | |
| CLr(0-24) (L/hr) | 24 | 25 | 12.03 (17.139) | 11.97 (30.549) | 11.82 | 11.09 | 106.61 (89.77, 126.60) |

%CV=percent coefficient of variation, AUC(0-12)=area under the plasma concentration-time curve from 0 to 12 hours, AUC(12-24)=area under the plasma concentration-time curve from 12 to 24 hours, N/A=not applicable, T=test treatment, R=reference treatment.

(a) Ratios and CIs are presented as percentages.

(b) Ratio (T/R) is the ratio of AUC(12-24) to AUC(0-12).

(c) Cmax and Tmax were estimated for the morning BID dose only.

(d) Tmax is presented as the median (minimum, maximum).

(e) p=0.905.

The 90% CI for the ratio of the LS means for the area under the plasma concentration-time curve from 0 to 24 hours (AUC(0-24)) was within the 80% to 125% range; therefore, total exposure to alogliptin from 0 to 24 hours was similar with BID and QD dosing. The 90% CIs for the ratio of the LS mean for the Cmax was not within the 80% to 125% range; however, this is expected for a drug with linear pharmacokinetics. No difference in the median Tmax values was observed between the 25 mg QD dose and the morning 12.5 mg BID dose. Renal clearance was similar with BID and QD dosing.

Mean DPP-4 inhibition following administration of alogliptin 12.5 mg BID and 25 mg QD for 7 days are shown in Figure 14 and Table 20.

Figure 14 Mean DPP-4 Inhibition vs Time Following Administration of Alogliptin 12.5 mg BID and 25 mg QD for 7 Days

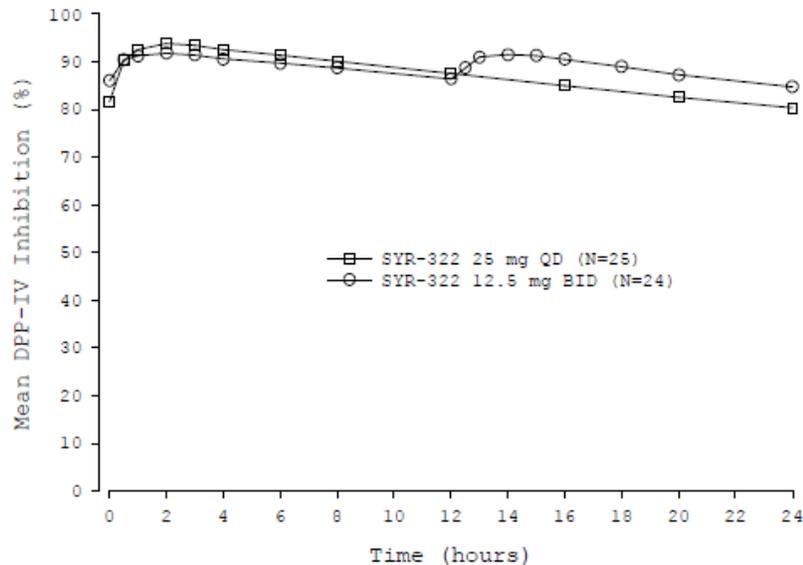


Table 20 Plasma Pharmacodynamic Parameters of Alogliptin (DPP-4 Inhibition) Following Administration of Alogliptin 12.5 mg BID and 25 mg QD for 7 Days

| Alogliptin Parameter (units) | N (T) | N (R) | Arithmetic Mean (%CV) | | LS Mean | | |
|------------------------------|-------|-------|----------------------------|-------------------------|----------------------------|-------------------------|------------------------------|
| | | | Alogliptin 12.5 mg BID (T) | Alogliptin 25 mg QD (R) | Alogliptin 12.5 mg BID (T) | Alogliptin 25 mg QD (R) | Ratio (T/R)-100 (90% CI) (a) |
| AUEC(0-24) (hr·%Inhibition) | 24 | 25 | 2132.09 (1.866) | 2093.63 (2.161) | 2135.00 | 2092.05 | 102.05 (101.50, 102.61) |
| Emax (%Inhibition) | 24 | 25 | 92.28 (1.537) | 94.42 (1.446) | N/A | N/A | N/A |
| Tmax (hr) (b) | 24 | 25 | 1.98 (0.500, 4.083) | 1.98 (0.517, 4.017) | N/A | N/A | N/A |
| E0 (%Inhibition) | 24 | 25 | 86.03 (2.833) | 81.69 (3.197) | 86.20 | 81.66 | 105.55 (104.70, 106.41) |
| E24 (%Inhibition) | 24 | 25 | 84.74 (2.802) | 80.30 (3.143) | 84.91 | 80.22 | 105.85 (104.91, 106.79) |

AUEC(0-24)=area under the international normalized ratio effect-time curve from 0 to 24 hours postdose, E0=effect observed after dosing, E24=effect observed at 24 hours after dosing, Emax=maximum drug-induced.

(a) Ratios and CIs are presented as percentages.

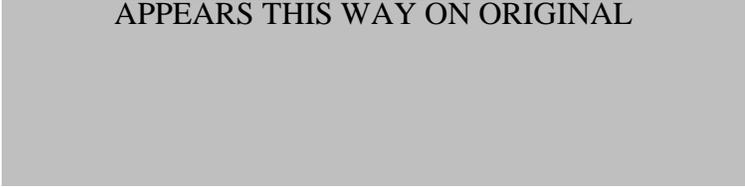
(b) Tmax is presented as the median (minimum, maximum).

The 90% CIs for the ratios of the LS means for AUEC(0-24), E0, and E24 were within the 80% to 125% range; therefore, DPP-4 inhibition was similar with BID and QD dosing. Peak inhibition (Emax) was also similar with BID and QD dosing. Inhibition at 24 hours postdose (E24) was $\geq 80\%$ with both BID and QD dosing.

No difference in the median Tmax values for DPP-4 inhibition was observed between the

morning 12.5 mg BID dose and the 25 mg QD dose.

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4.2 CLINICAL PHARMACOLOGY FILING MEMO

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

| | Information | | Information |
|----------------------------------|---------------------------|-------------------------|---|
| NDA/BLA Number | NDA 203414 | Brand Name | (b) (4) |
| OCP Division (I, II, III, IV, V) | II | Generic Name | YR-322MET |
| Medical Division | DMEP | Drug Class | DPP-4 inhibitor + biguanide |
| OCP Reviewer | Zhihong Li | Indication(s) | Type 2 diabetes mellitus |
| OCP Team Leader | Jayabharathi Vaidyanathan | Dosage Form | Tablet |
| Pharmacometrics Reviewer | TBD | Dosing Regimen | 12.5 mg/500 mg BID, 12.5 mg/1000 mg BID |
| Date of Submission | 11/22/2011 | Route of Administration | Oral |
| Estimated Due Date of OCP Review | 7/22/2012 | Sponsor | Takeda |
| Medical Division Due Date | | Priority Classification | Standard |
| PDUFA Due Date | 9/22/2012 | | |

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 | 3 | | LCMS 307.4, LCMS 307.6, LCMS 153 |
| I. Clinical Pharmacology | | 4 | | MET-101, MET-102, 322-005, 322-101 |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | X | 1 | | 322-101 |
| 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 - | X | 1 | | 322-005 |
| In-vivo effects on primary drug: | X | 1 | | 322-005 |
| In-vivo effects of primary drug: | X | 1 | | 322-005 |
| 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: | X | 1 | 322-101 |
| | Phase 3 clinical trial: | | | |
| Population Analyses - | | | | |
| | Data rich: | | | |
| | Data sparse: | | | |
| II. Biopharmaceutics | | | | |
| Absolute bioavailability | | | | |
| Relative bioavailability - | | | | |
| | solution as reference: | | | |
| | alternate formulation as reference: | | | |
| Bioequivalence studies - | | | | |
| | traditional design; single / multi dose: | X | 1 | BET-101 |
| | replicate design; single / multi dose: | | | |
| Food-drug interaction studies | | X | 1 | BET-102 |
| Bio-waiver request based on BCS | | | | |
| BCS class | | | | |
| Dissolution study to evaluate alcohol induced dose-dumping | | | | |
| III. Other CPB Studies | | | | |
| Genotype/phenotype studies | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | X | | |
| Literature References | | | | |
| Total Number of Studies | | | 7 | BET-101, BET-102, 322-101, 322-005, LCMS 307.4, LCMS 307.6, LCMS 153 |

On initial review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|-----|----|-----|---------|
| Criteria for Refusal to File (RTF) | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | X | | | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | X | | | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | X | | | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | X | | | |
| 5 | Has a rationale for dose selection been submitted? | X | | | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | X | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | X | | | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | X | | | |
| Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) | | | | | |
| Data | | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, | X | | | |

| | | | | | |
|-----------------------------|--|---|--|---|--|
| | submitted in the appropriate format (e.g., CDISC)? | | | | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | X | |
| Studies and Analyses | | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | X | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | | | X | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | | | X | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | | X | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | X | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | X | | | |
| General | | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | X | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | | X | |

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

| | |
|-----------------------------------|-----------|
| Zhihong Li, Ph.D. | 1/10/2012 |
| Reviewing Clinical Pharmacologist | Date |
| Jayabharathi Vaidyanathan, Ph.D. | 1/10/2012 |
| Team Leader/Supervisor | Date |

RECOMMENDATIONS:

- This NDA application is fileable from a clinical pharmacology perspective
- No comments in the 74-day letter
- OSI inspection needed for the pivotal BE study BET-101

BET-101:

Title: An Open-Label, Randomized, 2-Cohort, 4-Sequence, 4-Period Crossover Study to Determine the Bioequivalence of Alogliptin 6.25 mg and 12.5 mg and Metformin 500 mg and 1000 mg When Administered as Individual Tablets and as a Fixed-Dose Combination Tablet

Investigator: Aziz Laurent, MD

Study Center: PPD Phase I Clinic, 7551 Metro Center Drive, Suite 200, Austin, TX 78744

Assay Site: (b) (4)

BACKGROUND:

In accordance with 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 USC §355) and 21 CFR §314.50, Takeda Global R & D Center, Inc. has submitted this New Drug Application (NDA 203-414) for SYR-322MET as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

SYR-322MET is a fixed-dose combination product, the active components of SYR-322MET are alogliptin and metformin. Alogliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin is a biguanide. SYR-322MET is supplied as tablets at two strengths 12.5 mg alogliptin/500 mg metformin HCl, 12.5 mg alogliptin/1000 mg metformin HCl for oral administration. The proposed dosing regimen is 12.5 mg alogliptin/500 mg metformin HCl or 12.5 mg alogliptin/1000 mg metformin HCl BID.

A total of 7 clinical studies including 4 clinical pharmacology/biopharmaceutics studies are submitted in the NDA database. The conducted clinical pharmacology studies meet the regulatory requirements for filing and this application is fileable from a clinical pharmacology perspective. The filing meeting was held on 1/10/2012.

The clinical development of SYR-322MET includes 3 phase 3 studies and 4 phase 1 studies. The phase 3 studies included two 26-week studies designed to assess the efficacy and safety of alogliptin in combination with metformin for the treatment of T2DM (MET-302 and 322-008) and a 52-week study designed to assess the efficacy and safety of alogliptin in combination with metformin and pioglitazone for the treatment of T2DM (OPI-004). The phase 1 studies included 1 bioequivalence study (MET-101), 1 food-effect study (MET-102), 1 drug-interaction study with alogliptin and metformin (322-005), and 1 pharmacokinetic study that assessed QD versus BID dosing (322-101).

Study MET-101 is a pivotal bioequivalence study evaluated the bioequivalence of alogliptin and metformin when dosed orally as SYR-322MET tablets and as individual alogliptin and metformin HCl tablets. (b) (4) the commercial

formulation of the 2 proposed dosage strengths (12.5 mg + 500 mg and 12.5 mg + 1000 mg) were evaluated and met the standards for bioequivalence to coadministered individual alogliptin and metformin hydrochloride (HCl) tablets.

Study MET-102 is a food effect study with SYR-322MET tablets. Food did not affect total exposure (as AUC(0-tlqc) and AUC(0-inf)) to either alogliptin or metformin when administered as the highest proposed dosage strength (12.5 mg + 1000 mg) of the commercial formulation of SYR-322MET. Food also did not have any clinically significant effect on peak exposure to alogliptin nor did it have a statistically significant effect on Tmax of alogliptin. However, metformin Cmax decreased by 28% and Tmax of metformin was delayed by 1.5 hours when SYR-322MET was administered with food. The 90% CI for the ratio of the LS mean for Cmax of metformin that was below the 80% to 125% range (66.53%, 77.15%), and the change in Tmax was statistically significant. The results for alogliptin are consistent with the results of food-effect studies with alogliptin monotherapy tablets wherein food had no effect on exposure to alogliptin (alogliptin NDA 22-271, Study 322-026). The labeling for metformin states that peak and total exposure decreased 40% and 25%, respectively, and Tmax was delayed 35 minutes when a single 850 mg dose of metformin HCl was administered with food.

Study 322-101 was conducted to evaluate the pharmacokinetics and pharmacodynamics of alogliptin when dosed BID compared with QD dosing. In this study both daily exposure (AUC(0-24)) to alogliptin and DPP-4 inhibition (as AUEC(0-24), E0, and E24) were similar when alogliptin was dosed BID and QD.

Study 322-005 is a DDI study of alogliptin and metformin. No changes in peak or total exposure to alogliptin and no clinically meaningful changes in peak or total exposure to metformin were observed when alogliptin and metformin were coadministered.

Key clinical pharmacology review questions include:

- Are alogliptin and metformin bioequivalent between the SYR-322MET tablets and individual tablets?
- Is the alogliptin 12.5 mg BID dosing regimen supported by the PK study?
- Is there a DDI between alogliptin and metformin?
- Does the food effect study support dosing of SYP-322MET tablets with food?
- Dose the dose-response data support this NDA?

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/s/

ZHIHONG LI
07/27/2012

IMMO ZADEZENSKY
07/27/2012

| BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment | | | |
|---|--|---|--|
| Application No.: | NDA 203-414 | Reviewer: Houda Mahayni, Ph.D. | |
| Submission Dates: | November 22, 2011 May 24, 2012 June 12, 2012 | | |
| Division: | DMEP | Team Leader: Angelica Dorantes, Ph.D. | |
| | | QbD Liaison and Secondary Signature: Sandra Suarez Sharp, Ph.D. | |
| Applicant: | Takeda Global Research & Development Center | Biopharmaceutics Supervisor (Acting): Richard Lostritto, Ph.D. | |
| Trade Name: | --- | Date Assigned: | November 22, 2011 May 31, 2012 June 19, 2012 |
| Generic Name: | SYR-322 MET (Alogliptin/Metformin FDC) | Date of Review: | April 3, 2012 July 11, 2012 July 23, 2012 |
| Indication: | Treatment of Type 2 Diabetes | Type of Submission: A 505 (b) (2) Application | |
| Formulation/strengths | Film-coated Tablet/ (12.5/500 mg and 12.5/1000 mg) | | |
| Route of Administration | Oral | | |
| SUMMARY OF BIOPHARMACEUTICS FINDINGS: | | | |
| <p>SYR-322MET (Alogliptin/Metformin FDC) is a fixed-dose combination product composed of alogliptin and metformin HCl developed by Takeda for the treatment of type 2 diabetes mellitus (T2DM). The proposed formulation of the SYR-322MET is a film-coated tablet (b) (4)</p> | | | |
| <p>As a 505(b) (2) application, the Applicant used as a reference in the pivotal bioequivalence (BE) study (SYR-322MET-101) two NDAs: NDA 20-357 Glucophage® (Metformin HCl) Tablet marketed by Bristol-Myers Squibb, and NDA 22-271 Nesina® (Alogliptin) Tablet by Takeda Global Research & Development Center. (b) (4)</p> | | | |
| <p>The BE study was designed to determine BE of alogliptin and metformin hydrochloride when administered as individual tablets and as a fixed dose combination (FDC) product. The bioequivalence study was performed on the final SYR-322MET tablet formulation and the individual reference alogliptin and metformin hydrochloride tablets. This study was reviewed by OCP. Therefore, the Applicant is not requesting a biowaiver.</p> | | | |
| <p>Some aspects of the product and process development of SYR-322MET tablet were conducted under a Quality by Design (QbD) paradigm to ensure desired product performance in terms of quality, safety, and efficacy. The Applicant evaluated potential critical process parameters and raw material properties that might impact drug product quality (b) (4). The impact of these process parameters was evaluated using design of experiment (DOE). Also, the Applicant (b) (4)</p> | | | |
| <p>(b) (4) stated that dissolution testing will be performed for ongoing registration stability studies and annual stability studies.</p> | | | |

During the conduct of the review, FDA sent an IR Letter to the Applicant on May 7, 2012 requesting additional information. Included in the IR letter was two Biopharmaceutics requests: to provide data supporting the discriminating capability of the disintegration testing; and to provide disintegration and dissolution profiles of drug product batches tested in pivotal Phase 3 clinical trials and bioequivalence study (ies). The Applicant provided responses to the IR Letter on May 24, 2012, and revised any relevant document in Module 3 of the NDA on June 12, 2012.

This review focuses on a) the acceptability of the dissolution method and acceptance criterion; b) the acceptability of the disintegration acceptance criterion; c) the acceptability of the information provided in support of using disintegration testing in lieu of dissolution testing; d) the role of dissolution/disintegration in selection of the design space; e) the acceptability of information provided in support of the manufacturing site change.

a) Dissolution Method and Acceptance Criterion:

A single dissolution method for SYR-322MET film-coated tablets was developed. The Applicant selected USP Apparatus II (Paddle) at a rotation speed of 50 rpm in 0.01 mol/L hydrochloric acid (pH 2.0). The proposed acceptance criterion is (b) (4) (Q) dissolved in 15 minutes for both alogliptin and metformin HCl. The Applicant provided dissolution data to show the discriminating power of the method (b) (4)

The dissolution method discriminated between SYR-322MET typical tablets and side-batch tablets (b) (4). Therefore, the proposed dissolution method is acceptable. However, the following dissolution acceptance criterion need to be revised for both components and all strengths of the proposed product to:

$$Q = (b) (4) \text{ in } 15 \text{ min}$$

This recommendation is based on the performance of all clinical and stability batches and on the discriminating power findings of the method (b) (4)

b) Disintegration Acceptance Criterion:

The Applicant proposed to use in process disintegration testing (b) (4) instead of a dissolution testing at release. (b) (4) The Applicant justification of the proposed acceptance criterion (b) (4) is to ensure that dissolution profiles for alogliptin and metformin hydrochloride meet a dissolution specification of $Q = (b) (4)$ in 15 minutes. The proposed disintegration acceptance criterion (b) (4) is not acceptable (b) (4)

Therefore, the Applicant is requested to revise the acceptance criterion for disintegration time which is based on the performance of BE batches and primary stability batches for the 12.5 mg/1000 mg and 12.5 mg /500mg strengths as follows:

disintegration time: (b) (4)
(b) (4)

c) The acceptability of the Information Provided in Support of Using Disintegration Testing in lieu of Dissolution Testing:

The ICH Q6A guidance outlines that disintegration may be used in lieu of dissolution if the following is met:

1. A product contains a drug which is highly soluble throughout the physiological range (dose/solubility volume < 250 mL from pH 1.2 to 6.8)
2. The drug product is rapidly dissolving (dissolution >80% in 15 minutes at pH 1.2, 4.0 and 6.8)
3. Disintegration is shown to be more discriminating than dissolution, or
4. A relationship to dissolution has been established

(b) (4)

d) The role of Dissolution/Disintegration in the Selection of the Design Space

Because the Applicant planned to replace the dissolution testing with real-time release strategy using disintegration testing, the Applicant performed experiments to determine the critical process parameters that might impact drug product quality. (b) (4)

The Applicant assessed the impact of these process parameters on product quality using design of experiment (DOE). The Applicant performed development scale studies and full scale optimization studies. The development scale studies did not find any critical process parameters affecting dissolution or disintegration within the ranges studied because all possible process conditions resulted in an acceptable product. The full scale optimization studies showed (b) (4)

Therefore, the CMC reviewer is made aware of this observation, because there were insufficient data (e.g. dissolution profiles comparison with f_2 statistical testing, in vitro in vivo correlation (IVIVC) models, or in vivo bioequivalence studies) to determine whether batches manufactured throughout the drug product design space would result in products that are bioequivalent.

e) Manufacturing Site Change

The Applicant manufactured the primary stability batches at (b) (4) which is different from the commercial site (Takeda Osaka). The Applicant submitted batch analysis results of batches manufactured (b) (4) for primary registration stability studies and process validation lots manufactured at the Takeda Osaka. Based on the information provided, the dissolution data of the drug product manufactured at (b) (4) and Takeda sites are found similar.

Summary of Findings and Conclusions

(b) (4) The proposed dissolution method is acceptable. However, the dissolution acceptance criterion of (b) (4) (Q) dissolved in 15 minutes for both alogliptin and metformin HCl needs revision.

The proposed disintegration acceptance criterion (b) (4) is not acceptable (b) (4)

Therefore, we request that the disintegration acceptance criterion be revised.

In general, the data provided in terms of (b) (4) correlation between disintegration and dissolution support the Applicant's proposal of using disintegration testing in lieu of dissolution testing. Therefore, it is acceptable to replace dissolution testing with disintegration testing at drug product release.

The dissolution data of batches manufactured at (b) (4) and Takeda manufacturing sites are found acceptable.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 203-414 (alogliptin and metformin HCl) and its Amendments submitted on May 24, 2012 and June 12, 2012 and has the following comments which should be conveyed to the Applicant:

- Your proposal of using disintegration in lieu of dissolution as a release test for SYR-322MET tablets is acceptable. However, the following dissolution and disintegration acceptance criteria need to be revised as follows for the proposed product:
 - Revise the dissolution acceptance criterion for both components and all strengths of the proposed

product to: $Q = (b) (4)$ in 15 min

This requested revision is based on the performance of all clinical and stability batches and on the discriminating power the method (b) (4)

- Revise the disintegration acceptance criterion for the 12.5 mg/1000 mg and 12.5 mg /500mg strengths to:
 - (b) (4)
 - (b) (4)

This requested revision of acceptance criterion is based on the performance of BE batches and primary stability batches for the 12.5 mg/1000 mg and 12.5 mg /500 mg strengths.

Revise the specifications accordingly and submit and update sheet of specifications as soon as possible.

2. There were insufficient data (e.g. dissolution profiles comparison with f_2 statistical testing, in vitro in vivo correlation (IVIVC) models, or in vivo bioequivalence studies) to determine whether batches manufactured throughout the drug product design space would result in products that are bioequivalent. Therefore, you need to perform dissolution profile comparisons with f_2 testing (if feasible) for any movements outside the NOR and within the proposed design space to be handled within the Applicant's internal quality control system.

Comments to the CMC Reviewer:

The (b) (4) CMC reviewer is made aware of this observation, because there were insufficient data (e.g. dissolution profiles comparison with f_2 statistical testing, in vitro in vivo correlation (IVIVC) models, or in vivo bioequivalence studies) to determine whether batches manufactured throughout the drug product design space would result in products that are bioequivalent. Therefore, we recommend the following solutions to this issue:

- If from CMC perspective the control strategy implemented under the proposed process parameters ensures consistent product quality, then the Applicant should perform dissolution profile comparisons with f_2 testing for any movements outside the NOR and within the proposed design space to be handled within the Applicant's internal quality control system.
- If from CMC perspective the control strategy implemented under the proposed process parameters does NOT ensure consistent product quality, then the Applicant should tighten the proposed acceptable range of key process parameters (b) (4) to reflect those implemented for the biobatches.

Since there are pending issues for this NDA by its GRMP due date, from the Biopharmaceutics perspective a COMPLETE RESPONSE is recommended for NDA 203-414 for SYR-322MET Tablets. Note that the CR recommendation that is been given at this time is specifically due to an inconclusive agreement with the Applicant in terms of setting the appropriate dissolution and disintegration acceptance criteria for SYR-322MET Tablets. Once an agreement has been reached with the Applicant, which is expected to occur the week of July 30th, an addendum to this original review will be written. The addendum will include a revised Biopharmaceutics recommendation regarding the approval of this NDA.

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez Sharp, Ph.D.
Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

cc: DARRTS CC List: RLostritto; ADorantes

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/s/

HOUDA MAHAYNI
07/27/2012

SANDRA SUAREZ
07/27/2012

| BIOPHARMACEUTICS FILING REVIEW | | | |
|--|---|--|--------------------|
| Office of New Drug Quality Assessment | | | |
| Application No.: | NDA 203-414 (000) | Reviewer: Houda Mahayni, Ph.D. | |
| Division: | DMEP | | |
| Applicant: | Takeda Global Research & Development Center | Biopharmaceutics Team Leader: Angelica Dorantes, Ph.D. | |
| Trade Name: | (b) (4) | | |
| Generic Name: | SYR-322MET (Alogliptin/Metformin FDC) | Date Assigned: | November 22, 2011 |
| Indication: | Treatment of Type 2 Diabetes | Date of Review: | January 16, 2012 |
| Formulation | Film-coated Tablet | | |
| Route of Administration | Oral | | |
| SUBMISSIONS REVIEWED IN THIS DOCUMENT | | | |
| Submission date | CDER Stamp Date | Date of informal/Formal Consult | PDUFA DATE |
| November 22, 2011 | November 22, 2011 | November 22, 2011 | September 22, 2012 |
| Type of Submission: | Original NDA | | |
| Type of Consult: | Dissolution method and acceptance criteria and using disintegration test instead of dissolution test for release --- FILING REVIEW | | |
| REVIEW SUMMARY: | | | |
| <p>The applicant (b) (4) is seeking approval of only two strengths of SYR-322MET (Alogliptin/Metformin FDC) tablets, 12.5/500 mg and 12.5/100 mg. The applicant proposes BID dosing for SYR-422MET as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes Mellitus.</p> | | | |
| <p>The proposed commercial SYR-322MET tablets are (b) (4) film-coated.</p> | | | |
| <p>The quantitative composition of SYR-322MET tablets and the function of each of the components are provided in Table 1 below.</p> | | | |
| <p>Table 1: Composition of SYR-322MET tablets (b) (4) 12.5/500 mg, 12.5/1000 mg</p> | | | |

| Component | Reference to Quality Standards | Function | Quantity per Tablet (mg) | |
|--|---------------------------------|-------------------|--------------------------|------------------------------|
| | | | (b) (4) | (b) (4) |
| | | | 12.5mg +500mg | 12.5mg +1000mg (b) (4) |
| Alogliptin benzoate (As the free base) | In-house standard | Active ingredient | (b) (4) 17 (12.5) | 17 (12.5) (b) (4) |
| Mannitol | Ph.Eur., USP | | | |
| Microcrystalline cellulose | Ph.Eur., NF | | | |
| Povidone | Ph.Eur., USP (b) (4) | | | |
| Metformin hydrochloride | Manufacturer's standard (b) (4) | Active ingredient | (b) (4) 500 | 1000 (b) (4) |
| Crospovidone | Ph.Eur., NF (b) (4) | | | |
| Magnesium stearate | Ph.Eur., NF (b) (4) | | | |
| Film-Coating | | | (b) (4) | (b) (4) |
| Hypromellose 2910 | Ph.Eur., USP | | | (b) (4) |
| Talc | Ph.Eur., USP | | | |
| Titanium dioxide | Ph.Eur., USP (b) (4) | | | |
| Ferric oxide, yellow | 95/45/EC (E172), NF (b) (4) | | | |
| <i>Tablet weight</i> | | | (b) (4) 730 | 1350 |
| (a) | (b) (4) | | | |
| (b) Also meets USP. | | | | |
| The applicant reported that (b) (4) | | | | |
| SYR-322MET (12.5/500 mg and 12.5/1000 mg), met the standards | | | | |

for bioequivalence to co-administered individual alogliptin and metformin hydrochloride (HCl) tablets.

[Redacted] (b) (4)

The applicant proposes the following operating conditions for dissolution testing of SYR-322MET tablets as shown in Table 2 below.

Table 2: Summary of the Dissolution Method

| Method Parameter | Description |
|--------------------|---|
| Apparatus | USP dissolution apparatus 2 (paddle apparatus) |
| Agitation | 50 rpm |
| Dissolution medium | 0.01 mol/L hydrochloric acid |
| Deaeration | Not necessary |
| Vessel volume | 900 mL (±1%) |
| Vessel temperature | 37°C (±0.5°C) |
| Sampling time | 5, 15, 30 and 45 minutes (Other time points may be used, if necessary.) In the case of QC release testing or commercial stability testing, sampling may be done at the time-point specified in the specification (single time-point dissolution). |
| Sampling volume | 10 mL |

The proposed dissolution criterion is [Redacted] (b) (4) (Q) dissolved in 15 minutes for both alogliptin and metformin HCl.

The applicant stated that SYR-322MET is [Redacted] (b) (4)
coated [Redacted] (b) (4)

[Redacted] (b) (4) As a result, the applicant believes that in process disintegration testing [Redacted] (b) (4) can be performed instead of a dissolution test at release. However, for ongoing registration stability studies and annual stability studies, the applicant will continue to perform dissolution testing.

The proposed disintegration and dissolution acceptance criteria for SYR-322MET tablets are listed in Table 3 below.

Table 3: Disintegration and Dissolution Acceptance Criteria for SYR-322MET Tablets

| Test item | Acceptance criteria | Testing Requirement | Analytical procedure |
|-------------------------------|---------------------|---------------------|----------------------|
| Disintegration* | (b) (4) | Release | USP <701> |
| Dissolution (%) Alogliptin | (b) (4) | Stability | SYR-322MET-12184 |
| Metformin hydrochloride | (b) (4) | Stability | |

The primary registration stability batches were manufactured (b) (4). However, the commercial batches were manufactured at a different site (Takeda Osaka). The applicant reported that the first lot of each strength of batches manufactured (b) (4) for primary registration stability was used in the pivotal bioequivalence study. Also, the applicant reported that all equipment used for each unit operation at commercial scale is from the same equipment class to those used for development studies.

The biopharmaceutics review will focus on the proposed dissolution method and specifications, and the acceptability of using in process disintegration testing (b) (4) instead of a dissolution test at release.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 203-414 for filing purposes. We found this NDA filable from a biopharmaceutics perspective. There are no comments to be conveyed to the sponsor at this time.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

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

cc: NDA 203-414, M Hai, S Markofsky, S Tran

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/s/

HOUDA MAHAYNI
01/20/2012

ANGELICA DORANTES
01/20/2012