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APPLICATION NUMBER:

022271Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

memo

To: File

From: Tapash Ghosh, Ph.D., Office New Drug Quality Assessment, OPS, CDER

CC: Richard T. Lostritto, Ph.D., Angelica Dorantes, Ph. D. Office New Drug Quality Assessment, OPS, CDER

Date: 12/13/2012

Re: Biopharmaceutics Recommendation for NDA 22271 and 22426 – NESINA® (alogliptin) Tablets and Oseni® (alogliptin/pioglitazone) fixed-dose combination (FDC) tablets

Comments: On July 26 and 27, 2012, Takeda resubmitted NDA 22-271 (alogliptin tablets) and NDA 22426 in response to issues identified in Agency's April 2012 Complete Response letter.

Biopharmaceutics reviews of these two NDAs in DARRTs from the previous cycles (22-271 – 04/04/12 and 22-426 – 12/22/11) indicated that there are no outstanding Biopharmaceutics issues identified for NDA 22271 and 22426.

Recommendation: From the Biopharmaceutics perspective, both NDAs 22271 and 22426 are recommended for approval.

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/s/

TAPASH K GHOSH
12/18/2012

RICHARD T LOSTRITTO
12/18/2012

ONDQA (Biopharmaceutics) Review

NDA: 22-271 Resubmission
Submission Date: 07/25/2011
Product: NESINA® (alogliptin) tablets, 12.5 and 25 mg
Type of Submission: Original NDA Amendment
Applicant: Takeda
Reviewer: Tapash K. Ghosh, Ph.D.

SYNOPSIS

Background: In December 2007, Takeda submitted Original NDA 22-271 for NESINA® (alogliptin) Tablets. The proposed NESINA product, are oval, biconvex, film-coated tablets containing 25 mg, 12.5 mg or 6.25 mg of alogliptin indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. In June 2009, FDA sent a Complete Response letter for this NDA, requesting Takeda to conduct a cardiovascular safety trial for alogliptin.

Resubmission: On July 25, 2011, the Applicant resubmitted NDA 22-271 for NESINA® Tablets.

Review: The Biopharmaceutics review is focused on the evaluation and approvability of the dissolution method and acceptance criterion.

RECOMMENDATION

The provided data support the proposed dissolution testing conditions. The following dissolution method and acceptance criteria are acceptable.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
No. 2 (paddle)	50 rpm	900 mL	37°C	HCL 0.01 N	Q = (b) (4) at 15 min

From the Biopharmaceutics viewpoint, the Resubmission of NDA 22-271 for NESINA® (alogliptin) Tablets is recommended for approval.

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

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

BIOPHARMACEUTICS ASSESSMENT

- **Choice of Dissolution Conditions**

Dissolution Medium and Apparatus: Alogliptin benzoate has high solubility according to BCS class definitions with 47.0, 27.1, 27.6 and 21.9 mg/ml dissolved in 0.1 N HCl, 0.01 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer, respectively. The solubility meets the definition of highly soluble and significantly exceeds the sink conditions needed for the dissolution test (at least 0.083 mg/ml with a volume of 900 ml for a 25 mg dose). The dissolution medium consisting of 0.01 mol/L HCl was selected from the evaluated media for simplicity of laboratory procedures, and because the necessary solubility showed no dependence on pH. Apparatus 2 and was selected for the testing of alogliptin tablets.

Paddle Rotation Speed: A paddle rotation speed of 50 rpm was selected because alogliptin benzoate dissolved immediately using any aqueous medium across the physiological pH range at this speed. Additionally, this speed is the most commonly recommended and the slowest speed generally accepted for the paddle method.

Discriminating Ability: The discriminating capability of the selected testing conditions was not evaluated due to high solubility of alogliptin benzoate itself. Additionally, the same rapid and similar dissolution performance (i.e. greater than (b) (4) (Q) dissolved in 15 minutes) was observed regardless of media pH and formulation evaluated through the course of development.

Dissolution Profiles for Alogliptin Tablets: The dissolution profiles for 6 individual alogliptin tablets ((b) (4) 6.25mg, 12.5mg and 25mg) were investigated using 0.1 N HCl (pH 1.0), 0.01N HCl (pH 2.0), pH 4.5 acetate buffer and pH 6.8 phosphate buffer at 37°C with the paddle method at a rotation speed of 50 rpm. All profiles of alogliptin tablets ((b) (4) 6.25mg, 12.5mg and 25mg) were essentially the same regardless of the pH of the dissolution medium.

Table 5. Dissolution profiles for media with various pH Method Conditions

Experiment	Dissolution Medium
A	pH 1.2: 0.1N HCl (USP Gastric Fluid,Simulated,TS without pepsin)
B	pH 2.0: 0.01N HCl
C	pH 4.5: 0.05M Acetate buffer (USP)
D	pH 6.8: 0.05M Phosphate buffer (USP)

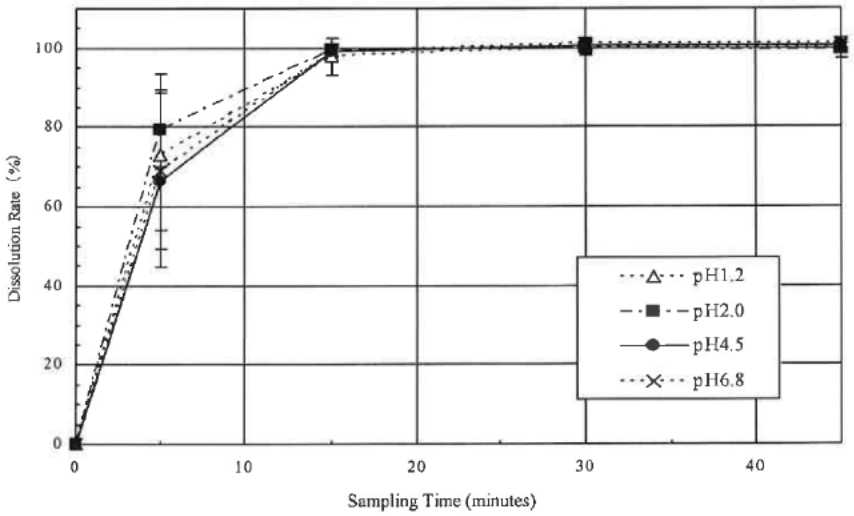

Figure 13. Dissolution Profiles for SYR-322 Tablets (3.125mg) with Various Media pH
Apparatus: Dissolution tester; (b) (4)

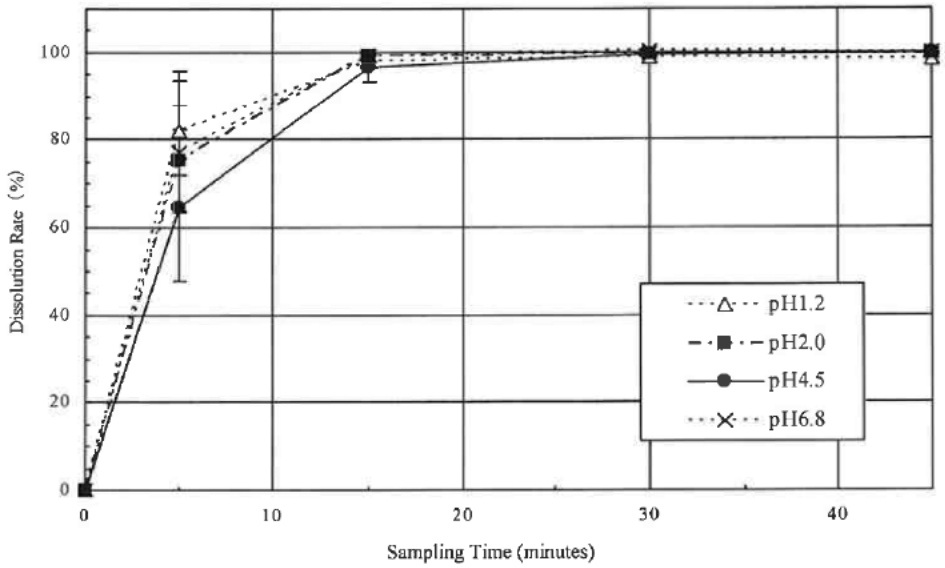

Figure 14. Dissolution Profiles for SYR-322 Tablets (6.25mg) with Various Media pH
Apparatus: Dissolution tester; (b) (4)

Selection of Dissolution Medium: Since the same dissolution profiles were observed regardless of pH of the media, 0.01 N HCl was chosen as the dissolution medium, for ease of preparation and equivalent solubility to that determined for the pH 2.0 to 6.8 conditions. Selecting the dissolution medium of low pH is also reasonable, because alogliptin tablets are intended to be an immediate release dosage form following oral administration. The temperature of 37°C was established.

- ***Proposed Dissolution Method:***

As the result of these studies, the proposed operating conditions for the dissolution of alogliptin tablets are shown below:

Apparatus: *Paddle apparatus*
Paddle rotation speed: *50 rpm*
Medium: *900mL of 0.01 N HCl (without deaeration)*

- **Proposed Acceptance Criterion**

The acceptance criterion was based on examination of dissolution results from all available data reported during batch release and stability testing. Dissolution profiles were obtained in the stability studies, with data collected for dissolution in 5 minutes, 15 minutes, 30 minutes and 45 minutes. The dissolution data from the 3 primary stability batches are provided in the following table.

Table 9 Dissolution Results for Alogliptin Tablets (12.5mg and 25mg) Stored at 25°C/60%RH and 40°C/75%RH (% Dissolved after 15 Minutes)

Assay Time	Alogliptin Tablets (12.5mg)			Alogliptin Tablets (25mg)		
	Z641601	Z641602	Z641603	Z641701	Z641702	Z641703
Release Test	NA	NA	NA	NA	NA	NA
12 M at 25°C/60%RH						
7-count bottle	100.2 (98.7-101.7)	100.3 (98.8-101.3)	99.5 (98.1-101.0)	98.4 (98.0-99.1)	100.4 (99.8-101.2)	99.1 (98.4-99.6)
30-count bottle	99.2 (98.0-99.9)	100.1 (99.2-101.7)	99.4 (98.4-100.8)	98.5 (96.7-99.8)	99.9 (98.8-101.0)	99.4 (99.1-99.8)
90-count bottle	99.5 (98.5-100.1)	101.3 (100.9-101.8)	99.3 (98.5-100.6)	98.3 (95.4-99.4)	100.5 (99.7-101.0)	99.4 (98.6-100.6)
500-count bottle	99.7 (99.4-100.0)	100.0 (98.2-101.8)	100.0 (97.3-101.7)	99.5 (98.9-100.1)	100.0 (99.3-100.6)	99.7 (99.1-100.6)
Aclar blister	100.0 (98.4-101.4)	100.5 (99.1-101.6)	99.4 (98.0-100.2)	98.2 (97.5-98.9)	100.0 (99.6-101.2)	99.5 (98.9-100.6)
6 M at 40°C/75%RH						
7-count bottle	97.6 (95.8-98.5)	97.4 (96.6-98.4)	98.2 (97.1-99.1)	98.1 (97.1-99.4)	99.3 (98.5-100.0)	98.4 (97.8-98.9)
30-count bottle	98.7 (97.8-99.6)	99.3 (98.0-101.1)	100.1 (99.5-101.3)	98.7 (97.8-99.7)	99.6 (98.7-100.2)	98.8 (98.0-99.6)
90-count bottle	97.8 (96.9-98.5)	98.1 (97.4-99.0)	99.7 (98.5-101.4)	99.6 (98.9-100.8)	99.2 (98.3-100.0)	99.3 (97.9-100.3)
500-count bottle	98.6 (97.5-99.4)	98.7 (97.6-99.6)	99.4 (97.0-100.4)	99.5 (97.7-101.6)	99.6 (98.7-100.4)	99.0 (97.9-100.0)
Aclar blister	98.4 (97.8-98.9)	99.5 (98.7-100.7)	98.6 (97.7-99.8)	98.4 (97.8-98.8)	100.0 (98.8-101.9)	98.6 (97.9-98.9)

Since complete dissolution was typically achieved in 15, an acceptance criterion of not less than (b) (4) (Q) dissolved in 15 minutes was selected.

Reviewer Comment:
The proposed dissolution method and acceptance criterion are acceptable.

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/s/

TAPASH K GHOSH
04/04/2012

ANGELICA DORANTES
04/04/2012

CLINICAL PHARMACOLOGY REVIEW: Amendment

NDA	22271
Submission Date(s)	July 25, 2011
Brand Name	Nesina®
Generic Name	Alogliptin benzoate
Reviewer	Sang M. Chung, Ph.D.
Team Leader (Acting)	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Takeda
Submission Type	Resubmission, Standard
Formulation Strength(s)	6.25 mg, 12.5 mg, and 25 mg tablets
Indication	To improve glycemic control in patients with type 2 diabetes mellitus as monotherapy or combination therapy with a PPARγ agonist, a sulfonylurea, metformin or insulin
Dosage & Administration	25 mg once daily; 12.5 mg once daily in subjects with moderate renal impairment; 6.25 mg once daily in subjects with severe renal impairment or end stage renal disease

This amendment is to update values in the clinical pharmacology review dated January 18, 2012 because there were numerical errors as follows (new values in red):

Reviewer's Comment (new, page 14): The sponsor's justifications are acceptable. Mean AUC_{0-t} is 4738.9 ng/mL*min (n=5) for subjects with mild renal impairment without the subject with the higher AUC value and is 3258.1 ng/mL*hr (n=24) for the pooled control group (consisting of N=6 matched control group per renal impairment category).

Reviewer's Comment (original, page 14): The sponsor's justifications are acceptable. Mean AUC_{0-t} is 3124.7 ng/ml*min (n=5) for subjects with mild renal impairment without the subject with the higher AUC value and is 3012.1 ng/ml*hr (n=6) for the matching control group.

The exposure increase in the mild renal impairment group was by 76% (arithmetic mean ratio) compared to that of the matching control group (3261.24 ng/mL*hr; n=6) or the entire control group (3258.1 ng/mL*hr; n=24). The corresponding increase becomes 45% after excluding the subject with the higher AUC value. No dose adjustment is recommended for subjects with mild renal impairment if there is no significant difference in the safety profiles between the mild renal

impairment and normal renal function patients in the Phase 3 program. Please refer Dr. Valerie Pratt's review for the conclusive assessment of the safety profiles.

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/s/

SANG M CHUNG
03/07/2012

JAYABHARATHI VAIDYANATHAN
03/07/2012

CLINICAL PHARMACOLOGY REVIEW

NDA	22271
Submission Date(s)	July 25, 2011
Brand Name	Nesina®
Generic Name	Alogliptin benzoate
Reviewer	Sang M. Chung, Ph.D.
Team Leader (Acting)	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Takeda
Submission Type	Resubmission, Standard
Formulation Strength(s)	6.25 mg, 12.5 mg, and 25 mg tablets
Indication	To improve glycemic control in patients with type 2 diabetes mellitus as monotherapy or combination therapy with a PPARγ agonist, a sulfonylurea, metformin or insulin
Dosage & Administration	25 mg once daily; 12.5 mg once daily in subjects with moderate renal impairment; 6.25 mg once daily in subjects with severe renal impairment or end stage renal disease

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the resubmission of NDA 22271 for Nesina® (alogliptin benzoate) and finds it acceptable.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The submission is to address the issues identified in the Agency's Complete Response Letter dated on June 26, 2009 (Attachment 3-1). Among the issues, clinical deficiencies were as follows:

- The NDA data have not ruled out an unacceptable increase in cardiovascular (CV) risk with alogliptin
- The NDA contains only uncontrolled data beyond week 26 and it substantially limits interpretability
- The sponsor should provide safety and tolerability in patients with mild renal impairment compared to those of patients with normal renal function because alogliptin area under the time-concentration curve (AUC) was increased by 70%, which may require a dose adjustment if those data are not available.

The sponsor addresses the clinical issues as follows:

- A prospective, double blind CV outcome study (Study 402) has been conducted to evaluate the incidence of Major Adverse CV Events (MACE). The first pre-specified prospective interim analysis indicates that the point estimates of the hazard ratios and its 95% confidence interval (CI) meet the regulatory goal post (b) (4)
- Since the original NDA, a total of 526 subjects (15.0%) who received alogliptin 25 mg and 472 subjects (16.1%) who received all comparators were exposed for at least 1 year (defined as ≥335 days).
- Alogliptin AUC increase in patients with mild renal impairment is primarily driven by one subject. Furthermore, analysis of adverse events (AEs) based on either baseline or endpoint renal status indicated that the incidence of AEs in subjects with mild renal impairment was similar to that observed in subjects with normal renal function. Therefore, dose adjustment based on mild renal impairment at baseline is not necessary.

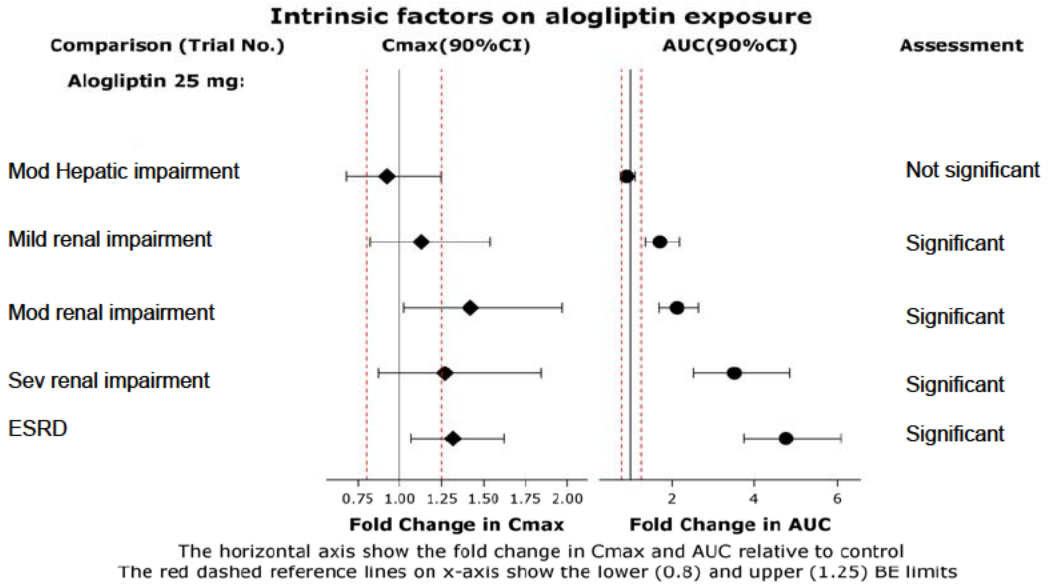
The dose adjustment for patients with mild renal impairment was the clinical pharmacology issue and it seems that the sponsor analysis and results reasonably address the issue.

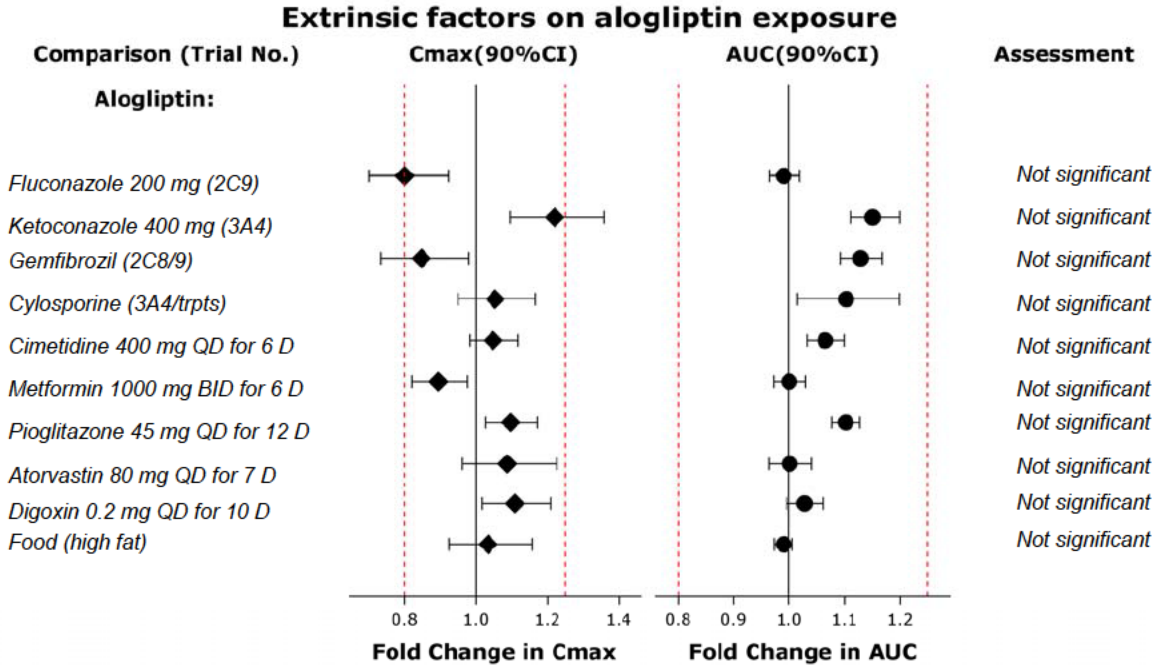
In addition, the sponsor included the following new clinical pharmacology data in the resubmission:

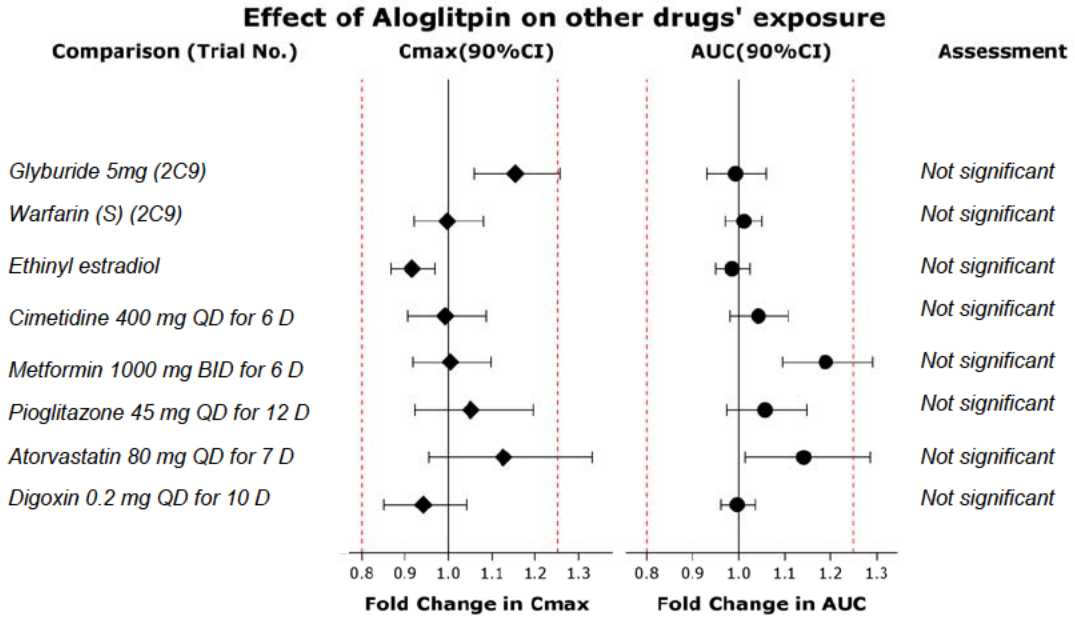
- Alogliptin absolute bioavailability is about 100% (Study SYR-322-103)
- Alogliptin pharmacokinetics and pharmacodynamics measured as DPP-4 inhibition following 12.5 mg twice daily for 7 days are comparable to those of 25 mg once daily for 7 days (Study SYR-322-101)
- There is no significant effect of voglibose on alogliptin exposure in Japanese subjects (Study SYR-322/CPH-004).

New clinical pharmacology data are acceptable except the drug interaction study (Study SYR-322/CPH-004). Voglibose (Basen®) has not been approved in US and its dose (0.2 mg TID) is significantly different from its analog (Precose®; 25 mg TID as the starting dose) approved in US. Therefore, the results may not be warranted for alogliptin labeling.

The clinical pharmacology data from the original submission indicate that intrinsic and extrinsic factors do not affect alogliptin exposure except renal impairment. In addition, alogliptin does not significantly affect exposure of other drugs including drugs with narrow therapeutic index such as warfarin, digoxin and oral contraceptive (see the following forest plots and the clinical pharmacology review dated on August 28, 2008).







2 Question Based Review

2.1 What is the absolute bioavailability?

Alogliptin bioavailability was assessed in an open-label, randomized, single-dose, 2-period crossover study in healthy subjects (n=24 planned, 21 analyzed; Study SYR-322-103). Subjects received a single oral dose of 25 mg (Treatment A; test) and a single intravenous (IV) dose of 12.5 mg (Treatment B; reference) with a 7-day washout interval. Study treatments and periods are summarized in Figure 1. Blood and urine sampling schedule are summarized in

Table 1.

Disposition of subjects and demographic characteristics are summarized in the supplemental figures and tables (Attachment 3-2). Mean alogliptin concentration-time profiles are shown in Figure 2 and its pharmacokinetic parameters are summarized in Table 2.

Alogliptin absolute bioavailability is about 100% (Table 2). Alogliptin pharmacokinetic parameters such as dose-normalized AUC, terminal half-life (t1/2) and fraction eliminated into urine (fe) were comparable between oral and IV dosing (table in Attachment 3-2). Clearance (CL), volume of distribution (Vz), t1/2 and fe(0-72 hour) were 14 L/hr, 416.7 L, 20.9 hr, and 64% dose, respectively, following IV dosing (table in Attachment 3-2).

<table>
<tr><th>Pretreatment period</th><th colspan="6">Treatment period</th></tr>
<tr><td>Screening</td><td>Check-in</td><td colspan="2">Period 1</td><td></td><td colspan="2">Period 2</td><td>Study exit/ET</td></tr>
<tr><td rowspan="4">Days -21 to -2</td><td rowspan="4">Day -1</td><td colspan="2">Day 1 dosing</td><td rowspan="4">Days 2 to 7</td><td>Day 8 dosing</td><td>Days 9 to 10</td><td rowspan="4">Day 11</td></tr>
<tr><td>Sequence I</td><td>A</td><td rowspan="2">B</td><td rowspan="2">Washout (a)</td></tr>
<tr><td>Sequence II</td><td>B</td><td>A</td></tr>
<tr><td colspan="6">confinement</td></tr>
</table>

(a) Washout began immediately after dosing.
Treatment A=25 mg of alogliptin administered orally in tablet form (test treatment), Treatment B=12.5 mg of alogliptin administered as a 30-minute IV infusion at a constant flow rate (reference treatment), ET=early termination

Figure 1 Study schematic (Study SYR-322-103)

Table 1 Pharmacokinetic blood and urine sampling schedule (Study SYR-322-103)

Plasma

Treatment	Scheduled time
Alogliptin 25 mg administered orally	Predose (within 1 hour prior to dose) and at 0.25 (15 min), 0.5 (30 min), 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose.
Alogliptin 12.5 mg administered IV	Predose (within 1 hour prior to dose) and at 0.083 (5 min), 0.167 (10 min), 0.25 (15 min), 0.5 (30 min), 0.583 (35 min), 0.667 (40 min), 0.75 (45 min), 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours after the start of infusion.

Urine

Study Day	Scheduled Time	
	25 mg orally	12.5 mg IV
-1 to 1 and 7 to 8	Predose (-12 to 0 hours)	Predose (-12 to 0 hours)
1 and 8	0 to 2 and 2 to 4 hours postdose	0 to 2 and 2 to 4 hours after the start of dosing
1 to 2 and 8 to 9	4 to 24 hours postdose	4 to 24 hours after the start of dosing
2 to 3 and 9 to 10	24 to 48 hours postdose	24 to 48 hours after the start of dosing
3 to 4 and 10 to 11	48 to 72 hours postdose	48 to 72 hours after the start of dosing

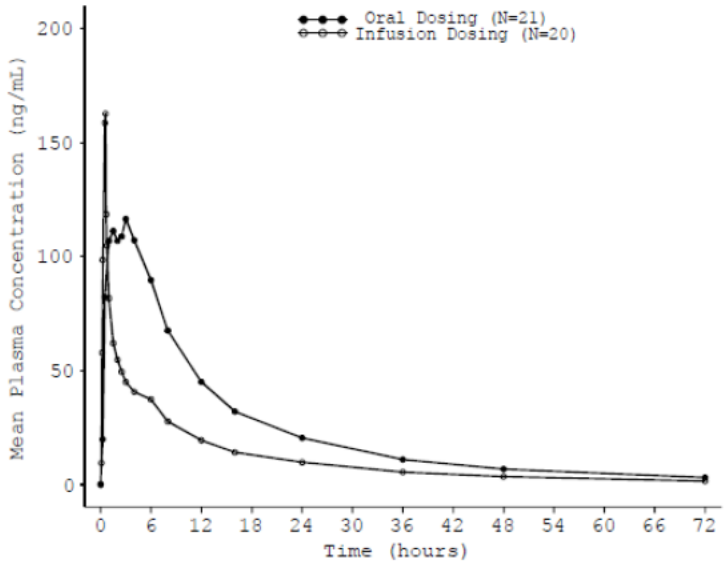


Figure 2 **Mean plasma concentration-time profiles by treatments (Study SYR-322-103)**

Table 2 **Statistical analysis of dose-adjusted plasma pharmacokinetic parameters of alogliptin oral 25 mg and alogliptin IV 12.5 mg (Study SYR-322-103)**

	LS Mean		
Parameter (unit)	Treatment A: Alogliptin 25 mg Oral (T) n=21	Treatment B: Alogliptin 12.5 mg IV (R) n=20	Ratio (T/R)·100 (90% CI) (a)
AUC(0-inf) ([ng·hr/mL]/mg) (b)	72.57	71.33	101.74 (99.01, 104.56)
AUC(0-tlqc) ([ng·hr/mL]/mg)	69.10	66.89	103.31 (100.38, 106.31)
AUC(0-24) ([ng·hr/mL]/mg)	52.69	51.45	102.42 (98.72, 106.26)
Cmax ([ng/mL]/mg)	5.74	13.54	42.38 (38.39, 46.79)
Tmax (hr) (c)	2.250	0.558	—

Source: Table 15.2.1.3.

T=test treatment, R=reference treatment, — =not applicable.

(a) Ratios and CIs are presented as percentages.

(b) AUC(0-inf) is used as absolute bioavailability.

(c) Tmax is presented as median, unadjusted for dose; P<0.001 using Wilcoxon signed rank test with matched subjects who received both treatments (n=20).

2.2 Is there any difference in alogliptin PK and PD between once-daily and twice daily dosing?

Alogliptin pharmacokinetics and pharmacodynamics was evaluated following 12.5 mg twice daily (BID) and 25 mg once daily (QD) for days in healthy subjects (Study SYR-322-101). Pharmacodynamic effects were measured by DPP-4 inhibition.

Study design is summarized in Figure 3. Subject disposition and demographic characteristics are summarized in supplemental table and figure (Attachment 3-2). Blood and urine sampling schedules are summarized in Table 3. Pharmacokinetic and pharmacodynamic profiles are shown in Figure 4. Alogliptin PK and PD parameters are summarized in Table 4 and Table 5.

Alogliptin AUCs were comparable between 25 mg QD and 12.5 mg BID for 7 days dosing with the least square geometric mean ratio (LSGMR; BID/QD, 90% CI) as 102.9 (97.6-108.6). Alogliptin Cmax was low as predicted following 12.5 mg BID compared to that of 25 mg QD with LSGMR (90% CI) as 65.4 (59.2-72.2). In addition, pharmacodynamics was comparable between both dosing regimens with LSGMR for the area under pharmacodynamic effect-time curve (AUEC(0-24)) as 102.1 (101.5-102.6). DPP-4 inhibition was above 80% for both dosing regimens 24 hours postdose.

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**
		A (n=14)	**Washout**	**B**	**Study Exit**
		B (n=14)		**A**	

(a) Samples for pharmacokinetic analyses were collected on Days 1 and 5 to 7.
(b) Subjects were randomized prior to dosing on Day 1.
A=alogliptin 25 mg QD=reference treatment.
B=alogliptin 12.5 mg BID=test treatment.

Figure 3 Study schematic (Study SYR-322-101)

Table 3 Sampling schedule (Study SYR-322-101)

PK samples

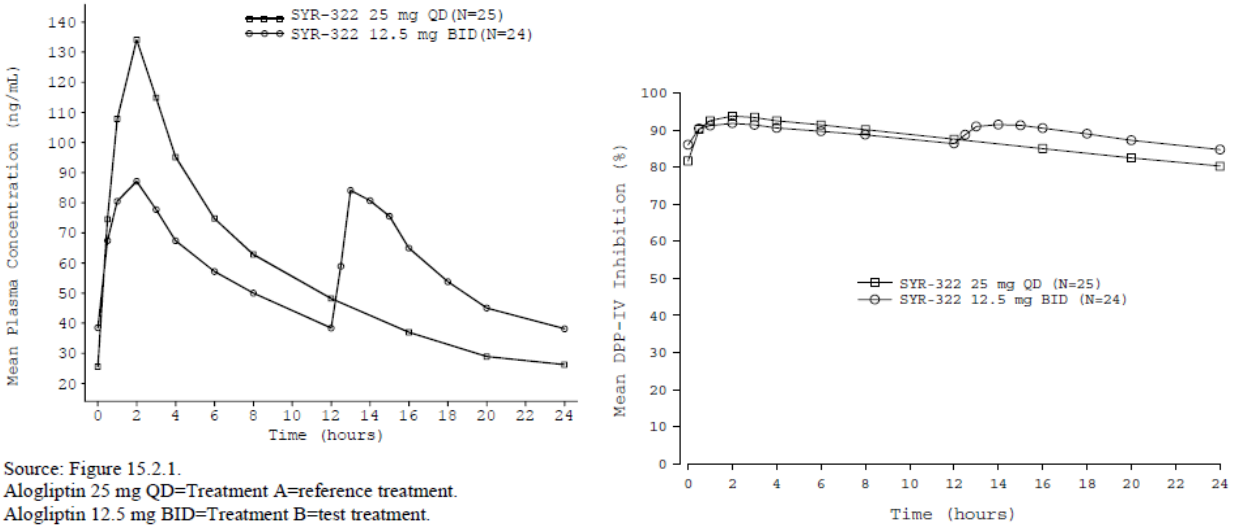
Treatment	Study Day	Scheduled Time
25 mg QD	Days 1, 5, and 6	Within 30 minutes prior to dose.
	Day 7	Within 30 minutes prior to dose, and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 hours postdose.
12.5 mg BID	Days 1, 5, and 6	Within 30 minutes prior to morning dose.
	Day 7	Within 30 minutes prior to morning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

Urine samples

Treatment	Study Day	Scheduled Time
25 mg QD	Day 1	-12 to 0 hours predose.
	Day 7	-12 to 0 hours predose and 0 to 24 hours postdose.
12.5 mg BID	Day 1	-12 to 0 hours predose.
	Day 7	-12 to 0 hours predose, 0 to 12, and 12 to 24 hours postdose (12 to 24 hour collection interval began immediately after evening dose).

PD samples

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.



Source: Figure 15.2.1.
Alogliptin 25 mg QD=Treatment A=reference treatment.
Alogliptin 12.5 mg BID=Treatment B=test treatment.

Figure 4 **Mean alogliptin plasma concentration-time profiles (left) and DPP-4 inhibition (right) by treatments (Study SYR-322-101)**

Table 4 Alogliptin PK parameters (Study SYR-322-101)

Analyte Parameter (units)	Arithmetic Mean (%CV)		LS Mean		
	Alogliptin 12.5 mg BID (T) n=24	Alogliptin 25 mg QD (R) n=25	Alogliptin 12.5 mg BID (T) n=24	Alogliptin 25 mg QD (R) n=25	Ratio (T/R)·100 (90% CI) (a)
Alogliptin Plasma					
AUC(0-24) (ng·hr/mL)	1383.58 (14.386)	1362.22 (17.877)	1378.53	1339.21	102.94 (97.57, 108.60)
AUC(0-12) AM	706.69 (15.364)	—	698.77	—	95.88 (93.39, 98.44) (b)
AUC(12-24) PM	676.89 (14.482)	—	670.01	—	(b)
Cmax (ng/mL)	92.65 (22.668)	144.26 (24.812)	91.02	139.23	65.38 (59.17, 72.24)
Cmin (ng/mL)	37.23 (17.577)	24.84 (21.977)	37.17	24.43	152.16 (145.27, 159.37)
Ctrough (ng/mL) (c)	38.62 (16.287)	24.59 (18.644)	—	—	—
Tmax (hr) (d,e,f)	1.98 (0.983, 3.017)	1.98 (0.517, 2.983)	1.98	1.98	—
Swing (%)	152.94 (37.830)	496.91 (34.473)	—	—	—
Fluctuation (%)	—	208.61 (20.585)	—	—	—
Fluctuation (0-12) (%)	92.29 (26.526)	—	—	—	—
Cavg (ng/mL)	—	56.80 (17.877)	—	—	—
Cavg (0-12) (ng/mL)	59.31 (15.370)	—	—	—	—
Cavg (12-24) (ng/mL)	56.14 (14.460)	—	—	—	—
Alogliptin Urine					
Ae(0-24) (mg)	16.36 (12.961)	16.03 (28.670)	16.25	14.85	109.41 (90.91, 131.68)
CLr(0-24) (L/hr)	12.03 (17.139)	11.97 (30.549)	11.82	11.09	106.61 (89.77, 126.60)
Fe(0-24) (%)	65.44 (12.961)	64.13 (28.670)	—	—	—

Source: Tables 15.2.1.4, 15.2.1.5, 15.2.1.6, and 15.2.1.11.
— =not applicable, %CV=percent coefficient of variation, T=test treatment (treatment B), R=reference treatment (treatment A).
(a) Ratios and CIs were presented as percentages.
(b) Value shown is the ratio of AUC(12-24) PM to AUC(0-12) AM.
(c) Alogliptin 25 mg QD N=75, alogliptin 12.5 mg BID N=74. Sample size for Ctrough is defined in the Statistical Analysis Plan as observed predose (trough) plasma concentration on Days 5, 6, and 7.
(d) Median (minimum, maximum) values are presented for Tmax.
(e) n=24 for alogliptin 25 mg QD Tmax LS Mean and AUC(0-tau).
(f) P=0.905.

Table 5 Mean DPP-4 inhibition on Day 7 (Study SYR-322-101)

Analyte Parameter (units)	Arithmetic Mean (%CV)		LS Mean		
	Alogliptin 25 mg QD (A)	Alogliptin 12.5 mg BID (B)	Alogliptin 25 mg QD (R)	Alogliptin 12.5 mg BID (T)	Ratio (T/R)·100 (90% CI) (a)
Alogliptin Plasma	n=25	n=24	n=25	n=24	
AUEC(0-24) (%Inhibition) (hr)·	2093.63 (2.161)	2132.09 (1.866)	2092.05	2135.00	102.05 (101.50, 102.61)
AUEC(0-tau) (%Inhibition) (hr)·	2093.63 (2.161)	1064.80 (1.659)	—	—	—
Emax (%Inhibition)	94.42 (1.446)	92.28 (1.537)	—	—	—
Tmax (hr) (b)	1.98 (0.517, 4.017)	1.98 (0.500, 4.083)	—	—	—
E0 (%Inhibition)	81.69 (3.197)	86.03 (2.833)	81.66	86.20	105.55 (104.70, 106.41)
E12 (%Inhibition)	—	86.40 (2.624)	—	—	—
E24 (%Inhibition)	80.30 (3.143)	84.74 (2.802)	80.22	84.91	105.85 (104.91, 106.79)

Source: Tables 15.2.1.8 and 15.2.1.9.
— =not applicable, E12=observed effect at 12 hours postdose for BID dosing regimen, T=test treatment (treatment B), R=reference treatment (treatment A).
(a) P-value<0.001 for treatment difference for AUEC, E0, and E24.
(b) Median (minimum, maximum) values are presented for Tmax.

Reviewer's comments: The relationship between alogliptin plasma concentrations and data of plasma DPP-4 inhibition is known to be direct without a delay. Therefore, it seems reasonable to assume that alogliptin concentration - DPP-4 inhibition profiles are comparable between the dosing regimens. Individual data indicate PK-PD relationship is comparable between dosing regimens (Figure 5).

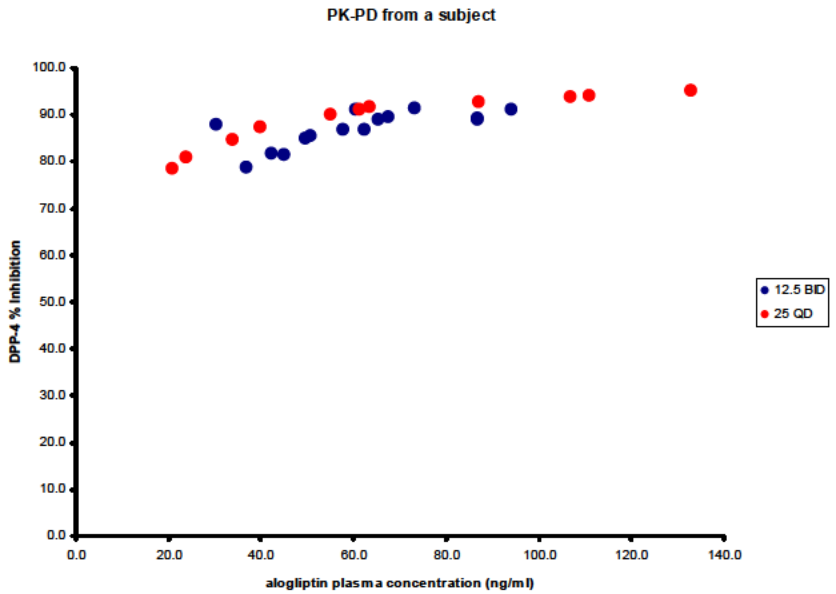


Figure 5 **DPP-4 inhibition vs. alogliptin concentrations following multiple dose (Day 7) by dosing regimens**

2.3 What is the effect of voglibose on alogliptin exposure?

The effect of voglibose 0.2 mg TID for 6 days on 25 mg alogliptin exposure was evaluated using an open-label study in Japanese (n=10; Study SYR-322/CPH-004). Study design is summarized in Figure 6.

DAY	-28 to -2	-1	1	2 to 5	6 to 10	11	12 to 13	14	21
Procedures	S	Hospital A & pre-study E	E & A	E	E & A	E & A	E & A	E & Hospital discharge	Follow-up
alogliptin			SYR-322 25 mg			SYR-322 25 mg			
voglibose					Voglibose 0.2 mg TID	Voglibose 0.2 mg TID	Voglibose 0.2 mg TID		
		←			confinement			→	

S: Screening, E: Examination, A: Admission

Figure 6 **Study schematic (Study SYR-322/CPH-004)**

Disposition of subjects are shown in the supplemental figures (Attachment 3-2). Mean (SD) plasma concentration-time profiles for alogliptin are shown in Figure 7. Its metabolites concentration-time profiles are shown in the supplemental figures (Attachment 3-2). PK parameters of alogliptin and its metabolites are summarized in Table 10. The LSGMR of alogliptin and its metabolites with and without voglibose are summarized in Table 12. The statistical analysis indicates that voglibose reduced alogliptin AUC(0-72) by 23.2% and Cmax by 10.3%.

Reviewer's comments: Voglibose (Basen®), an alpha-glucosidase inhibitor, has not been approved in US and its dose (0.2 mg TID) is different from an analog (Precose®; 25 mg TID as the starting dose) approved in US. The results of this DDI may not be warranted for alogliptin labeling.

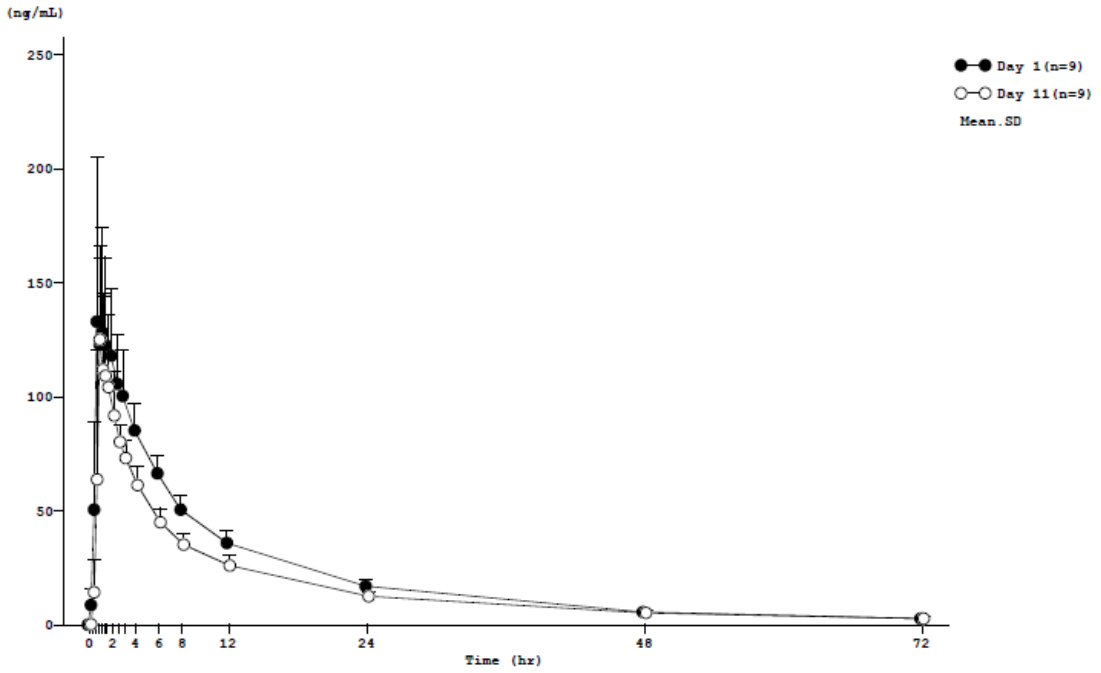


Figure 7 **Mean (SD) plasma concentration-time profiles by treatments (Study SYR-322/CPH-004)**

Table 6 **Statistical analysis of pharmacokinetic parameters for alogliptin and its metabolites (Study SYR-322/CPH-004)**

Parameter (units)	N		LS Mean			
	Day 1	Day 11	Day 1	Day 11	Ratio (Day 11/Day 1) (%) (a)	90% CI (%) (a)
SYR-322Z						
AUC(0-72) (ng•hr/mL)	9	9	1502.684	1154.043	76.8	74.6, 79.1
AUC(0-tlqc) (ng•hr/mL)	9	9	1502.684	1154.043	76.8	74.6, 79.1
AUC(0-inf) (ng•hr/mL)	9	9	1567.581	1229.169	78.4	75.8, 81.1
Cmax (ng/mL)	9	9	145.797	130.752	89.7	75.7, 106.2
CLr (L/hr)	9	9	11.390	11.061	97.1	91.3, 103.3
M-I						
AUC(0-72)	9	9	10.349	9.206	89.0	82.5, 95.9
AUC(0-tlqc)	9	9	9.427	8.385	89.0	82.5, 95.9
AUC(0-inf)	7	7	19.164	17.479	91.2	86.0, 96.8
Cmax	9	9	0.347	0.348	100.5	88.5, 114.0
M-II						
AUC(0-72)	9	9	58.125	41.225	70.9	66.9, 75.2
AUC(0-tlqc)	9	9	56.570	40.111	70.9	66.2, 76.0
AUC(0-inf)	9	9	58.778	42.087	71.6	67.2, 76.3
Cmax	9	9	5.402	4.427	81.9	73.8, 91.0

Day 1: without voglibose, Day 11: with voglibose
Source: Table 14.n, Table 14.o, Table 14.p, Table 14.q.
(a) The ratio and CI values presented in the source data have been converted to percentages for presentation in this CSR.

2.4 Is no dose adjustment for patients with mild renal impairment acceptable?

Based on findings from the PK study in the original submission, the sponsor proposed a dose adjustment for patients with moderate renal impairment to 12.5 mg, and those with severe renal impairment and end stage renal disease (ESRD) requiring dialysis to 6.25 mg because alogliptin AUC_{0-t} increased by 108%, 219%, and 281%, respectively, compared to that of healthy subjects. The sponsor did not propose a dose adjustment for patients with mild renal impairment though mean AUC_{0-t} in the group was increased by 69% (Table 7). The Agency recommended a dose adjustment to 12.5 mg for this sub-group and also requested further sub-group analysis for adverse event (AE) comparability.

In this resubmission, the sponsor indicates that AUC increase of 69% for patients with mild renal impairment is driven by one subject and AUCs of the remaining 5 subjects are comparable those of normal subjects. In addition, the sponsor concludes that the incidence of AEs by the baseline and endpoint renal status are similar between subjects with mild renal impairment and those with normal renal function, both receiving 25 mg dose. Therefore, they propose that no dose adjustment is needed in mild renal impaired patients.

Reviewer's Comment: The sponsor's justifications are acceptable. Mean AUC_{0-t} is 3124.7 ng/ml*min (n=5) for subjects with mild renal impairment without the subject with the higher AUC value and is 3012.1 ng/ml*hr (n=6) for the matching control group. The above values indicate that inclusion of one subject results in the observed higher mean value for the mild renal impairment sub-group. The relationship between creatinine clearance and AUC or Cmax supports the sponsor's justifications as well (Figure 8). Furthermore, the safety analysis on the incidence by the baseline and endpoint renal status supports that patients with mild renal impairment appear not to be a sub-group at risk for higher AEs (Table 8 and 9). The renal function biomarker in the PK study was based on Cockcroft-Gault (CG) formula and those in the AE analysis are based on both CG and MDRD (Modification of Diet in Renal Disease) formulas. The sponsor indicates that the majority of subjects for alogliptin 25 mg group and all comparators group had the normal renal function by the CG formula, while the majority was classified as mild renal impairment based on MDRD formula. The above difference between estimated glomerular filtration (eGFR) methods may not be a confounding factor for the AE analysis because similarity conclusion on the AE incidences is comparable between eGFR methods.

Table 7 Alogliptin pharmacokinetic parameters for patients with mild renal impairment and statistical analysis compared to those of healthy subjects

Parameter (units)	Arithmetic Mean (%CV)		Geometric Least Squares Means		Ratio (T/R) *100 (b) 90% CI (%) (c) Impairment Group Difference (P-Value) (d)
	Mild N=6	Healthy N=6	Mild N=6	Healthy N=6	
AUC(0- tlqc) (ng·hr/mL)	5554.08 (37)	3198.66 (11)	5348.65	3156.46	169.451 (134.497, 213.488) 0.002
AUC(0-inf) (ng·hr/mL)	5738.80 (39)	3261.24 (10)	5506.56	3216.92	171.175 (134.835, 217.310) 0.003
Cmax (ng/mL)	327.50 (26)	285.83 (29)	313.34	278.22	112.622 (82.60, 153.553) 0.500
Tmax (hr)	1.667 (75)	1.475 (120)	1.25(a)	0.68 (a)	n/a 0.368 (e)
CL/F(L/hr)	9.53 (27)	15.48 (11)	n/a	n/a	n/a
Vz/F(L)	549.41 (27)	624.15 (18)	n/a	n/a	n/a
T1/2(hr)	40.41 (12)	27.89 (14)	n/a	n/a	n/a

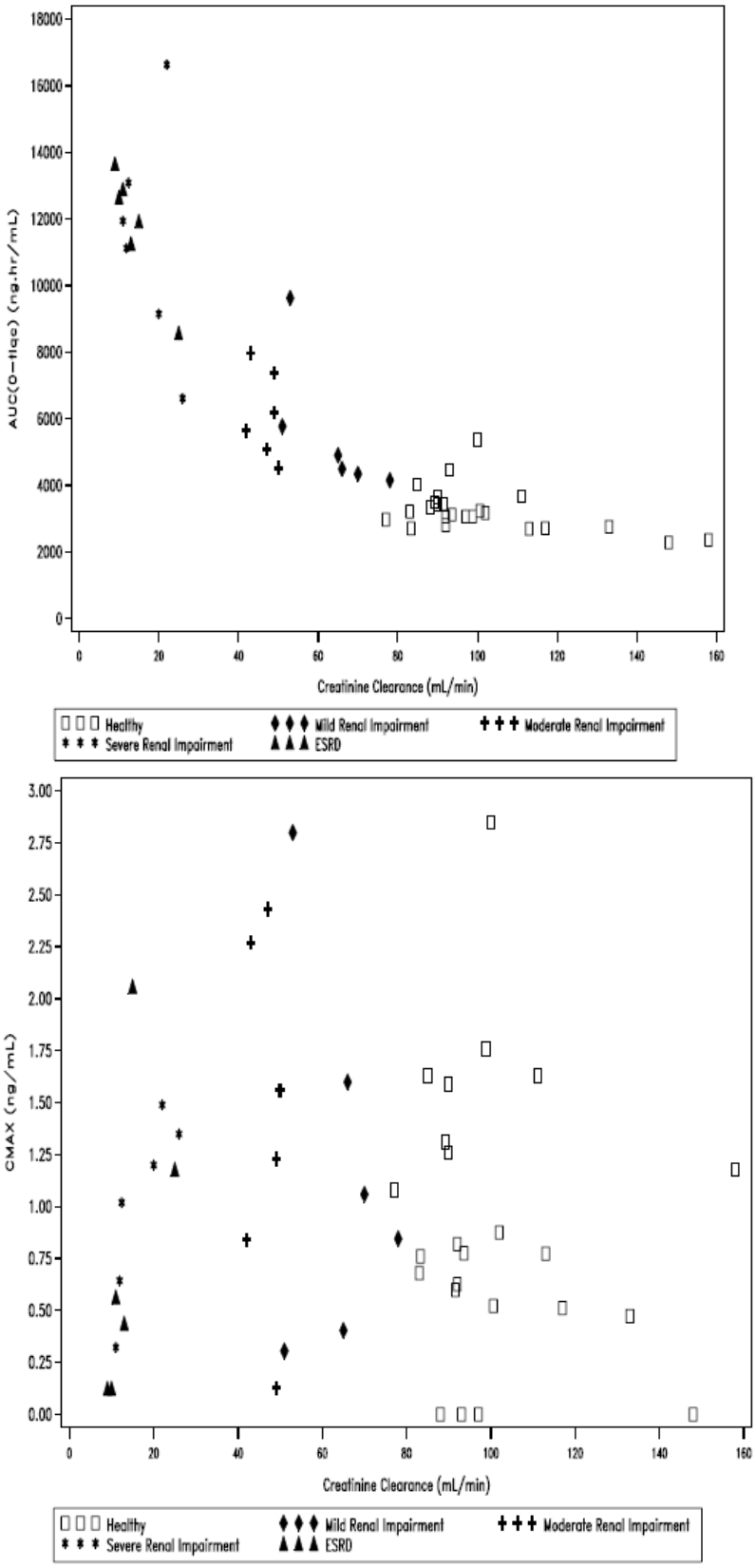


Figure 8 **AUC (left) and Cmax versus creatinine clearance.**

Table 8 AEs by Endpoint Renal Function (Cockcroft-Gault) and Preferred Term (Controlled Phase 2 and 3 Study Group)

	Number (%) of Subjects											
	All Comparators (a) N=2934				Alogliptin 25 mg N=3500				All Alogliptin (b) N=5232			
Preferred Term	Normal N=1470	Mild N=952	Moderate N=304	Severe N=19	Normal N=1832	Mild N=1070	Moderate N=355	Severe N=28	Normal N=2925	Mild N=1588	Moderate N=449	Severe N=30
Common AEs (≥3% of Subjects Overall in Any Presented Grouping)												
Subjects with at Least 1 AE	850 (57.8)	550 (57.8)	184 (60.5)	11 (57.9)	1148 (62.7)	629 (58.8)	195 (54.9)	21 (75.0)	1844 (63.0)	955 (60.1)	260 (57.9)	23 (76.7)
Headache	66 (4.5)	32 (3.4)	5 (1.6)	0	82 (4.5)	42 (3.9)	12 (3.4)	0	125 (4.3)	71 (4.5)	18 (4.0)	0
Nasopharyngitis (c)	56 (3.8)	29 (3.0)	11 (3.6)	1 (5.3)	85 (4.6)	34 (3.2)	9 (2.5)	1 (3.6)	140 (4.8)	53 (3.3)	11 (2.4)	1 (3.3)
Urinary tract infection (c)	55 (3.7)	35 (3.7)	14 (4.6)	1 (5.3)	59 (3.2)	44 (4.1)	24 (6.8)	1 (3.6)	99 (3.4)	75 (4.7)	35 (7.8)	1 (3.3)
Upper respiratory tract infection (c)	43 (2.9)	24 (2.5)	3 (1.0)	0	88 (4.8)	28 (2.6)	6 (1.7)	0	130 (4.4)	42 (2.6)	8 (1.8)	0
Hypertension	40 (2.7)	32 (3.4)	12 (3.9)	0	56 (3.1)	37 (3.5)	8 (2.3)	0	96 (3.3)	51 (3.2)	10 (2.2)	1 (3.3)
Diarrhea	56 (3.8)	36 (3.8)	11 (3.6)	0	56 (3.1)	29 (2.7)	5 (1.4)	1 (3.6)	81 (2.8)	47 (3.0)	6 (1.3)	1 (3.3)
AEs of Interest (≥1% of Subjects Overall in Alogliptin 25 mg Grouping)												
Rash	16 (1.1)	9 (0.9)	1 (0.3)	0	29 (1.6)	14 (1.3)	3 (0.8)	0	40 (1.4)	20 (1.3)	5 (1.1)	0
Pruritus	3 (0.2)	6 (0.6)	3 (1.0)	0	24 (1.3)	14 (1.3)	5 (1.4)	0	35 (1.2)	19 (1.2)	6 (1.3)	0
Edema peripheral	46 (3.1)	12 (1.3)	5 (1.6)	0	57 (3.1)	24 (2.2)	5 (1.4)	2 (7.1)	86 (2.9)	35 (2.2)	6 (1.3)	2 (6.7)
Influenza	41 (2.8)	25 (2.6)	5 (1.6)	0	49 (2.7)	31 (2.9)	3 (0.8)	0	76 (2.6)	41 (2.6)	4 (0.9)	0
Bronchitis	25 (1.7)	26 (2.7)	1 (0.3)	0	40 (2.2)	16 (1.5)	9 (2.5)	0	68 (2.3)	24 (1.5)	11 (2.4)	0
Pharyngitis	18 (1.2)	12 (1.3)	1 (0.3)	0	30 (1.6)	10 (0.9)	3 (0.8)	0	47 (1.6)	20 (1.3)	4 (0.9)	0
Sinusitis	21 (1.4)	10 (1.1)	3 (1.0)	0	33 (1.8)	5 (0.5)	1 (0.3)	0	49 (1.7)	6 (0.4)	3 (0.7)	0
Gastroenteritis	12 (0.8)	8 (0.8)	4 (1.3)	0	19 (1.0)	10 (0.9)	5 (1.4)	0	28 (1.0)	16 (1.0)	6 (1.3)	0

Source: IAS Table 8.4.2.1Ra, IAS Table 8.4.9.2Ra, and IAS Table 8.4.2.9Ra.
(a) The All Comparators Grouping combines placebo and active comparator groups, which are not shown in the table.
(b) The All Alogliptin Grouping combines 25 mg with the 6.25, 12.5, 50, and 100 mg groups, which are not shown in the table.
(c) Nasopharyngitis, urinary tract infection, and upper respiratory tract infection were AEs of interest reported by ≥1% of subjects in the Alogliptin 25 mg Grouping, which are not repeated below.
Note: sample sizes may be smaller due to a lack of post-randomization data for subjects in the ongoing Study 402.

Table 9 AEs by Endpoint Renal Function (MDRD) and Preferred Term (Controlled Phase 2 and 3 Study Group)

	Number (%) of Subjects											
	All Comparators (a) N=2934				Alogliptin 25 mg N=3500				All Alogliptin (b) N=5232			
Preferred Term	Normal N=473	Mild N=1775	Moderate N=467	Severe N=31	Normal N=539	Mild N=2120	Moderate N=599	Severe N=27	Normal N=854	Mild N=3270	Moderate N=839	Severe N=29
Common AEs (≥3% of Subjects Overall in Any Presented Grouping)												
Subjects with at Least 1 AE	255 (53.9)	1048 (59.0)	270 (57.8)	22 (71.0)	337 (62.5)	1301 (61.4)	333 (55.6)	22 (81.5)	533 (62.4)	2024 (61.9)	501 (59.7)	24 (82.8)
Headache	23 (4.9)	67 (3.8)	13 (2.8)	0	33 (6.1)	87 (4.1)	16 (2.7)	0	46 (5.4)	139 (4.3)	29 (3.5)	0
Nasopharyngitis (c)	14 (3.0)	69 (3.9)	13 (2.8)	1 (3.2)	24 (4.5)	86 (4.1)	18 (3.0)	1 (3.7)	37 (4.3)	140 (4.3)	27 (3.2)	1 (3.4)
Urinary tract infection (c)	17 (3.6)	70 (3.9)	15 (3.2)	3 (9.7)	13 (2.4)	88 (4.2)	27 (4.5)	0	27 (3.2)	137 (4.2)	46 (5.5)	0
Upper respiratory tract infection (c)	15 (3.2)	47 (2.6)	8 (1.7)	0	34 (6.3)	74 (3.5)	14 (2.3)	0	47 (5.5)	116 (3.5)	17 (2.0)	0
Hypertension	8 (1.7)	54 (3.0)	21 (4.5)	1 (3.2)	16 (3.0)	70 (3.3)	14 (2.3)	1 (3.7)	27 (3.2)	109 (3.3)	20 (2.4)	2 (6.9)
Diarrhea	15 (3.2)	73 (4.1)	14 (3.0)	1 (3.2)	14 (2.6)	67 (3.2)	8 (1.3)	2 (7.4)	23 (2.7)	96 (2.9)	14 (1.7)	2 (6.9)
AEs of Interest (≥1% of Subjects Overall in Alogliptin 25 mg Grouping)												
Rash	3 (0.6)	22 (1.2)	1 (0.2)	0	9 (1.7)	31 (1.5)	6 (1.0)	0	13 (1.5)	44 (1.3)	8 (1.0)	0
Pruritus	0	9 (0.5)	3 (0.6)	0	3 (0.6)	34 (1.6)	6 (1.0)	0	6 (0.7)	46 (1.4)	8 (1.0)	0
Edema peripheral	12 (2.5)	40 (2.3)	11 (2.4)	0	13 (2.4)	59 (2.8)	14 (2.3)	2 (7.4)	18 (2.1)	82 (2.5)	27 (3.2)	2 (6.9)
Influenza	16 (3.4)	42 (2.4)	13 (2.8)	0	15 (2.8)	53 (2.5)	15 (2.5)	0	24 (2.8)	78 (2.4)	19 (2.3)	0
Bronchitis	6 (1.3)	41 (2.3)	5 (1.1)	0	5 (0.9)	50 (2.4)	10 (1.7)	0	13 (1.5)	74 (2.3)	16 (1.9)	0
Pharyngitis	8 (1.7)	22 (1.2)	1 (0.2)	0	10 (1.9)	31 (1.5)	2 (0.3)	0	15 (1.8)	51 (1.6)	5 (0.6)	0
Sinusitis	1 (0.2)	25 (1.4)	8 (1.7)	0	10 (1.9)	25 (1.2)	4 (0.7)	0	12 (1.4)	40 (1.2)	6 (0.7)	0
Gastroenteritis	4 (0.8)	15 (0.8)	5 (1.1)	0	6 (1.1)	22 (1.0)	6 (1.0)	0	9 (1.1)	32 (1.0)	9 (1.1)	0

Source: IAS Table 8.4.2.1Ra, IAS Table 8.4.9.2Ra, and IAS Table 8.4.2.8Ra.
(a) The All Comparators Grouping combines placebo and active comparator groups, which are not shown in the table.
(b) The All Alogliptin Grouping combines 25 mg with the 6.25, 12.5, 50, and 100 mg groups, which are not shown in the table.
(c) Nasopharyngitis, urinary tract infection, and upper respiratory tract infection were AEs of interest reported by ≥1% of subjects in the Alogliptin 25 mg Grouping, which are not repeated below.
Note: sample sizes may be smaller due to a lack of post-randomization data for subjects in the ongoing Study 402.

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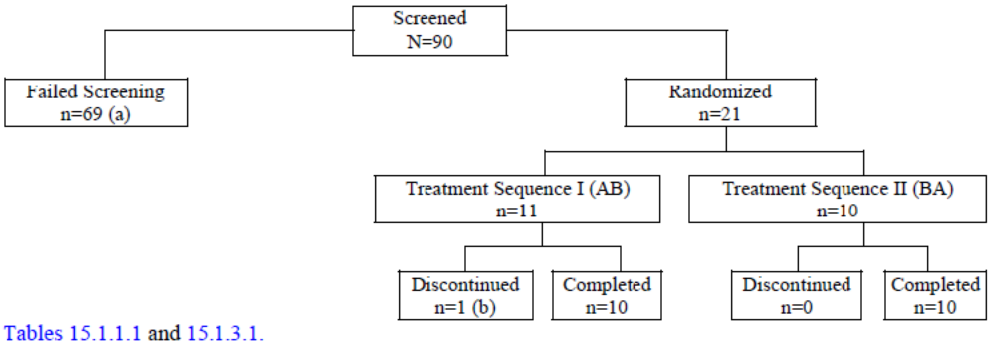
3.2 Supplemental figures and tables

Table 10 Investigational products (Study SYR-322-103)

Study Drug	Lot No.	Expiration/Retest Date
Alogliptin 25 mg tablets (phase 3 tablets)	7F079	30 November 2008
Alogliptin for preparation of a sterile solution for IV administration	0319081	13 May 2008



Sources: Tables 15.1.1.1 and 15.1.3.1.
Treatment A=25 mg of alogliptin administered orally in tablet form (test treatment), Treatment B=12.5 mg of alogliptin administered as a 30-minute IV infusion at a constant flow rate (reference treatment).
(a) Reasons for screen failure were failure to meet entrance criteria (51 subjects), voluntary withdrawal (14 subjects), and "other" (4 subjects).
(b) Reason for discontinuation was abnormal cardiac telemetry prior to IV dosing.

Figure 9 Disposition of subjects (Study SYR-322-103)

Table 11 Summary of Demographic and Other Baseline Characteristics of Randomized Subjects (Study SYR-322-103)

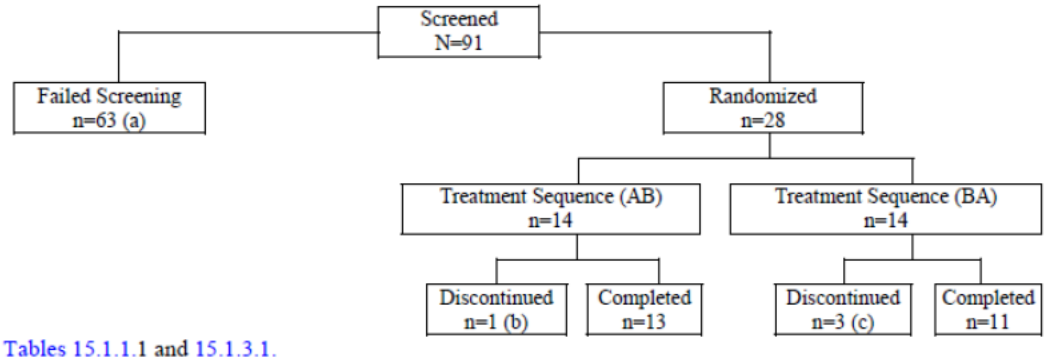
Characteristic	Treatment sequence (a)		Overall N=21
	Sequence 1: AB N=11	Sequence 2: BA N=10	
Gender, n (%)			
Male	2 (18.2)	5 (50.0)	7 (33.3)
Female	9 (81.8)	5 (50.0)	14 (66.7)
Mean age (SD), yr	32.3 (10.74)	33.9 (10.77)	33.0 (10.52)
Race, n (%)			
White	7 (63.6)	7 (70.0)	14 (58.3)
Black or African American	3 (27.3)	3 (30.0)	6 (25.0)
Asian	1 (9.1)	0	1 (4.2)
Ethnicity, n (%)			
Hispanic or latino	5 (45.5)	4 (40.0)	9 (42.9)
Not Hispanic or Latino	6 (54.5)	6 (60.0)	12 (57.1)
Mean weight (SD), kg	67.28 (11.808)	74.77 (14.663)	70.85 (13.460)
Mean height (SD), cm	164.1 (7.19)	168.1 (8.25)	166.0 (7.79)
Mean BMI (SD), kg/m2	24.99 (3.891)	26.30 (3.667)	25.61 (3.751)

Table 12 **Alogliptin pharmacokinetic parameters (Study SYR-322-103)**

Parameter (unit)	Arithmetic Mean (%CV)	
	Treatment A: Alogliptin 25 mg Oral	**Treatment B: Alogliptin 12.5 mg IV**
Plasma		
Dose-adjusted		
AUC(0-inf) ([ng□hr/mL]/mg)	73.49 (15.778)	73.02 (16.364)
AUC(0-tlqc) ([ng□hr/mL]/mg)	69.96 (15.659)	68.47 (16.258)
AUC(0-24) ([ng□hr/mL]/mg)	53.46 (16.868)	52.46 (15.047)
Cmax ([ng/mL]/mg)	5.94 (27.903)	13.88 (21.484)
Unadjusted		
AUC(0-tlqc) (ng□hr/mL)	1749.04 (15.659)	855.82 (16.258)
AUC(0-inf) (ng□hr/mL)	1837.21 (15.778)	912.74 (16.364)
AUC(0-24) (ng□hr/mL)	1336.51 (16.868)	655.80 (15.047)
Cmax (ng/mL)	148.51 (27.903)	173.47 (21.484)
Tmax (hr) (a)	2.00 (0.500, 6.000)	0.56 (0.500, 0.683)
λz (1/hr)	0.04 (11.141)	0.03 (26.140)
T1/2 (hr)	19.61 (11.431)	20.86 (20.120)
CL/F (L/hr)	13.93	□
CL (L/hr)	-	14.04 (15.525)
Vz/F (L)	392.79 (18.008)	-
Vz (L)	-	416.71 (20.824)
Urine		
Ae(0-24) (mg)	12.04 (16.493)	6.53 (12.162)
Ae(0-72) (mg)	15.33 (13.775)	8.05 (12.582)
Fe(0-24) (%)	48.15 (16.493)	52.24 (12.162)
Fe(0-72) (%)	61.31 (13.775)	64.36 (12.582)
CLr(0-24) (L/hr)	9.24 (23.933)	10.17 (19.233)
CLr(0-72) (L/hr)	9.00 (22.812)	9.56 (19.300)

Table 13 Investigational products (Study SYR-322-101)

Study Drug	Lot No.	Expiration/Retest Date
Alogliptin 25 mg	Z6419021	31-Oct-2007
Alogliptin 12.5 mg	Z6418021	31-Oct-2007



Source: Tables 15.1.1.1 and 15.1.3.1.
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).

Figure 10 disposition of subjects (Study SYR-322-101)

Table 14 summary of demographic characteristics of subjects (Study SYR-322-101)

Characteristic	Treatment Sequence (a)		
	AB n=14	BA n=14	Overall N=28
Gender, n (%)			
Male	11 (39.3)	9 (32.1)	20 (71.4)
Female	3 (10.7)	5 (17.9)	8 (28.6)
Mean age (SD), yr	32.9 (7.64)	30.4 (10.07)	31.7 (8.87)
Race, n (%) (b)			
Black	10 (35.7)	10 (35.7)	20 (71.4)
White	4 (14.3)	4 (14.3)	8 (28.6)
Multiracial	1 (3.6)	1 (3.6)	2 (7.1)
American Indian or Alaska Native	1 (3.6)	0 (0.0)	1 (3.6)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (3.6)	1 (3.6)
Mean weight (SD), kg	81.54 (14.538)	79.84 (10.755)	80.69 (12.578)
Mean height (SD), cm	173.8 (9.34)	171.9 (8.35)	172.9 (8.75)
Mean BMI (SD), kg/m^2	27.00 (4.423)	27.04 (3.558)	27.02 (3.939)

Source: Table 15.1.2.2.
(a) Treatment A=alogliptin 25 mg QD=reference treatment, Treatment B=alogliptin 12.5 mg BID=test treatment.
(b) If a subject's CRF indicated more than 1 race, that subject was summarized for each race that was indicated and for multiracial.

Table 15 Steady-state assessment of predose concentrations of alogliptin (Study SYR-322-101)

Analyte Study Day	n	LS Mean (ng/mL)	Assessment of Steady State (P-value)		
			Day Effect	vs Day 6	vs Day 7
Alogliptin 25 mg QD					
5	25	22.35	<0.001	<0.001	<0.001
6	25	25.16	—	—	0.976
7	25	25.14	—	—	—
Alogliptin 12.5 BID					
5	25	37.30	0.033	0.012	0.488
6	25	39.10	—	—	0.065
7	24	37.78	—	—	—

Source: Table 15.2.1.3.
— =not applicable.

Table 16 Investigational Product (**Study SYR-322/CPH-004**)

Investigational medicinal product	Dosage form	Dose	Appearance	Lot No.
SYR-322 25-mg tablet	Tablet	One tablet contained 25 mg of SYR-322 as a free base.	Yellow film-coated tablet with a score on both sides	Z641U034
Voglibose 0.2-mg tablet	Tablet	One tablet contained 0.2 mg voglibose	White to yellowish white plain tablets with score	Z548V132

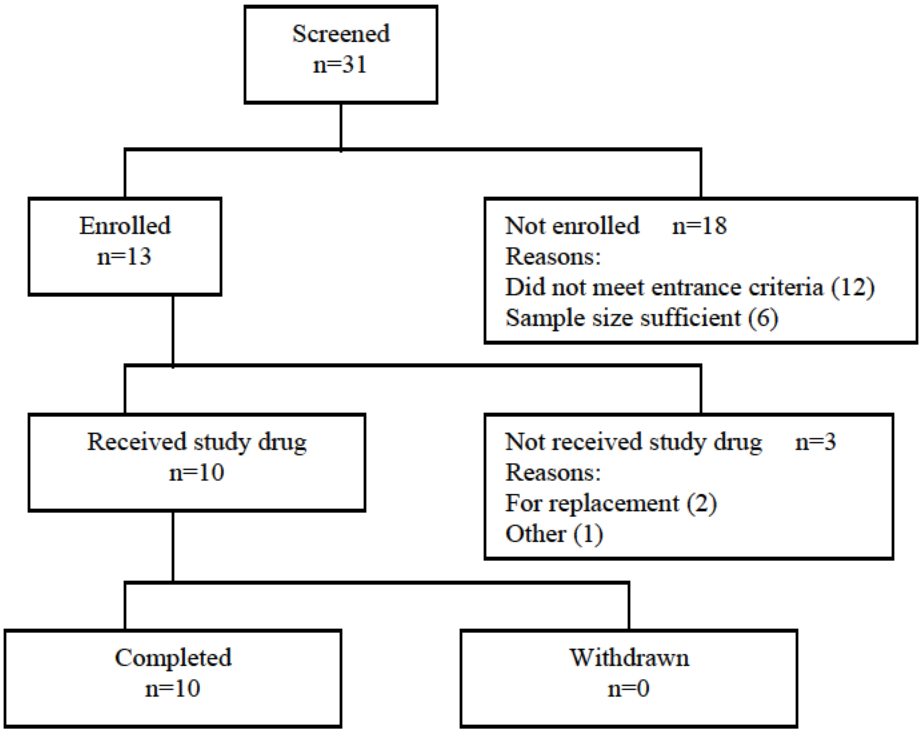


Figure 11 **Disposition of subjects (Study SYR-322/CPH-004)**

Table 17 **Alogliptin pharmacokinetic parameters following 25 mg without or with voglibose (Study SYR-322/CPH-004))**

Variable	Summary Statistics			
	Day 1 (without voglibose)		Day 11 (with voglibose)	
	N	Mean (SD)	N	Mean (SD)
AUC(0-72) (ng•hr/mL)	9	1512.24 (181.547)	9	1162.28 (149.919)
AUC(0-tlqc) (ng•hr/mL)	9	1512.24 (181.547)	9	1162.28 (149.919)
MRT(0-tlqc) (hr)	9	14.949 (1.2787)	9	15.760 (1.8611)
Cmax (ng/mL)	9	156.33 (67.524)	9	134.22 (29.857)
Tmax (hr)	9	1.000 (0.75, 3.00)*	9	0.750 (0.75, 3.00)*
AUC(0-inf) (ng•hr/mL)	9	1577.72 (191.297)	9	1240.13 (177.524)
λz (hr^{-1})	9	0.0422 (0.00628)	9	0.0362 (0.00614)
T1/2 (hr)	9	16.7382 (2.25144)	9	19.7240 (3.37068)
CL/F (L/hr)	9	16.06 (1.900)	9	20.52 (2.820)
MRT (hr)	9	18.327 (2.1336)	9	20.951 (3.9596)

* Median (minimum, maximum)

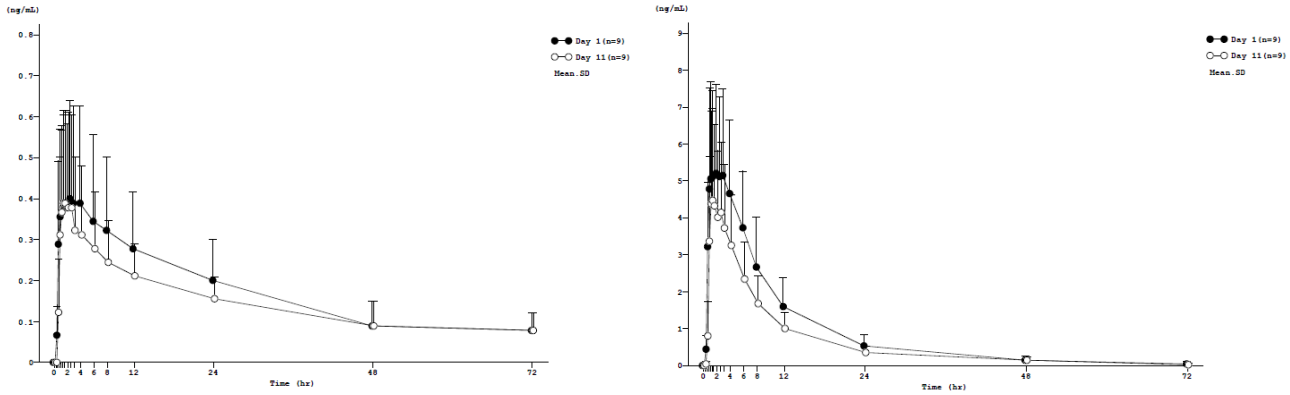


Figure 12 **mean (SD) plasma concentration-time profiles for metabolites by treatments: M-I (left panel) and M-II (right panel) (Study SYR-322/CPH-004)**

Table 18 **Pharmacokinetic parameters for metabolites (Study SYR-322/CPH-004)**

M-I

Variable	Summary Statistics			
	Day 1 (without voglibose)		Day 11 (with voglibose)	
	N	Mean (SD)	N	Mean (SD)
AUC(0-72) (ng•hr/mL)	9	12.22 (6.213)	9	10.40 (4.485)
AUC(0-tlqc) (ng•hr/mL)	9	11.96 (6.642)	9	10.13 (4.953)
MRT(0-tlqc) (hr)	9	22.760 (6.6041)	9	23.871 (6.9461)
Cmax (ng/mL)	9	0.44 (0.270)	9	0.43 (0.250)
Tmax (hr)	9	1.250 (0.75, 2.50)**	9	1.000 (0.75, 2.50)**
AUC(0-inf)* (ng•hr/mL)	7	19.39 (3.145)	7	17.56 (1.823)
λz* (hr^{-1})	7	0.0233 (0.00690)	7	0.0201 (0.00515)
T1/2* (hr)	7	32.4203 (11.85075)	7	36.2544 (10.39184)
MRT* (hr)	7	50.834 (20.0175)	7	57.477 (16.7432)

* It was not possible to estimate the elimination rate constant in 2 subjects.

** Median (minimum, maximum)

M-II

Variable	Summary Statistics			
	Day 1 (without voglibose)		Day 11 (with voglibose)	
	N	Mean (SD)	N	Mean (SD)
AUC(0-72) (ng•hr/mL)	9	63.18 (30.212)	9	44.48 (19.203)
AUC(0-tlqc) (ng•hr/mL)	9	61.98 (30.761)	9	43.54 (19.552)
MRT(0-tlqc) (hr)	9	10.812 (2.3406)	9	11.082 (2.2485)
Cmax (ng/mL)	9	5.83 (2.519)	9	4.87 (2.374)
Tmax (hr)	9	2.000 (0.75, 4.00)*	9	1.500 (0.75, 4.00)*
AUC(0-inf) (ng•hr/mL)	9	64.23 (31.774)	9	45.43 (19.688)
λz (hr^{-1})	9	0.0697 (0.02291)	9	0.0593 (0.01752)
T1/2 (hr)	9	11.1896 (4.46613)	9	12.8718 (4.89735)
MRT (hr)	9	12.876 (3.0913)	9	13.947 (3.3681)

* Median (minimum, maximum)

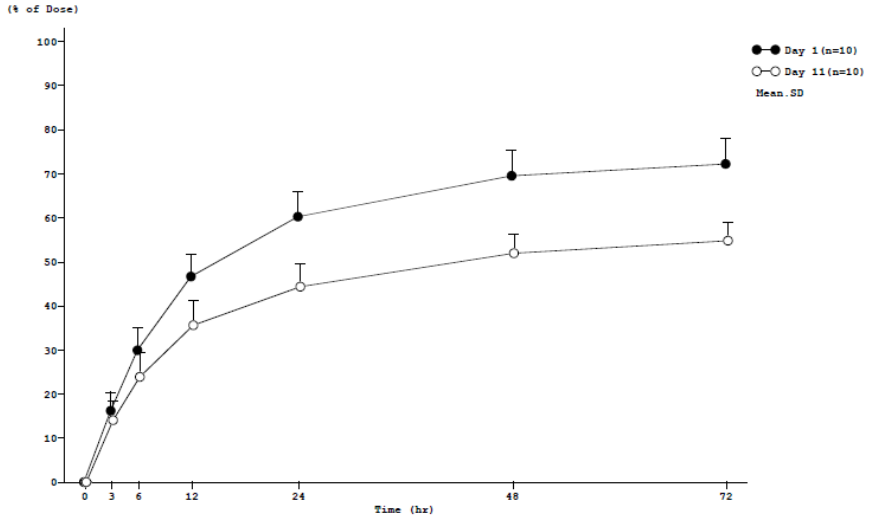


Figure 13 **cumulative urinary excretion ratio of alogliptin (Study SYR-322/CPH-004))**

Table 19 **Cumulative urinary excretion ratio up to 72 hours for alogliptin and its metabolites (Study SYR-322/CPH-004))**

Variable / Visit		Summary Statistics	
		N	Mean (SD)
SYR-322Z (% of Dose)	Day 1: 0 to 72 hr	10	72.261 (5.8869)
	Day 11: 0 to 72 hr	10	54.830 (4.2277)
M-I (% of Dose)	Day 1: 0 to 72 hr	10	0.528 (0.2956)
	Day 11: 0 to 72 hr	10	0.420 (0.2293)
M-II (% of Dose)	Day 1: 0 to 72 hr	10	3.308 (1.0394)
	Day 11: 0 to 72 hr	10	2.285 (0.9142)
Total (% of Dose)	Day 1: 0 to 72 hr	10	76.098 (5.9491)
	Day 11: 0 to 72 hr	10	57.537 (4.5255)

Day 1: without voglibose, Day 11: with voglibose

Table 20 **Renal clearance of alogliptin (Study SYR-322/CPH-004)**

Variable / Visit		Summary Statistics	
		N	Mean (SD)
CLr (L/hr)	Day 1	9	11.52 (1.818)
	Day 11	9	11.22 (2.046)

Day 1: without voglibose, Day 11: with voglibose

3.3 Individual study synopsis

3.3.1 Study SYR-322-103

2.0 SYNOPSIS

Title of Study:
An Open-Label, Randomized, Single-Dose, 2-Period Crossover Study to Evaluate the Absolute Bioavailability of Alogliptin in Healthy Adult Subjects

Name of Sponsor:
Takeda Global Research & Development Center, Inc.

Name of Finished Product:
Alogliptin

Investigator:	**Study Center:**
Thomas Hunt, MD	PPD Development 7551 Metro Center Drive, Suite 200 Austin, TX 78744

Publications Based on the Study:
None

Study Period:	**Phase of Development:**
09 April 2008 to 16 May 2008	Phase 1

OBJECTIVES
The objectives of this study were to determine the bioavailability, safety, and tolerability of a tablet formulation of alogliptin after a 12.5 mg intravenous (IV) dose and a 25 mg oral dose in healthy adult subjects.

METHODS
This was a phase 1, single-center, open-label, randomized, 2-sequence, 2-period crossover study to evaluate the absolute bioavailability of alogliptin in healthy adult subjects. Subjects were assigned randomly to 1 of 2 treatment sequences and received a single dose of alogliptin 25 mg administered orally (Treatment A [test treatment]) and a single dose of alogliptin 12.5 mg administered IV (Treatment B [reference treatment]). The 2 treatments were separated by a 7-day washout interval that began immediately after dosing on Day 1. Blood and urine samples for pharmacokinetic analyses were collected at designated time points during the study.

Study Schematic:

Pretreatment Period		Treatment Period (a)					
Screening	Check-in	Period 1			Period 2		Study Exit/ET
Days -21 to -2	Day -1	Day 1 Dosing		Days 2 to 7	Day 8 Dosing	Days 9 to 10	Day 11
		Sequence I	A	Washout (a)	B	Washout (a)	
		Sequence II	B		A		
	←Confinement→						

(a) Washout began immediately after dosing.
Treatment A=25 mg of alogliptin administered orally in tablet form (test treatment), Treatment B=12.5 mg of alogliptin administered as a 30-minute IV infusion at a constant flow rate (reference treatment), ET=early termination

Number of Subjects (Planned and Analyzed):
Planned: 24 subjects.
Analyzed: Pharmacokinetics—21 subjects; Safety—21 subjects.

Main Criteria for Inclusion:
Subjects must have been healthy men or nonpregnant, nonlactating women, aged 18 to 55 years, inclusive; weighed at least 50 kg (110 lb); had a screening body mass index between 18 and 32 kg/m^2, inclusive; been willing to sign the informed consent form; and had no known hypersensitivity to alogliptin or related compounds.

Title of Study:

An Open-Label, Randomized, Single-Dose, 2-Period Crossover Study to Evaluate the Absolute Bioavailability of Alogliptin in Healthy Adult Subjects

Test Product, Dose and Mode of Administration, Lot Number:

Drug	Dose	Form	Route	Lot Number
Alogliptin	25 mg	Tablet	Oral	7F079

Reference Therapy, Dose and Mode of Administration, Lot Number:

Drug	Dose	Form	Route	Lot Number
Alogliptin	12.5 mg	Bulk drug	IV	0319081

Duration of Treatment:

The duration of the study was 12 days, including Check-in (Day -1).

Criteria for Evaluation:

Pharmacokinetics:

The following pharmacokinetic parameters were derived using noncompartmental methods for each subject from plasma concentration data of alogliptin: area under the plasma concentration-time curve (AUC) from time 0 to time 24 hours after the start of dosing (AUC[0-24]); AUC from time 0 to time of last quantifiable concentration (AUC[0-tlqc]); AUC from time 0 extrapolated to infinity (AUC[0-inf]); maximum observed plasma concentration (Cmax); total clearance after IV administration (CL); apparent clearance after oral administration (CL/F); terminal elimination rate constant (λz); terminal elimination half-life (T1/2); time to reach Cmax (Tmax); volume of distribution during the terminal phase after IV administration (Vz); and apparent volume of distribution during the terminal phase after oral administration (Vz/F).

The following pharmacokinetic parameters were derived using noncompartmental methods for each subject from urine concentration data of alogliptin: total amount of drug excreted in the urine during the intervals of 0 to 2, 2 to 4, 4 to 24, 24 to 48, 48 to 72, 0 to 24, and 0 to 72 hours after the start of dosing; fraction of drug excreted in urine from time 0 to 24 hours after the start of dosing (Fe[0-24]); fraction of drug excreted in urine from time 0 to 72 hours after the start of dosing (Fe[0-72]); renal clearance from time 0 to 24 hours after the start of dosing (CLr[0-24]); renal clearance from time 0 to 72 hours after the start of dosing (CLr[0-72]); and urinary excretion rate during the collection intervals of 0 to 2, 2 to 4, 4 to 24, 24 to 48, and 48 to 72 hours after the start of dosing.

Safety:

Safety variables were adverse events, clinical laboratory test results, vital sign measurements, 12-lead electrocardiogram (ECG) results, physical examination findings, and cardiac telemetry and tolerance assessments during the IV treatment period.

Statistical Methods:

Pharmacokinetic Analysis:

An analysis of variance (ANOVA) was performed on the natural logarithmic-transformed dose-adjusted values of AUC(0-24), AUC(0-tlqc), AUC(0-inf), and Cmax with sequence, period, and treatment as fixed effects and subject nested within sequence as a random effect. The Wilcoxon signed rank test was performed on unadjusted Tmax.

Within the framework of the ANOVA model for dose-adjusted natural logarithms of AUC(0-24), AUC(0-tlqc), AUC(0-inf), and Cmax, the ratios of the least squares (LS) mean of the test treatment (Treatment A, oral alogliptin) to the LS mean of the reference treatment (Treatment B, IV alogliptin) and the 90% confidence interval (CI) for each ratio were provided. The ratios were obtained by taking the antilogarithm of the difference between the LS means on the natural logarithmic scale, and the 90% CIs were obtained by taking the antilogarithm of the 90% CIs for the difference between the LS means on the natural logarithmic scale.

Title of Study:

An Open-Label, Randomized, Single-Dose, 2-Period Crossover Study to Evaluate the Absolute Bioavailability of Alogliptin in Healthy Adult Subjects

Safety Analysis:

Safety variables are presented in the data listings; adverse events and vital sign measurements were summarized with descriptive statistics. Out-of-range laboratory test results and vital sign measurements that met the predefined criteria for very low or very high values were flagged and summarized.

SUMMARY OF RESULTS

Subject Disposition:

Twenty-one subjects (7 men and 14 women) with a mean age of 33.0 years were enrolled in the study, 20 subjects completed the study, and 1 subject was discontinued prior to IV dosing.

Pharmacokinetic Results:

	LS Mean		
Dose-Adjusted Parameter (unit)	Treatment A: Alogliptin 25 mg Oral (T) n=21	Treatment B: Alogliptin 12.5 mg IV (R) n=20	Ratio (T/R)·100 (90% CI) (a)
AUC(0-inf) ([ng·hr/mL]/mg) (b)	72.57	71.33	101.74 (99.01, 104.56)
AUC(0-tlqc) ([ng·hr/mL]/mg)	69.10	66.89	103.31 (100.38, 106.31)
AUC(0-24) ([ng·hr/mL]/mg)	52.69	51.45	102.42 (98.72, 106.26)
Cmax ([ng/mL]/mg)	5.74	13.54	42.38 (38.39, 46.79)
Tmax (hr) (c)	2.250	0.558	—

T=test treatment, R=reference treatment, — =not applicable.
(a) Ratios and CIs are presented as percentages.
(b) AUC(0-inf) is used as absolute bioavailability.
(c) Tmax is presented as median, not adjusted for dose; P<0.001 using Wilcoxon signed rank test with matched subjects who received both treatments (n=20).

The dose-adjusted AUC(0-inf) of alogliptin was similar following administration of a 25 mg oral dose and a 12.5 mg IV dose infused over 30 minutes. The absolute bioavailability of orally administered alogliptin was approximately 102% (AUC[0-inf]), with a 90% CI between 99% and 105%.

Median Tmax was approximately 1.7 hours longer when alogliptin was administered orally versus as an IV infusion.

Safety Results:

Overall, 3 of 21 subjects (14.3%) experienced at least 1 treatment-emergent adverse event during the study. Headache was the only adverse event experienced by more than 1 subject. Headache was reported by 2 subjects during treatment with IV alogliptin and by 1 subject during treatment with oral alogliptin.

One subject (Subject 029) experienced headache during both treatment periods; these events were considered by the investigator to be possibly related to study drug. No other adverse events were considered to be possibly related to study drug, and none were considered to be probably or definitely related to study drug.

All adverse events were considered by the investigator to be mild in intensity.

No deaths, other serious adverse events, or other significant adverse events occurred, and no subject discontinued study drug due to an adverse event.

No serum chemistry or hematology test result; vital sign measurement; ECG result; or physical examination finding was reported as an adverse event. No clinically significant abnormalities in cardiac telemetry results, clinically significant changes in condition, or abnormal findings of local tolerance assessments were reported.

Title of Study:
An Open-Label, Randomized, Single-Dose, 2-Period Crossover Study to Evaluate the Absolute Bioavailability of Alogliptin in Healthy Adult Subjects
CONCLUSIONS:
• The dose-adjusted AUC(0-inf) of alogliptin was similar following administration of a 25 mg oral dose and a 12.5 mg IV dose infused over 30 minutes. The absolute bioavailability of orally administered alogliptin was approximately 102% (AUC[0-inf]), with a 90% CI between 99% and 105%. • Alogliptin 25 mg administered orally in tablet form and alogliptin 12.5 mg administered as an IV infusion were well tolerated as administered in this study.
Date of Report:
11 December 2008

Schedule of Assessment

Study Procedure	Pretreatment Period		Treatment Period									
	Screening	Check-in	Period 1						Period 2			ET/ Study Exit (a)
Days	*-21 to -2*	*-1*	*1*	*2*	*3*	*4*	*5-6*	*7*	*8*	*9*	*10*	*11*
Informed consent	X											
Inclusion/exclusion	X	X										
Medical history/concurrent medica Conditions/demographics	X											
Physical examination	X	X										X
Vital sign measurements (b)	X	X	X	X					X	X		X
Height, weight, and BMI (c)	X	X										X
12-lead ECG	X	X										X
Clinical laboratory tests (d)	X	X						X				X
Drug and alcohol screens	X	X										
Serum pregnancy test (e)	X	X										X
HBsAg and HCV screens	X											
Cardiac telemetry (f)			X						X			
IV tolerance assessment (g)			X	X					X	X		
PK blood sample (h,i)			X	X	X	X			X	X	X	X
PK urine collection (j,i)		X	X	X	X	X		X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Check restrictions (k)		X										
Pretreatment events/adverse event monitoring (l)	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration			X						X			

ET=early termination, BMI=body mass index, ECG=electrocardiogram, HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus antibody, PK=pharmacokinetic.

(a) For Early Termination, Study Exit procedures were performed as soon as possible after the subject discontinued study participation.

(b) Vital sign measurements were body temperature, blood pressure, respiratory rate, and pulse. Measurements were taken for both treatments at Screening, at Check-in, within 1.5 hours prior to dose/start of infusion (0 hour), at 2 and 6 hours after the start of dosing on Day 1 and Day 8, at 24 hours after dosing (Day 2 and Day 9), and at Study Exit (Day 11) or Early Termination. In addition, during the IV treatment only, additional vital sign measurements were taken at approximately 20 and 50 minutes after the start of infusion on Days 1 and 8. (PK samples were collected before vital signs were taken when the timing of procedures overlapped.

(c) Height for calculation of body mass index was only measured at Screening. Weight was measured at Screening, Check-in (Day -1), and Study Exit (Day 11) or ET.

(d) Clinical laboratory tests (hematology, serum chemistry, and urinalysis [Screening only]) were performed at Screening, at Check-in (Day -1), on Day 7, and on Day 11 or at ET.

(e) Serum pregnancy tests were performed (women only) at Screening, Check-in, and Study Exit (Day 11) or ET (if applicable).

(f) During the IV dosing period only, continuous cardiac telemetry was performed between 1 hour prior to and 4 hours after the start of infusion.

(g) During the IV dosing period only, the condition of the infusion site for each subject was monitored for erythema, pruritus, or swelling at the end of IV infusion and at 2 and 24 hours after the start of infusion. In addition, each subject was observed for clinically significant changes in condition such as respiratory symptoms, facial flushing, swelling, or indication of a drop in blood pressure at approximately 10 and 30 minutes after the start of infusion.

(h) For IV administration, blood samples for PK analyses were collected before dosing (within 1 hour prior to dose) and at 0.083 (5 min), 0.167 (10 min), 0.25 (15 min), 0.5 (30 min), 0.583 (35 min), 0.667 (40 min), 0.75 (45 min), 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours after the start of dosing. For oral administration, blood samples for PK analyses were collected before dosing (within 1 hour prior to dose) and at 0.25 (15 min), 0.5 (30 min), 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours after dosing. The PK samples were collected before any other assessments were performed, if scheduled at the same time point.

(i) Not performed for Early Termination.

(j) All voided urine for PK analyses was collected before dosing (-12 to 0 hour) and after the start of dosing over the following intervals: 0 to 2, 2 to 4, 4 to 24, 24 to 48, and 48 to 72 hours.

(k) Subject compliance with restrictions on medications, nutraceuticals, multivitamins, and products containing alcohol, caffeine or xanthine-related compounds, grapefruit juice, or Seville-type oranges was monitored.

(l) Pretreatment events were monitored from the time the subject signed the informed consent through the time of the first dose. Adverse events were monitored from the time of first dose through the end of the study. A follow-up telephone call was made at 14 days following the last dose of study drug for collection of any adverse events since Study Exit. Spontaneously reported adverse events or serious adverse events were collected up to 14 days or 30 days, respectively, after the last dose of study drug.

3.3.2 Study SYR-322-101

2.0 SYNOPSIS

Title of Study: 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	
Name of Sponsor: Takeda Global Research & Development Center, Inc.	
Name of Finished Product: Alogliptin	
Investigator: Sandra Connolly, MD	**Study Center:** MDS 1930 Heck Ave. Building 2 Neptune, NJ 07753
Publications Based on the Study: None	
Study Period: 27 April 2007 to 09 June 2007	**Phase of Development:** Phase 1
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.	
METHODS This was a phase 1, single-center, open-label, randomized, 2-period crossover study to evaluate the multiple-dose pharmacokinetics and pharmacodynamics of SYR-322 (hereafter referred to as alogliptin) following 12.5 mg BID vs 25 mg QD dosing in healthy male and female subjects. 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 (1 dose every 12 hours) for 7 days per treatment period. A washout interval of 7 days (beginning immediately after dosing on Day 7 of Treatment Period 1) separated the 2 treatment periods. Blood and urine samples for pharmacokinetic and blood samples for pharmacodynamic analyses were collected at designated time points during the study.	

Title of Study:

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

Study Schematic:

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 prior to dosing on Day 1.
A=alogliptin 25 mg QD=reference treatment.
B=alogliptin 12.5 mg BID=test treatment.

Number of Subjects (Planned and Analyzed):

Planned: 28 subjects.

Analyzed: Pharmacokinetics—26 subjects; Pharmacodynamics—25 subjects; Safety—28 subjects.

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects must have been healthy men or nonpregnant, nonlactating women, aged 18 to 55 years, inclusive; weighed at least 50 kg (110 lb); had a screening body mass index between 18 and 32 kg/m^2, inclusive; had been willing to sign the informed consent form; had alanine aminotransferase and aspartate aminotransferase levels less than the upper limit of normal; and had no active liver disease or jaundice.

Test Product, Dose and Mode of Administration, Lot Number:

Drug	Dose	Form	Route	Lot Number
Alogliptin	12.5 mg BID	Tablet	Oral	Z6418021

Reference Therapy, Dose and Mode of Administration, Lot Number:

Drug	Dose	Form	Route	Lot Number
Alogliptin	25 mg QD	Tablet	Oral	Z6419021

Duration of Treatment:

The duration of the study was 23 days, including Check-in for Period 1 (Day -1).

Criteria for Evaluation:

Pharmacokinetics:

The following pharmacokinetic parameters were derived using noncompartmental methods for each subject from plasma concentration data of alogliptin on Day 7 of each treatment period: area under the plasma concentration-time curve (AUC) from time 0 to time tau (AUC[0-tau]); AUC from time 0 to 24 hours (AUC[0-24]); maximum observed plasma concentration (Cmax); minimum observed plasma concentration (Cmin); time to reach Cmax (Tmax); observed predose (trough) plasma concentration (Ctrough) on Days 5, 6, and 7; percent swing, percent fluctuation; and average plasma concentration during dosing interval.

Title of Study:

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

The following pharmacokinetic parameters were derived using noncompartmental methods for each subject from urine concentration data of alogliptin on Day 7 of each treatment period: total amount of drug excreted in urine from time 0 to 24 hours (Ae[0-24]), renal clearance from time 0 to 24 hours (CLr[0-24]), and fraction of drug excreted in urine from time 0 to 24 hours.

Pharmacodynamics:

The pharmacodynamic effect of alogliptin was measured by the extent of DPP-4 inhibition. The following pharmacodynamic effect parameters were calculated: area under the pharmacodynamic effect curve from time 0 to 24 hours (AUEC[0-24]), area under the pharmacodynamic effect curve from time 0 to tau, maximum observed pharmacodynamic effect (Emax), time to reach Emax (Tmax), observed effect at time 0 for BID and QD dosing regimens (E0), observed effect at 12 hours postdose for BID dosing regimen; and observed effect at 24 hours postdose for BID and QD dosing regimens (E24).

Safety:

Safety variables were physical examination findings, clinical laboratory test results, adverse events, 12-lead electrocardiogram (ECG) findings, and vital sign measurements.

Statistical Methods:

Pharmacokinetic Analysis:

At Day 7, to evaluate the effect of 12.5 mg BID vs 25 mg QD dosing of alogliptin, an analysis of variance (ANOVA) with fixed effects for sequence, period, treatment, and random effect for subject nested within sequence was performed on natural logarithms of AUC(0-24), Ae(0-24), Cmax, Cmin, and CLr(0-24) of alogliptin. The Wilcoxon signed rank test was applied to Tmax to determine the difference between test and reference treatments.

Within the framework of ANOVA for the natural logarithms of AUC(0-24), Cmax, Cmin, Ae(0-24), and CLr(0-24), the 90% confidence intervals (CIs) for the ratio of the least squares (LS) mean of test treatment (BID dosing regimen) relative to the reference treatment (QD dosing regimen) were provided. The 90% CIs on the original scale were obtained by taking the antilog of the 90% CIs for the difference between the LS means on the natural logarithmic scale. In addition, when subjects received BID dosing, 90% CIs for the ratios of the LS mean test treatment (BID PM) relative to the reference treatment (BID-AM) for AUC(0-tau), Cmin, and Cmax were obtained to determine the effect of circadian variation on alogliptin exposure.

Assessment of steady-state alogliptin plasma concentrations was based on the analysis of the natural logarithm of Ctrough values on Days 5, 6, and 7. The following model was used:

Ln(concentration)=subject(sequence)+period+treatment+day+day×treatment+sequence.

Subject nested in sequence was a random effect while all others were fixed effects. If the interaction term was not statistically significant at the 10% level, then it was excluded from the model. Otherwise, assessment of steady state was done for each treatment separately. Within the model, if there was a significant day effect, a pairwise t-test was used to assess the achievement of steady state by comparing the Ctrough values between study days. In the event that there was statistical significance regarding steady state, the statistical analysis was used in conjunction with scientific judgment in assessing the overall impact of the nonattainment of steady state on the primary conclusions of the results of the pharmacokinetic analysis.

Title of Study:

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

Pharmacodynamic Analysis:

An ANOVA was used for the natural logarithms of AUEC(0-24), E0, and E24 with sequence, period, and treatment as fixed effects and subject nested within sequence as a random effect to evaluate the effect of 12.5 mg BID vs 25 mg QD dosing of alogliptin on the pharmacodynamic variables,. Within the model, P-values of treatment difference between the LS means were obtained from the contrasts of the ANOVA model using a t-test.

Safety Analysis:

Safety variables are presented in the data listings; adverse events and vital sign measurements also were summarized with descriptive statistics. Out-of-range laboratory test results and vital sign measurements that met the predefined criteria for very low or very high values were flagged and summarized.

SUMMARY OF RESULTS

Subject Disposition:

Twenty-eight subjects (20 men and 8 women) with a mean age of 31.7 years were enrolled in the study, 24 subjects completed the study, and 4 subjects discontinued. Reasons for discontinuation included voluntary withdrawal (1 subject), "other" (2 subjects), and adverse event (1 subject).

Pharmacokinetic Results:

	LS Mean				
Parameter (units)	N	Alogliptin 12.5 mg BID (T)	N	Alogliptin 25 mg QD (R)	Ratio (T/R)-100 (90% CI) (a)
AUC(0-24) (ng·hr/mL)	24	1378.54	25	1339.21	102.94 (97.57, 108.60)
AUC(0-12) AM	24	698.77	24	—	95.88 (93.39, 98.44) (b)
AUC(12-24) PM	24	670.01	24	—	—
Cmax (ng/mL)	24	91.02	25	139.23	65.38 (59.17, 72.24)
Cmin (ng/mL)	24	37.17	25	24.43	152.16 (145.27, 159.37)
Tmax (hr) (c,d)	24	1.98	24	1.98	—

— = not applicable, T=test treatment (alogliptin 12.5 mg BID), R=reference treatment (alogliptin 25 mg QD).
(a) Ratios and CIs are presented as percentages.
(b) Value shown is the ratio of AUC(12-24) PM to AUC(0-12) AM.
(c) Median values are presented for Tmax.
(d) P=0.905.

The 90% CI for the ratio of the LS means of AUC(0-24) for the 12.5 mg BID dose to 25 mg QD dose was within the 80% to 125% range. Therefore, total exposure from time 0 to 24 hours was similar between the QD and BID dosing regimens.

The swing parameter for BID dosing was much lower than for QD dosing. This is to be expected, as QD dosing typically generates higher Cmax and lower Cmin values than BID dosing. However, as mentioned in the previous paragraph, total exposure as measured by AUC(0-24) for alogliptin was similar for the BID and QD regimens.

The 90% CIs for the ratios of the LS means for Cmax and Cmin were not within the 80% to 125% range due to the study design and dosing regimen.

No difference in the median Tmax values of alogliptin (1.98 hr) was observed when alogliptin was administered as 25 mg QD compared with the AM dosing of 12.5 mg BID.

Title of Study:

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

Pharmacodynamic Results:

The 90% CIs for the ratios of the LS means were within the 80% to 125% range for AUEC(0-24), E0, and E24. Therefore, the extent of DPP-4 inhibition was similar between the QD and BID dosing regimens.

Peak inhibition of DPP-4, as measured by Emax, was similar when subjects received the BID regimen (mean Emax=92.28%) when compared with the QD regimen (mean Emax=94.42%). In addition, inhibition at 24 hours postdose, as measured by E24, was ≥80% during BID dosing (mean E24=84.74%) and during QD dosing (mean E24=80.30%).

No difference in the median Tmax values (1.98 hr) for DPP-4 inhibition was observed when alogliptin was administered as 25 mg QD compared with the AM dosing of 12.5 mg BID.

Safety Results:

Nineteen of 28 subjects (67.9%) experienced at least 1 treatment-emergent adverse event during Treatment Periods 1 and 2. Treatment-emergent adverse events were similar in frequency during dosing with alogliptin 25 mg QD (13/28 subjects [46.4%]) and during dosing with alogliptin 12.5 mg BID (12/28 subjects [42.9%]).

The most common treatment-emergent adverse events reported during the study were headache (4 of 28 subjects [14.3%]); somnolence, fatigue, pollakiuria, and diarrhea (3 of 28 subjects [10.7%] each); and upper abdominal pain, dyspepsia, and papular rash (2 of 28 subjects [7.1%] each).

Ten of 28 subjects (35.7%) experienced treatment-emergent adverse events that were considered by the investigator to be possibly related to study drug during Treatment Periods 1 and 2. Diarrhea (3 subjects), pollakiuria (3 subjects), dyspepsia (2 subjects), fatigue (2 subjects), and headache (2 subjects) were the only treatment-related adverse events reported for >1 subject. Eight adverse events that were considered by the investigator to be possibly related to study treatment occurred in 5 of 28 subjects (17.9%) during dosing with alogliptin 25 mg QD. During dosing with alogliptin 12.5 mg BID, 11 adverse events that were considered by the investigator to be possibly related to study treatment occurred in 7 of 28 subjects (25.0%). No event was considered by the investigator to be probably or definitely related to study drug.

The majority of treatment-emergent adverse events were mild in intensity; 2 subjects experienced adverse events of moderate intensity. One subject experienced headache and dysmenorrhea of moderate intensity during dosing with alogliptin 12.5 mg BID. One subject experienced an adverse event of blood creatine phosphokinase increased (5898 U/L [normal range, 38 U/L – 265 U/L]) of moderate intensity following treatment with alogliptin 25 mg QD during Treatment Period 1 that resulted in the discontinuation of study drug and withdrawal of the subject from the study. The investigator considered the event to be not related to study drug.

No deaths or serious adverse events occurred in this study.

No hematology, urinalysis, ECG, or vital sign result was reported as an adverse event.

CONCLUSIONS:

- Total exposure (AUC[0-24]) results were similar between alogliptin 12.5 mg BID and alogliptin 25 mg QD.
- Comparison of pharmacodynamic results (ie, DPP-4 inhibition parameters) showed that alogliptin 12.5 mg BID was similar to alogliptin 25 mg QD. In addition, DPP-4 inhibition at 24 hours postdose was ≥80% during both dosing regimens. Current literature suggests that DPP-4 inhibition of ≥80% is necessary in order to achieve an optimal chronic glucose lowering effect.
- Alogliptin 25 mg QD and alogliptin 12.5 mg BID were well tolerated as administered in this study.

Date of Report:

07 February 2008

3.3.3 Study SYR-322/CPH-004

2.0 SYNOPSIS

Title of Study: An Open-Label Study to Assess the Effect of Voglibose on the Pharmacokinetics of SYR-322 in Healthy Male Subjects	
Name of Sponsor: Takeda Pharmaceutical Company Limited	
Name of Active Ingredient: SYR-322	
Name of Finished Product: Not yet determined	
Investigator(s): Akira Maeda, Non-executive Physician	**Study Center(s):** Honjo Clinic II, Medical Co. LTA
Publication (reference): None	
Study Period (years): Date first subject signed consent, 20 August 2007 to date of last subject's last visit, 25 September 2007	**Phase of Development:** Phase 2
OBJECTIVES To assess the effects of voglibose on the pharmacokinetics and safety of SYR-322 in Japanese healthy adult male subjects in an open-label manner.	
METHODOLOGY This was an open-label study in Japanese healthy adult male subjects. It was conducted at a single study center. Each subject received 25 mg of SYR-322 as a single dose on Day 1. Following a 5-day washout period, subjects received 0.2 mg of voglibose three times daily for 8 days (Days 6 to 13) and a single dose of 25 mg SYR-322 on the 6th day of administration of voglibose (Day 11). Plasma concentrations and urinary excretion rates of SYR-322 on Day 1 were compared with those on Day 11 to assess the effects of voglibose on the pharmacokinetics of SYR-322. **Number of Subjects:** Planned: 10 subjects Analyzed: Plasma pharmacokinetic analysis set—9 subjects, Urine pharmacokinetic analysis set—10 subjects, Safety analysis set—10subjects **Diagnosis and Main Criteria for Inclusion:** To qualify for study participation, subjects had to be healthy males; aged 20 to 35 years, inclusive; been able to comprehend and willing to sign a written information/consent form; The subject weighs 50 kg or more and has a BMI of 18.5 kg/m^2 or more, but less than 25.0 kg/m^2 at the screening.	
Test Product, Dose and Mode of Administration/Lot Number:	
	Batch/Lot Number
SYR-322; SYR-322 25-mg tablet, oral preparation	Z641U034
Voglibose; voglibose 0.2-mg tablet, oral preparation	Z548V132

Duration of Treatment:
For SYR-322, each subject orally received one SYR-322 25-mg tablet 30 minutes before the start of breakfast with 150 mL of water on Days 1 and 11 (2 days).
For voglibose, each subject orally received one voglibose 0.2-mg tablet three times daily immediately before each meal with 150 mL of water from Day 6 through Day 13 (8 days).

Criteria for Evaluation:
[Primary endpoint]

Pharmacokinetic: Plasma concentrations and urinary excretion rates of unchanged SYR-322 (free base) referred to as SYR-322Z, and its metabolites M-I and M-II.

[Secondary endpoint]

Safety: Adverse events, vital signs, body weight, resting 12-lead electrocardiogram (ECG) findings, and laboratory test data.

Statistical Methods:
Pharmacokinetic analysis
Summary statistics were calculated for plasma concentrations of SYR-322Z and its main metabolites M-I and M-II at each protocol-specified blood sampling time point by treatment phase (for each of the SYR-322-alone and SYR-322/voglibose combination phases). Changes in the concentrations were illustrated (by subject, means and standard deviation [SD], and box-and-whisker plots).
Summary statistics were also calculated for pharmacokinetic parameters [except AUMC(0-tlqc) and AUMC(0-inf)] by treatment phase (for each of the SYR-322-alone and SYR-322/voglibose combination phases).
Analysis of variance (ANOVA) was applied to log-transformed AUC(0-72), AUC(0-tlqc), AUC(0-inf), or Cmax values of SYR-322Z and its metabolites M-I and M-II to estimate the two-sided confidence intervals (confidence coefficient, 90% and 95%) for differences between the treatment phases (value in the SYR-322/voglibose combination phase − value in the SYR-322-alone phase). Based on the confidence intervals, the effect of voglibose on the pharmacokinetics of SYR-322 was assessed. For reference, the same analysis was performed on non-log-transformed data.
Summary statistics of the cumulative urinary excretion rate were calculated by treatment phase (for each of the SYR-322-alone and SYR-322/voglibose combination phases). Changes in the cumulative urinary excretion rates were illustrated (by subject, means and SD, and box-and-whisker plots). In addition, summary statistics of renal clearance (CLr) of SYR-322Z were calculated by treatment phase (for each of the SYR-322-alone and SYR-322/voglibose combination phases).
Each treatment phase was defined as follows: the "SYR-322-alone phase" was defined as the time of administration of SYR-322 on Day 1, while the "SYR-322/voglibose combination phase" was defined as the time of administration of SYR-322 on Day 11.

Safety analysis;

Adverse events were presented by "severity" and "causal relationship with the investigational product" for each treatment phase (for each of the SYR-322-alone, multiple-dose voglibose-alone, and SYR-322/voglibose combination phases). For vital signs, body weight, ECG findings and laboratory test data, summary statistics were calculated at each assessment point, and profiles were illustrated in figures by subject. In addition, summary statistics of pre- and post-administration differences (value at each assessment point after administration − value at baseline) were calculated. For reference, a one-sample t-test was applied to the pre- and post-administration differences. For vital signs, resting 12-lead ECG findings, and laboratory test data, cross tables comparing values before and after administration were prepared, based on pre- and post-administration judgments of "below the reference range," "within the reference range" and "above the reference range." When no upper limit of reference was present, "below the reference range" and "within the reference range" were used for cross tabulation. Similarly, when no lower limit of reference was present, "within the reference range" and "above the reference range" were used. For ECG findings, the criteria of "within the normal limits," "abnormal but not clinically significant" and "abnormal and clinically significant" were used.

Each treatment phase was defined as follows: the "SYR-322-alone phase" was defined as the period from Day 1 through the morning administration of voglibose on Day 6, the "multiple-dose voglibose-alone phase" as the period from after the morning administration of voglibose on Day 6 through the administration of SYR-322 on Day 11, and the "SYR-322/voglibose combination phase" as the period after the administration of SYR-322 on Day 11.

SUMMARY OF RESULTS

Subject Disposition:

A total of 31 subjects were screened at the study center. Of these, 13 subjects were enrolled in the study. The main reason for screen failures was ineligibility based on the results of the screening. Ten subjects received the investigational product and completed the study. Three subjects did not receive the investigational product; two of these were reserve subjects.

Pharmacokinetic Result:

Data from 9 out of 10 subjects who received investigational products were evaluated for the pharmacokinetic population (plasma), since one subject was excluded due to sample hemolysis. Data from all 10 subjects were evaluable in the pharmacokinetic population (urine).

1. Plasma Concentrations

(1) SYR-322Z

The LS mean values of the AUC(0-inf) of SYR-322Z were 1567.581 ng•hr/mL on Day 1 (without voglibose) and 1229.169 ng•hr/mL on Day 11 (with voglibose). Thus, the value on Day 11 (with voglibose) was 21.6% lower than that on Day 1 (without voglibose). The 90% CI for AUC(0-inf) ranged from 75.8 to 81.1%. The 90% CIs for AUC(0-72) and AUC(0-tlqc) were similar to that for AUC(0-inf). The LS mean values of the Cmax of SYR-322Z were 145.797 ng/mL on Day 1 (without voglibose) and 130.752 ng/mL on Day 11 (with voglibose). Thus, the value on Day 11 (with voglibose) was 10.3% lower than that on Day 1 (without voglibose). The 90% CI for Cmax ranged from 75.7 to 106.2%.

(2) M-I

The LS mean values of the AUC(0-inf) of M-I were 19.164 ng•hr/mL on Day 1 (without voglibose) and 17.479 ng•hr/mL on Day 11 (with voglibose). Thus, the value on Day 11 (with voglibose) was 8.8% lower than that on Day 1 (without voglibose). The 90% CI for AUC(0-inf) ranged from 86.0 to 96.8%. The 90% CIs for AUC(0-72) and AUC(0-tlqc) were similar to that for AUC(0-inf). The LS mean values of the Cmax of M-I were 0.347 ng/mL on Day 1 (without voglibose) and 0.348 ng/mL on Day 11 (with voglibose). Thus, the value on Day 11 (with voglibose) was similar to that on Day 1 (without voglibose). The 90% CI for Cmax ranged from 88.5 to 114.0%.

(3) M-II

The LS mean values of the AUC(0-inf) of M-II were 58.778 ng•hr/mL on Day 1 (without voglibose) and 42.087 ng•hr/mL on Day 11 (with voglibose). Thus, the value on Day 11 (with voglibose) was 28.4% lower than that on Day 1 (without voglibose). The 90% CI for AUC(0-inf) ranged from 67.2 to 76.3%. The 90% CIs for AUC(0-72) and AUC(0-tlqc) were similar to that for AUC(0-inf). The LS mean values of the Cmax of M-II were 5.402 ng/mL on Day 1 (without voglibose) and 4.427 ng/mL on Day 11 (with voglibose). Thus, the value on Day 11 (with voglibose) was 18.1% lower than that on Day 1 (without voglibose). The 90% CI for Cmax ranged from 73.8 to 91.0%.

2. Urinary excretion

(1) SYR-322Z

Up to 72 hours after administration, the cumulative urinary excretion ratio of SYR-322Z was estimated to be 72.3% on Day 1 (without voglibose) and 54.8% on Day 11 (with voglibose). The renal clearance values for SYR-322Z were 11.52 and 11.22 L/hr on Day 1 (without voglibose) and Day 11 (with voglibose).

(2) M-I

Up to 72 hours after administration, the cumulative urinary excretion ratio of M-I was estimated to be 0.5% on Day 1 (without voglibose) and 0.4% on Day 11 (with voglibose).

(3) M-II

Up to 72 hours after administration, the cumulative urinary excretion ratio of M-II was estimated to be 3.3% on Day 1 (without voglibose) and 2.3% on Day 11 (with voglibose).

(4) Total (SYR-322Z + M-I + M-II)

Up to 72 hours after administration, the cumulative urinary excretion ratio of total (SYR-322Z + M-I + M-II) was estimated to be 76.1% on Day 1 (without voglibose) and 57.5% on Day 11 (with voglibose).

Safety Result:

Coadministration of SYR-322 with voglibose appeared to be safe and well tolerated in healthy adult male subjects based on the following results:

- No adverse events were observed in this study.
- None of the changes in any laboratory tests was considered to be of clinical significance.
- No clinically relevant abnormal findings in vital signs and body weight were observed in the study. There were no abnormal physical examination findings. No clinically relevant abnormal ECG findings were observed.

CONCLUSIONS:

- The AUC(0-inf) and Cmax of SYR-322Z after administration with voglibose were lower than those after administration without voglibose (decreases of 21.6% and 10.3% in AUC(0-inf) and Cmax of SYR-322Z, respectively).
- The cumulative urinary excretion ratio of SYR-322Z after administration with voglibose was approximately 20% lower than that without voglibose.
- Coadministration of SYR-322 with voglibose appeared to be safe and well tolerated in healthy adult male subjects.

Date of Report:

14 March 2008

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

/s/

SANG M CHUNG
01/18/2012

JAYABHARATHI VAIDYANATHAN
01/18/2012

CLINICAL PHARMACOLOGY REVIEW

NDA	22-271
Submission Date(s)	December 27, 2007
Brand Name	Nesina®
Generic Name	Alogliptin benzoate
Reviewers	Sang M. Chung, Ph.D. and Luke Bi, Ph.D.
Team Leader	Sally Choe, Ph.D.
Pharmacometric Reviewer	Justin Earp, Ph.D.
Secondary Pharmacometric Reviewer	Rajnikanth Madabushi, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Takeda
Submission Type	Standard
Formulation Strength(s)	6.25 mg, 12.5 mg, and 25 mg tablets
Indication	To improve glycemic control in patients with type 2 diabetes mellitus as monotherapy or combination therapy with a PPARγ agonist, a sulfonylurea, metformin or insulin
Dosage & Administration	25 mg once daily; 12.5 mg once daily in subjects with moderate renal impairment; 6.25 mg once daily in subjects with severe renal impairment or end stage renal disease

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4.2.9 Study SYR-322-022: A Phase 1, Single-Blind, Placebo-Controlled, Randomized, Parallel-Group Study to Evaluate the Possible Effects of Age, Gender, and Race on the Safety and Pharmacokinetics of Single and Multiple Doses of SYR-322 in Healthy Adult Subjects *47*
4.2.10 Study SYR-322-006: An Open-Label, Parallel-Group Comparison Study of Single-Dose Pharmacokinetics of SYR110322 in Subjects with Mild or Moderate Renal Impairment and Healthy Volunteers *52*
4.2.11 Study SYR-322-023: An Open-Label Evaluation of the Single Dose Pharmacokinetics of SYR-322 in Subjects With and Without Hepatic Impairment *56*
4.2.12 Study SYR-322-015: An Open-Label, Multiple-Dose Study to Assess the Drug-Drug Interaction Between SYR-322 and Caffeine, Tolbutamide, Dextromethorphan, Midazolam, and Fexofenadine Administered Concomitantly to Healthy Adult Subjects *58*
4.2.13 Study SYR-322-018: An Open-Label Study to Assess the Effect of SYR-322 on Glyburide in Healthy Adult Subjects *65*
4.2.14 Study SYR-322-021: SYR-322-021: A Randomized, Single-Blind, Placebo-Controlled Assessment of the Pharmacokinetics and Pharmacodynamics of Warfarin in the Presence of Multiple Doses of SYR-322 in Healthy Male and Female Subjects *67*
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4.2.16 Study SYR-322-017: A Phase 1, Open-Label, Randomized, Multiple-Dose, Crossover Study to Assess the Drug-Drug Interaction of SYR-322 and Pioglitazone *74*
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4.2.21 Study SYR-322-020: A Phase 1, Randomized, Open-Label, Single-Dose, Crossover Study to Determine the Effect of Cyclosporine (Neoral®) on the Pharmacokinetics of SYR-322 in Healthy Male Subjects *101*
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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA 22-271 for Nesina® (alogliptin benzoate) and finds it acceptable provided providing that the Agency and the sponsor agree on the labeling. In addition, if the safety profile of Nesina® is acceptable by the clinical division, based on the exposure-response relationships regarding efficacy and safety reviewed by the Office of Clinical Pharmacology, both 12.5 mg and 25 mg of Nesina® are acceptable doses.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The sponsor has submitted the NDA 22-271 for Nesina® (alogliptin benzoate) for the indication of improving glycemic control in patients with type 2 diabetes mellitus (T2D). Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4) where DPP-4 inhibitors increase incretin hormones, namely glucagon-like peptide–1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). One of the important physiologic functions of GLP-1 and GIP is the stimulation of glucose-dependent insulin secretion from the pancreas.

The proposed dose of alogliptin is 25 mg once daily. Dose adjustment is recommended by the sponsor for subjects with moderate and severe renal impairment, and end stage renal disease (ESRD) because of the exposure increases observed in those subjects: 12.5 mg for subjects with moderate renal impairment and 6.25 mg for subjects with severe renal impairment or ESRD.

A total of 30 clinical pharmacology/clinical studies conducted for the evaluation of Nesina® are as follows:

- 24 Phase 1 studies,
- One Phase 2 study,
- Five Phase 3 studies for monotherapy and combination with a peroxisome proliferator-activated receptor gamma (PPARγ), metformin, a sulfonylurea, or insulin

The minimum effective dose of alogliptin was 12.5 mg, which also achieved the apparent maximum effect in the Phase 2 dose-ranging study. This study evaluated 6.25 mg, 12.5 mg, 25 mg, 50 mg, and 100 mg QD on lowering glycosylated hemoglobin (HbA1c), the surrogate efficacy endpoint for anti-diabetic treatment. Based on these Phase 2 study results, two doses, 12.5 mg and 25 mg, were selected for further clinical evaluation in the Phase 3 studies. Alogliptin treatment effect for both doses on lowering HbA1c was significantly greater than that of placebo in all Phase 3 studies. Overall, there is no clear

incremental benefit in starting with 25 mg over 12.5 mg alogliptin for HbA1c reduction. From clinical pharmacology perspectives, both 12.5 mg and 25 mg seem acceptable.

Incidence of hypoglycemia with Nesina® 25 mg monotherapy was comparable to that of placebo. No exposure-safety relationship was observed for either serious treatment emergent cardiac events or renal function with respect to alogliptin exposure. Please refer to the clinical and pharmacometric reviews for more detail on alogliptin efficacy and safety.

About 68% of the oral dose was excreted in the urine as alogliptin and it indicates that renal excretion is the major elimination pathway for alogliptin. Alogliptin was metabolized to N-dealkylated alogliptin (M1) by CYP2D6 and acetylated alogliptin (M2). The alogliptin metabolites were regarded as minor because exposure of M1 was less than 1% and M2 was less than 4% of alogliptin exposure following alogliptin single and multiple dose administration. While the DPP-4 inhibitory activity of M1 was similar to that of alogliptin, that of M2 was not significant against DPP-4.

Alogliptin exposure increase was proportional to alogliptin dose increase after multiple dosing (25 mg-400 mg). Mean time to reach Cmax (Tmax), clearance (CL/F), volume of distribution (Vdz/F), and half-life following 25 mg single dose administration were 1-2 hour, 16.9 L/h, 609.6 L, and 25.6 hour, respectively. Food did not significantly affect the alogliptin exposure. Alogliptin AUC_{0-t} increased by 28% and 19% in elderly and in women, respectively, compared to that of matching control groups. In addition, AUC_{0-t} increased by 28% in white subjects compared to that of black subjects. Alogliptin AUC_{0-t} increased by 69%, 108%, 219% and 281% in subjects with mild, moderate, and severe renal impairment and ESRD, respectively, compared to that of control subjects. Moderate hepatic impairment did not significantly affect the alogliptin exposure.

Metabolic modulators (i.e., fluconazole, ketoconazole, gemfibrozil, cyclosporine, pioglitazone, cimetidine, metformin, atorvastatin, and digoxin) did not significantly affect alogliptin exposure. In addition, alogliptin did not significantly affect exposure of P450 probe substrates (i.e., caffeine, tolbutamide, dextromethorphan, and midazolam), fexofenadine, glyburide, (S)-warfarin, (R)-warfarin, ethinyl estradiol, norethindrone, cimetidine, metformin, pioglitazone, atorvastatin, and digoxin.

There was no clinically meaningful effect of alogliptin on QTc intervals following 50 mg or 400 mg dose of alogliptin. Commercial formulations were bioequivalent to formulations used in Phase 3 studies. Review of the Division of Scientific Investigation on this pivotal BE study is pending at this time.

2 Question Based Review

2.1 General attributes

2.1.1 *What are the highlights of the properties of the drug or the formulation as they relate to clinical pharmacology review?*

Aqueous solubility of alogliptin benzoate (Figure 1) was 19.2 mg/mL (sparingly soluble) and it indicates that the highest proposed dose (25 mg) is soluble in 250 mL water. Partition coefficient ($C_{octanol}/C_{aqueous}$) at pH 7.0 and 25 °C was -0.9. Permeability from Caco-2 study was similar to that of mannitol, a reference compound for low-permeable drugs and this indicates that alogliptin Caco-2 cell permeability is low. Net permeability ratio between apical to basal vs. basal to apical was less than 2 and this indicates that net P-glycoprotein impact on alogliptin transport in Caco-2 cell is insignificant. Alogliptin urinary excretion in human was 76% of oral dose indicating that alogliptin absorption is high.

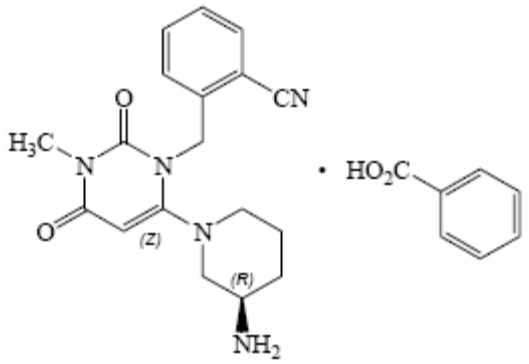


Figure 1 **Structural formula of alogliptin benzoate (MW 461.51 for benzoate salt and 339.39 for free base)**

Alogliptin and its major metabolites did not show *in vitro* inhibitory activity against potential off target enzymes, namely DPP-2, DPP-8, DPP-9, PREP, FAPa/seprase, and tryptase with greater than 100,000 nmol/L for IC_{50}. DPP-2 is known to induce quiescent T-cell apoptosis, and DPP-8/9 is involved in multiple toxicities including mortality, alopecia, thrombocytopenia, anemia, enlarged spleen, and associated histopathologic findings.

2.2 General clinical pharmacology

2.2.1 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response)?*

Maintaining higher than 80% DPP-4 inhibition over 24 hours is known to be required in order to achieve desirable chronic glucose lowering in T2D and 25 mg was the minimum dose achieving this DPP-4 inhibition goal (Figure 2 and 3).

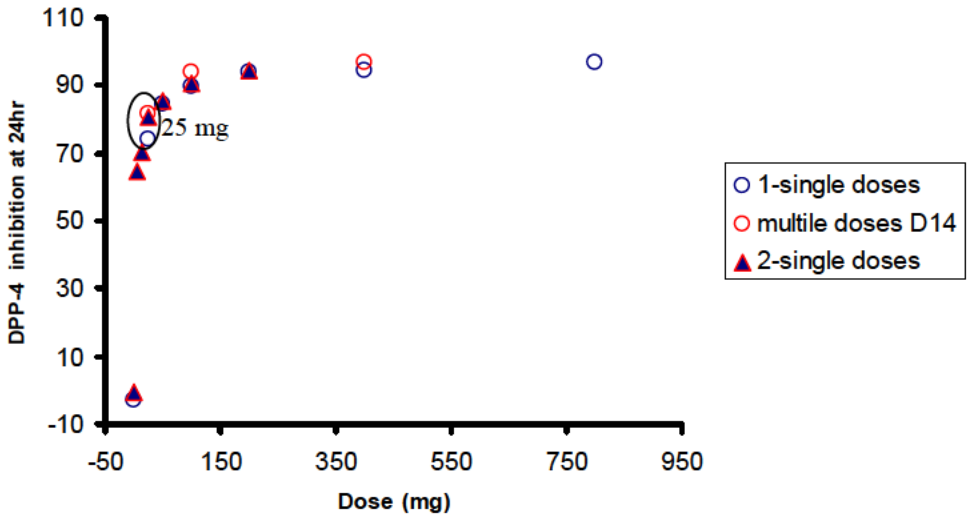


Figure 2 **DPP-4 inhibition versus doses (data from Study 001, 002 and CPH-001)**

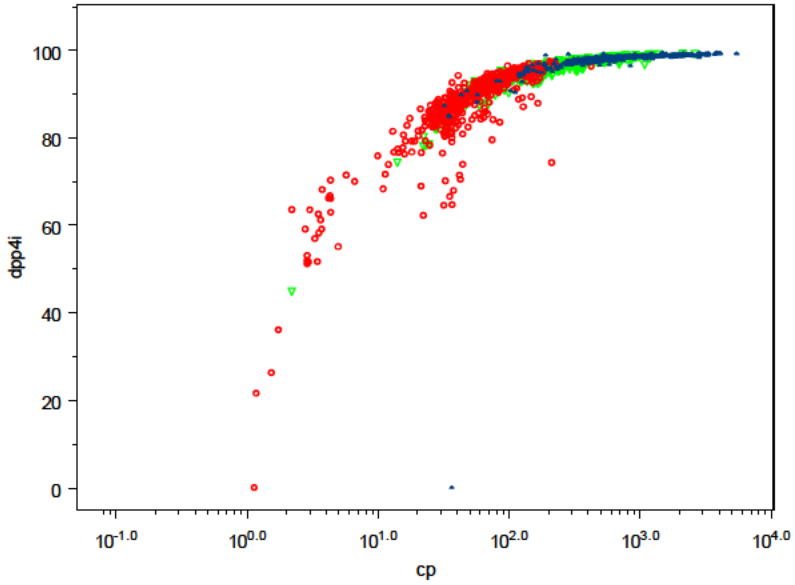


Figure 3 **Plasma DPP-4 inhibition versus alogliptin plasma concentrations in T2D at Day 14 following QD (data from Study 002); red circle – 25 mg QD, green triangle – 100 mg QD, and blue triangle – 400 mg QD (data from Study 002)**

The HbA1c lowering effect of 6.25 mg, 12.5 mg, 25 mg, 50 mg, and 100 mg was evaluated in the Phase 2 dose-ranging study. There was statistically significant effect of alogliptin on HbA1c lowering at all doses except at 6.25 mg (Figure 4). The study results indicate that 12.5 mg is the minimum effective where also an apparent maximum effect is achieved. Based on these Phase 2 study results, 12.5 mg and 25 mg were selected for further clinical evaluation in the Phase 3 studies.

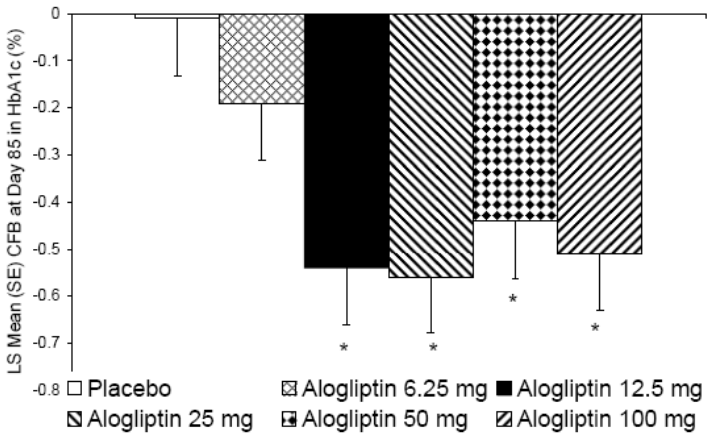


Figure 4 Change from baseline in HbA1c (%) on Day 85 for Study 003 (dose ranging study)

The HbA1c lowering effect of 12.5 mg and 25 mg was statistically significant compared to that of placebo (Figure 5). Treatment effect of 25 mg was slightly greater than that of 12.5 mg in four of five Phase 3 trials (Table 1).

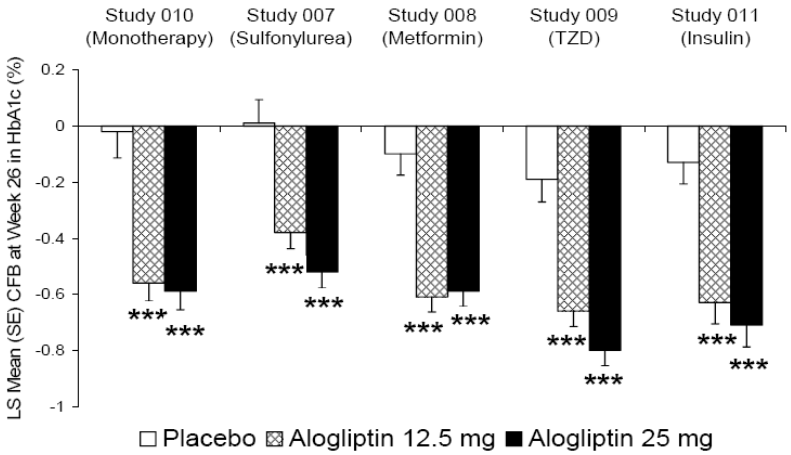


Figure 5 Change from baseline in HbA1c (%) at Week 26 for Phase 3 studies

Table 1 Placebo-corrected change from baseline in HbA1c at Week 26 by treatment

	Alogliptin vs Placebo		
Add-on Therapy	**Alogliptin 12.5 mg**	**Alogliptin 25 mg**	**Difference Between Alogliptin 12.5 mg and 25 mg.**
As monotherapy (010)	-0.54%***	-0.57%***	-0.03%
Add-on to metformin (008)	-0.50%***	-0.48%***	0.02%
Add-on to a TZD (009)	-0.47%***	-0.61%***	-0.14%
Add-on to a sulfonylurea (007)	-0.39%***	-0.53%***	-0.14%
Add-on to insulin (011)	-0.51%***	-0.59%***	-0.08%

***P<0.001 compared with placebo. Difference between alogliptin doses derived by subtracting alogliptin 12.5 mg from the alogliptin 25 mg dose.
Source: Studies 010, 007, 008, 009, and 011, Table 15.2.1.1.1.

However, no concentration (or dose)-effect relationship was evident for alogliptin in reducing serum HbA1c concentrations and therefore, there is no clear benefit in starting with 25 over 12.5 mg alogliptin for serum HbA1c reduction. In addition, serum HbA1c

concentrations were reduced to similar extents at 12.5 and 25 mg alogliptin compared to the placebo group indicating that at 12.5 mg, the apparent maximum activity might have been achieved.

No exposure-safety relationship was observed for either serious treatment emergent cardiac events or renal function with respect to alogliptin exposure.

The range of trough concentrations of alogliptin in individuals with serious cardiac events was similar to those experiencing no adverse events. This suggests that serious cardiac events in these individuals are not exposure-related at the studied doses (Figure 6)

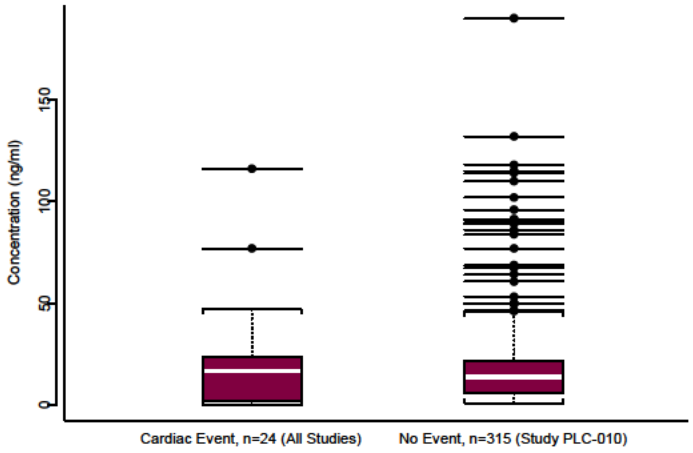


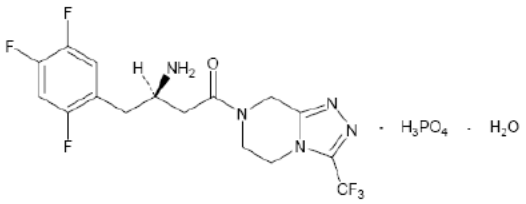
Figure 6 **Steady-State Trough Concentrations at 4 weeks for Patients with and without Adverse Cardiac Events**

Time courses of creatinine clearance for each individual showed no evidence of deterioration of renal function throughout the 52-week alogliptin study duration. Please refer to the pharmacometric review for more detail on alogliptin efficacy and safety.

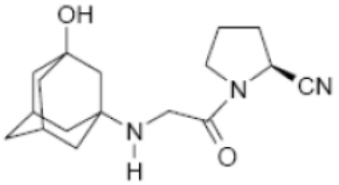
- Previous experience with DPP-4 inhibitors

The Agency has approved the first DPP-4 inhibitor, Januvia® (sitagliptin phosphate, NDA 21-995) on October 16, 2006 and taken an approvable action on vildagliptin (NDA (b) (4)) (b) (4)

Januvia®: Approved dosing regimen of Januvia® is 100 mg once daily and it is adjusted to 50 mg once daily for subjects with moderate renal impairment and 25 mg once daily for subjects with severe renal impairment and ESRD. Sitagliptin is mainly excreted in urine (79% of dose). Sitagliptin AUC was increased by 1.6-, 2- and 4-fold in subjects with mild, moderate, and severe renal impairment and ESRD compared to that of control group, respectively. 100 mg and 200 mg of sitagliptin were evaluated in Phase 3 studies where 200 mg showed greater HbA1c lowering effect than 100 mg.



Vildagliptin: Vildagliptin's absolute bioavailability is 85%. About 85% of dose is excreted in urine as vildagliptin (23% of dose) and its metabolites. Major metabolite (57% of dose) was hydrolysis at the cyano moiety without CPY enzyme involvement. The proposed dosage regimen was (b) (4)



2.2.2 *Does this drug prolong the QT or QTc interval?*

The effect of alogliptin on QT interval was assessed in a single-blind, randomized, placebo-, and positive-controlled design following two parallel supra-therapeutic multiple doses (50 mg or 400 mg QD for 7 days; Study 019). It was concluded that there was no significant effect of alogliptin on QT prolongation. Please see the review by QT IRT under IND 69707 for more details.

Alogliptin following 50 mg and 400 mg were not positively associated with QTcF of greater than 450 ms while moxifloxacin was positively associated with QTcF of greater than 450 ms in the categorical analysis.

The slope in the QTcF vesus alogliptin concentrations was 1.6 ms/1000ng/mL(Figure 7). It indicates that the mean ddQTcF is less than 5 ms at a mean Cmax of approximately 2800 ng/mL. This Cmax is about 19-fold higher than the mean Cmax at the therapeutic dose (145 ng/mL at 25 mg).

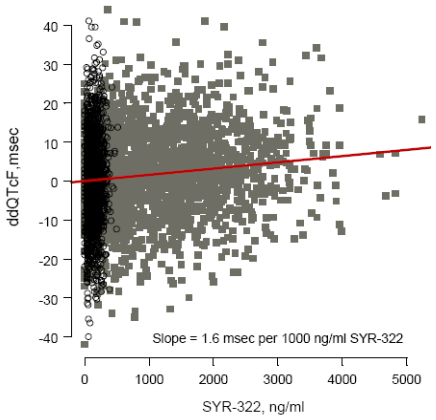


Figure 7 Concentration – QTcF relationship

2.2.3 *What are the PK characteristics of the drug and its major metabolite?*

- Absorption, distribution, metabolism, and elimination

Permeability of alogliptin (0.888 -1.23 x10^{-6} cm/sec) was similar to that of mannitol, a reference for low permeability across Caco-2 cells. The net flux ratio (apical to basal/basal to apical) was 0.7 and 1.7 at 1 hour and 2 hours, respectively.

About 68% of oral dose of alogliptin was excreted in urine (Study 014). The mean recovery of radioactivity was 89% (76% in urine and 13% in feces) over 120 hours post-dose (Figure 8). Alogliptin elimination half-life was 25.61 hour (44% CV) and metabolites plasma exposure was less than 5% of alogliptin exposure.

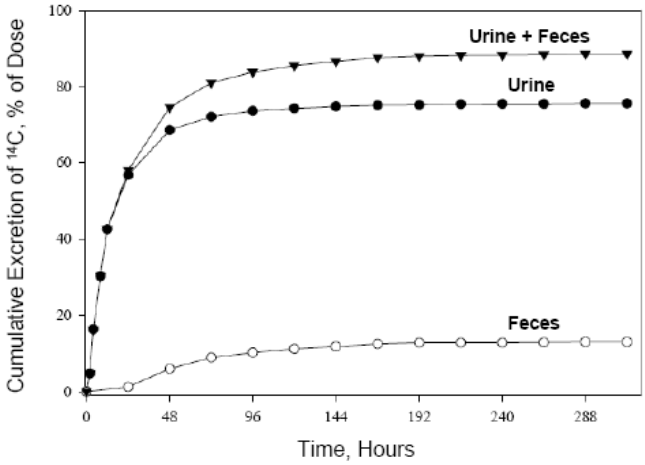


Figure 8 Mean cumulative profiles of urinary and fecal excretion of radioactivity following 25 mg alogliptin containing 100 µCi of ^{14}C

Alogliptin plasma protein binding was concentration dependent and ranged from 28% to 38% in concentration range of 10µg/mL to 0.01µg/mL.

Time to reach Cmax ranged from 1 hour to 2 hour (Study 014 and 027). Clearance (CL/F) and volume of distribution (Vd/F) following oral 25 mg dose was 16.88 L/hr and 609.6 L, respectively (Study 014). Alogliptin pharmacokinetic parameters following 12.5 mg and 25 mg are summarized in Table 2 from the pivotal BE study results (Study 027).

Table 2 Alogliptin pharmacokinetic parameters following 12.5 mg and 25 mg

Parameter (units)	Arithmetic Mean (%CV)		LS Mean (a)		
	Treatment D: SYR-322 25 mg Proposed Commercial Tablet (T)	Treatment C: SYR-322 25 mg Phase 3 Tablet (R)	Treatment D: SYR-322 25 mg Proposed Commercial Tablet (T)	Treatment C: SYR-322 25 mg Phase 3 Tablet (R)	Ratio T/R·100 (90% CI) (a)
Plasma	n=36	n=36	n=36	n=36	
AUC(0-tlqc) (ng·hr/mL)	1447.03 (14.994)	1441.35 (15.478)	1431.56	1424.56	100.49 (98.64, 102.38)
AUC(0-inf) (ng·hr/mL)	1530.52 (15.418)	1525.36 (16.330)	1512.90	1505.58	100.49 (98.73, 102.28)
Cmax (ng/mL)	125.77 (29.051)	118.63 (23.067)	120.95	115.47	104.75 (98.50, 111.38)
Tmax (hr) (b,c)	1.00 (0.500, 6.017)	1.00 (0.500, 6.000)	1.00	1.00	—
CL/F (L/hr)	16.72 (15.727)	16.83 (17.297)	—	—	—
Urine	n=35	n=35			
Ae(0-24) (mg)	8.81 (31.998)	8.67 (36.979)	—	—	—
CLr (L/hr)	8.41 (36.444)	8.13 (40.010)	—	—	—
Fe (%)	35.23 (31.998)	34.67 (36.979)	—	—	—

Sources: Tables 15.2.1.2, 15.2.1.8, and 15.2.1.12.
— =not applicable, T=test treatment, R=reference treatment.
(a) Ratios and confidence intervals are presented as percentages.
(b) Tmax is presented as median (minimum, maximum).
(c) P=0.162

Alogliptin seems to be metabolically stable in hepatocytes with less than 0.6% degradation over 3 hours. Alogliptin was metabolized to N-demthylated alogliptin (M1) by CYP2D6 and to N-acetylated metabolite (M2) (Figure 9). DPP-4 inhibition activity of M1 was similar to that of alogliptin and M2 was not active against DPP-4 inhibition. Exposure of M1 and M2 was less than 1% and 4% of alogliptin, respectively.

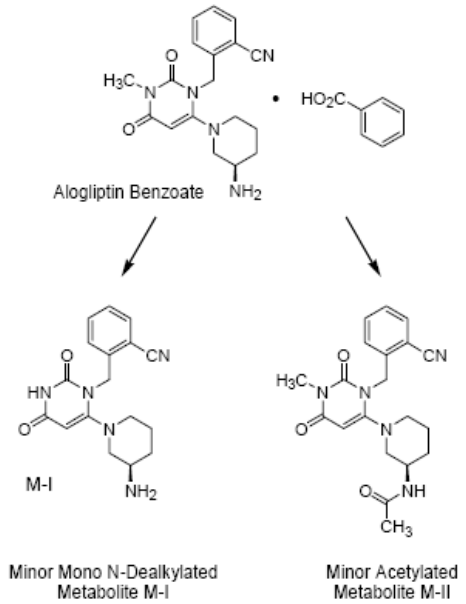


Figure 9 Major metabolic pathways

Alogliptin did not show inhibition potential on CYP1A2, 2C8, 2C9, and 2C19 at 100 µmol/L in pooled human liver microsomes (from 9 individuals). Alogliptin showed inhibition potential on CYP2D6 but its IC_{50} (>100 µM) was significantly higher than Cmax (100 µM) (Table 3). Alogliptin increased dextromethorphan AUC, *in vivo* 2D6 substrate, by 26% and it indicates that clinical consequence of 2D6 inhibition by alogliptin is not significant. Alogliptin showed inhibition potential on CYP3A4/5 after pre-incubation (Table 3). However, alogliptin did not change *in vivo* 3A4 substrates (i.e., midazolam and atorvastatin) exposure.

Table 3 *In vitro* evaluation of alogliptin as an inhibitor of human CYP enzymes

		Direct inhibition		Metabolism-dependent inhibition (MDI)		
		Zero-minute pre-incubation		30-minute pre-incubation		
		IC50 (µM)	Maximum inhibition at 100 µM (%) [a]	IC50 (µM)	Maximum inhibition at 100 µM (%)[a]	MDI potential [b]
CYP1A2	Phenacetin *O*-deethylation	> 100	NA	> 100	13	little or no
CYP2C8	Paclitaxel 6α-hydroxylation	> 100	NA	> 100	NA	little or no
CYP2C9	Diclofenac 4´-hydroxylation	> 100	NA	> 100	NA	little or no
CYP2C19	*S*-Mephenytoin 4´-hydroxylation	> 100	4.2	> 100	6.2	little or no
CYP2D6	Dextromethorphan *O*-demethylation	> 100	27	> 100	27	little or no
CYP3A4/5	Midazolam 1´-hydroxylation	> 100	1.2	78 ± 11	56	yes
CYP3A4/5	Testosterone 6β-hydroxylation	> 100	0.9	> 100	46	yes

Notes Values were calculated using the average data obtained from duplicates for each incubation condition. The IC50 values were calculated using XLFit.

[a] Maximum inhibition (%) is calculated using the following formula and data for the highest concentration of test article for which usable data were collected from the IC50 determinations (results are rounded to two significant figures): Maximum inhibition (%) = 100% – Percent solvent control (see Appendix 4)

[b] Metabolism-dependent inhibition was determined by comparison of IC50 values with and without pre-incubation and by visual inspection of the IC50 plot.

NA Not applicable; inhibition was not observed at the highest concentration of SYR110322 evaluated (100 µM).

Alogliptin did not show induction potential on CYP1A2, 2B6, 2C9, and 2C19 but only induction potential on CYP3A4/5 at 100 µmol/L in human hepatocytes with 27.6% activity of rifampin, a positive control for induction. Alogliptin following multiple doses did not affect exposure of 3A4 substrates, namely midazolam and atorvastatin and the results indicate that alogliptin is not an *in vivo* inducer for CYP3A4/5.

- Dose-exposure relationship

Alogliptin pharmacokinetics was linear across the single doses (25 mg, 50 mg, 100 mg, 200 mg, 400 mg and 800 mg; Study 001) in healthy subjects and multiple doses (25 mg, 100 mg and 400 mg QD for 14 days; Study 002) in T2D patients. Slopes (its 90% confidence interval) between alogliptin exposure and doses were estimated using a power model (Table 4).

Table 4 Slopes between alogliptin exposure and doses

slope (90% CI)	AUC_{0-t}	Cmax
single dose	1.052 (1.010-1.095)	1.214 (1.150-1.278)
multiple dose	0.9520 (0.91-1.00)	1.0080 (0.94-1.07)

Accumulation ratio on Day 14 was 1.34 and 1.09 for AUC_{0-24hr} and Cmax, respectively, following 25 mg QD in T2D patients.

2.3 Intrinsic Factors

2.3.1 *What intrinsic factors (e.g., age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?*

- Disease

Alogliptin exposure in T2D patients was slightly lower than that of healthy subjects following 400 mg QD in a cross study comparison (Table 5) and the difference appears to be clinically insignificant.

Table 5 Alogliptin exposure comparison between healthy subjects and T2D patients following 400mg QD

	Day 1		steady-state*	
	AUC_{0-24} (ng hr/mL)	Cmax (ng/mL)	AUC_{0-24} (ng hr/mL)	Cmax (ng/mL)
Healthy subjects (Study 019)	20162	2794	23646	2844
T2D (Study 002)	15823	2420	20675	2560

* Day 7 for healthy subjects (n=64) and Day 14 for T2D patients (n=14-15)

- US study vs. Japanese study

There was no significant alogliptin exposure or DPP-4 inhibition difference observed between studies conducted in US and Japan in a cross study comparison (Figure 10). About 80% of study population was Caucasian in the US study (Study 001) and Study

CPH-001 population was all Japanese. This indicates that alogliptin exposure in Japanese is not significantly different to that of Caucasian.

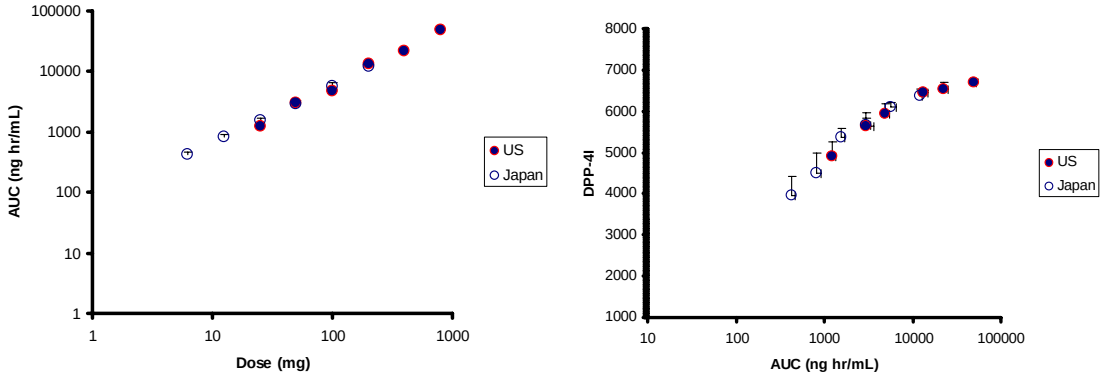
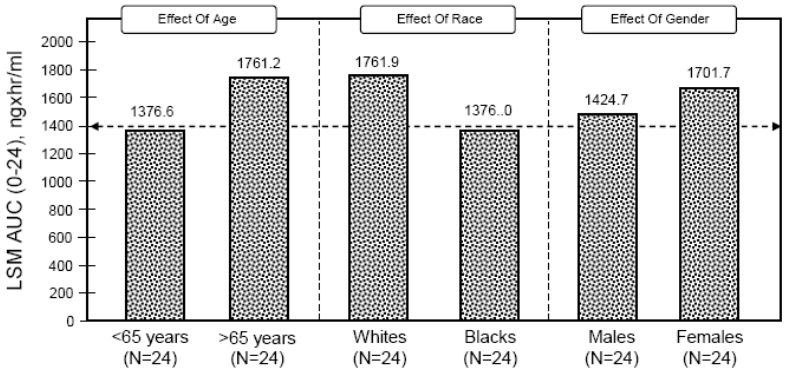


Figure 10 **AUC versus dose (left) or DPP-4 inhibition versus AUC between US study (Study 001) and Japanese study (CPH-001) following single doses**

- Age, gender and race

Elderly subjects had 28% higher AUC_{0-24} than those of young subjects and Cmax in the elderly subjects was not significantly different to that of young subjects. Women had 19% and 22% higher in AUC_{0-24} and Cmax than those of men, respectively. White subjects had 28% and 20% higher in AUC_{0-24} and Cmax than those of Black subjects, respectively (Figure 11).

The sponsor concluded that the alogliptin PK changes with age, gender and race were not clinically meaningful. Exposure of alogliptin metabolites were less than 4% of alogliptin. Therefore, metabolites exposure changes were not considered clinically important.



Source: Study 022.

Figure 11 **AUC by treatment groups**

Reviewer's Comments:

- A total of eight treatment sub-groups were utilized in assessing for the effect of age, sex, and race on alogliptin exposure (Figure 12). The sponsor pooled these sub-groups by age, sex or race. For example, young Black men, young White men, young

Black women and young White women groups were pooled for young age groups. However, there was statistically significant effect of age (i.e., young White men vs. elderly White men), sex (i.e., young White men vs. young White women) and race on alogliptin exposure. In addition, there was interaction between age and sex on alogliptin exposure as indicated by 97% exposure increase in elderly White women compared to young White men. Therefore, the sponsor's pooled data analysis is not acceptable. Creatinin clearance in the elderly White women was about half of that in the young White men and it indicates renal function decrease mainly attributes exposure increase in the elderly White women.

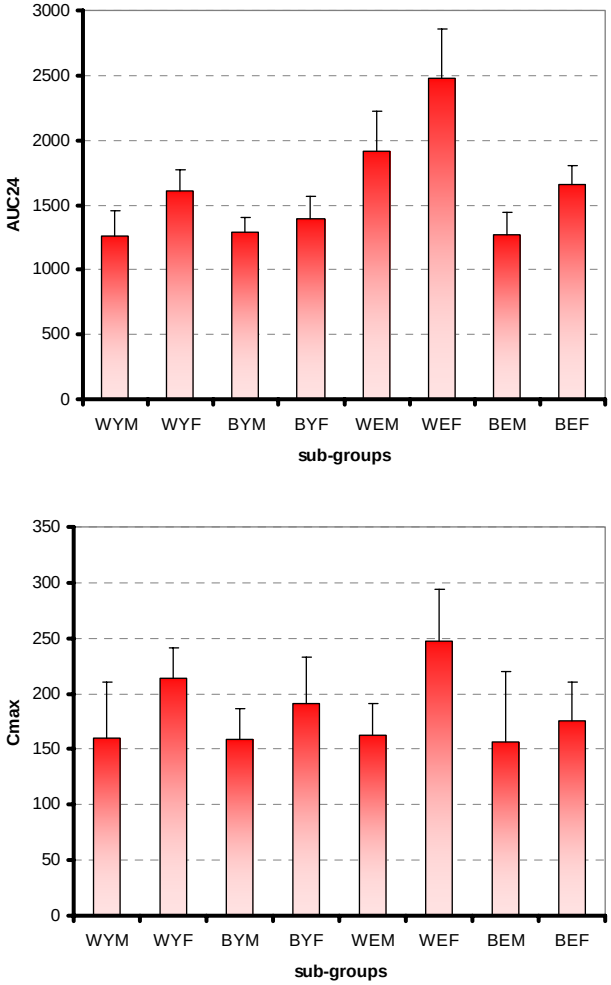


Figure 12 **AUC (upper) and Cmax (lower) by treatment groups: WYM-White young male, WYF-White young female, BYM-Black young male, BYF-Black young female, WEM-White elderly male, WEF-White elderly female, BEM-Black elderly male, BEF-Black elderly female**

- Renal impairment

Renal function clearly affected alogliptin exposure (Figure 13). Alogliptin AUC increase by 69%, 108%, 219% and 281% in subjects with mild, moderate, severe renal impairment and ESRD, respectively, compared to that of control subjects. Cmax also

increased by 13%, 42%, 27%, and 32% in subjects with mild, moderate, severe and ESRD, respectively, compared to that of control subjects. Metabolite (M1) exposure significantly increased with renal impairment (Figure 14). However, it may not be clinically meaningful because those exposures were significantly lower (<4%) than that of alogliptin.

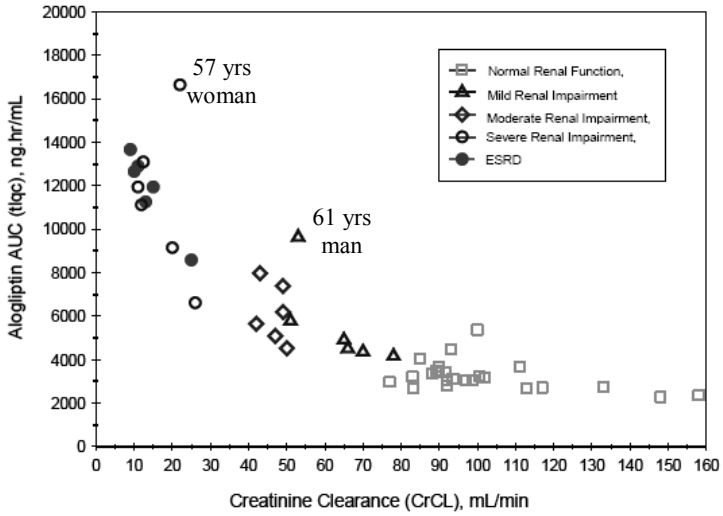


Figure 13 AUC(0-t) vs. CrCl by renal status

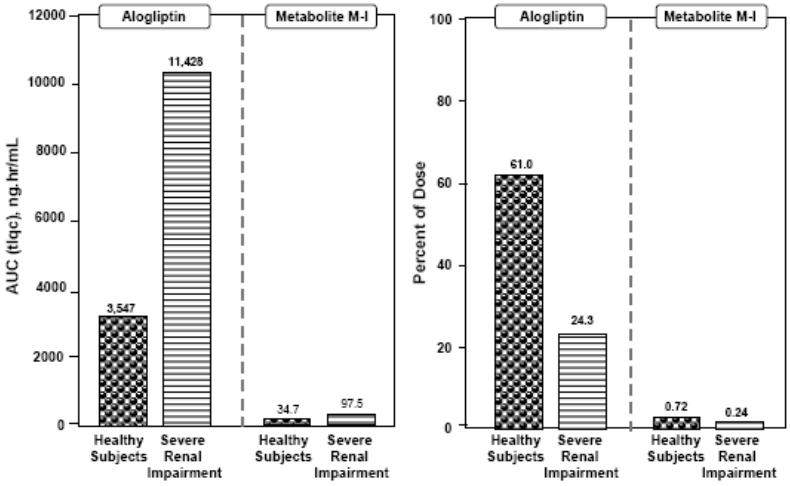


Figure 14 AUC_{0-t} (left) and urinary excretion (right) by renal status following 50 mg single dose

Dose adjustment is recommended for subjects with moderate and severe renal impairment, and end stage renal disease (ESRD) because of exposure increase: 12.5 mg for patient with moderate renal impairment and 6.25 mg for patient with severe renal impairment or ESRD.

Reviewer's Comments:

We recommend dose adjustment to 12.5 mg for subject with mild renal impairment because of mean exposure increase by 69% in the subjects. There will not be efficacy compromise for the dose adjustment with 69% exposure increase because HbA1c lowering effect of 12.5mg (-0.54% in monotherapy) is comparable to that of 25 mg (-0.57% in monotherapy).

- Hepatic impairment

Moderate hepatic impairment classified by Child-Pugh system did not significantly affect alogliptin exposure (Table 6).

Table 6 Alogliptin pharmacokinetic parameters in subject with moderate hepatic impairment following 25 mg single dose

		LS Mean		
Parameter (units)	N	Subjects with Moderate Hepatic Impairment (T)	Healthy Subjects (R)	Ratio T/R·100 (90% CI) (a)
AUC(0-tlqc) (ng·hr/mL)	8	1281.27	1424.40	89.95 (73.41, 110.22)
AUC(0-inf) (ng·hr/mL)	8	1362.28	1497.11	90.99 (74.19, 111.60)
Cmax (ng/mL)	8	113.52	122.94	92.34 (68.27, 124.90)
Tmax (hr) (b,c)	8	2.00	1.50	N/A

Source: Study 023.
N/A=not applicable, R=reference treatment, T=test treatment.
(a) Ratios and CIs are presented as percentages.
(b) Tmax is presented as median (minimum, maximum).
(c) P=0.091.

2.4 Extrinsic Factors

2.4.1 *What are the drug-drug interaction studies?*

Drug interaction was evaluated as follows and results are summarized in Table 7.

- The effect of metabolic modulators (fluconazole, ketoconazole, gemfibrozil and cyclosporine) on alogliptin exposure,
- The effect of alogliptin on other drugs (caffeine, tolbutamide, dextromethorphan, midazolam, fexofenadine, glyburide, warfarin, ethinyl estradiol and norethindrone),
- Drug interaction between alogliptin and other drugs (cimetidine, metformin, pioglitazone, atorvastatin and digoxin).

Alogliptin increased dextromethorphan AUC (2D6 substrate) by 26% and fexofenadine AUC (P-gp and OATP substrate) by 32%. However, these are not clinically meaningful. Gemfibrozil and cyclosporine significantly increased M-I exposure but it may not be clinically meaningful because of insignificant exposure (<1% of alogliptin).

Table 7 Results of in vivo drug interaction studies

Perturber	Substrate	GMR (90% CI)	
		AUC	Cmax
fluconazole 200 mg (2C9)	alogliptin 25 mg at Day 11	99.14 (96.45-101.89)	80.43 (70.10-92.28)
	M-I at Day 11	118.75 (101.03-139.57)	116.21 (105.93-127.48)
ketoconazole 400 mg (3A4)	alogliptin 25 mg at Day 11	115.39 (110.99-119.97)	122.04 (109.55-135.94)
	M-I at Day 11	100.65 (88.30-114.74)	136.17 (123.42-150.24)
gemfibrozil (2C8/9)	alogliptin 25 mg at Day 11	112.88 (109.20-116.69)	84.74 (73.30-97.96)
	M-I at Day 11	191.14 (164.78-221.71)	172.64 (157.10-189.73)
cyclosporine 600 mg (p-gp)	alogliptin 25 mg at Day 1	110.29 (101.46-119.88)	105.35 (95.13-116.65)
	M-I at Day 1	147.24 (129.99-166.79)	154.40 (137.57-173.29)
alogliptin 25 mg QD for 7 days	glyburide 5 mg (2C9)	99.40 (93.14-106.08)	115.36 (105.98-125.57)
alogliptin 25 mg QD for 7 days	(S)-warfarin (2C9) stable dose	101.09 (97.22-105.11)	99.75 (92.11-108.02)
	(R)-warfarin (1A2)	98.80 (94.2-103.60)	98.56 (92.03-105.56)
	PT, INR	no statistical difference	
alogliptin 25 mg QD for 21 days	ethinyl estradiol	98.59 (94.92-102.40)	91.62 (86.77-96.73)
	norethindrone	102.48 (99.51-105.55)	103.05 (97.73-108.66)
	PD: LH, FSH, ER, progesterone, and SHBG	no statistical difference	
alogliptin 100 mg QD 7 days (cocktail study)	caffeine 200 mg (1A2)	104.90 (92.47-119.01)	97.57 (91.77-103.74)
	tolbutamide 500 mg (2C9)	97.41 (93.07-101.96)	99.58 (95.76-103.54)
	dextromethorphan 30 mg (2D6)	125.97 (107.82-147.17)	132.02 (113.81-153.14)
	midazolam 4 mg (3A4)	107.55 (97.88-118.19)	112.68 (101.70-124.84)
	fexofenadine 60 mg (P-gp)	132.05 (110.78-157.41)	117.47 (95.38-144.67)
alogliptin 100 mg QD for 6 days vs. Cimetidine 400 mg QD for 6 days	cimetidine alogliptin	104.3 (98.2-110.7) 106.5 (103.2-109.9)	99.3 (90.7-108.7) 104.8 (98.4-111.6)
alogliptin 100 mg QD for 6 days vs. metformin 1000 mg BID for 6 days	metformin alogliptin	118.9 (109.5-129.1) 100.0 (97.2-102.9)	100.4 (91.9-109.7) 89.5 (82.0-97.7)
alogliptin 25 mg QD for 12 days vs. pioglitazone 45 mg QD for 12 days (2C8)	pioglitazone alogliptin	105.78 (97.49-114.78) 110.22 (107.75-112.75)	105.13 (92.34-119.68) 109.65 (102.55-117.25)
alogliptin 25 mg QD for 7 days vs. atorvastatin 80 mg QD for 7 days	atorvastatin alogliptin	114.17 (101.36-128.59) 100.07 (96.35-103.94)	112.66 (95.43-133.00) 108.68 (96.26-122.70)
alogliptin 25 mg QD for 10 days vs. digoxin 200 mg QD for 10 days	digoxin alogliptin	99.71 (96.02-103.55) 102.79 (99.46-106.23)	94.16 (85.16-104.11) 110.79 (101.61-120.80)

Underlined values indicate out of BE criteria.

2.4.2 *What is the food effect on alogliptin exposure?*

There was no significant food effect on alogliptin exposure following 25 mg single dose in healthy subjects (Study 026; Figure 15 and GMR with 90%CI in the figure).

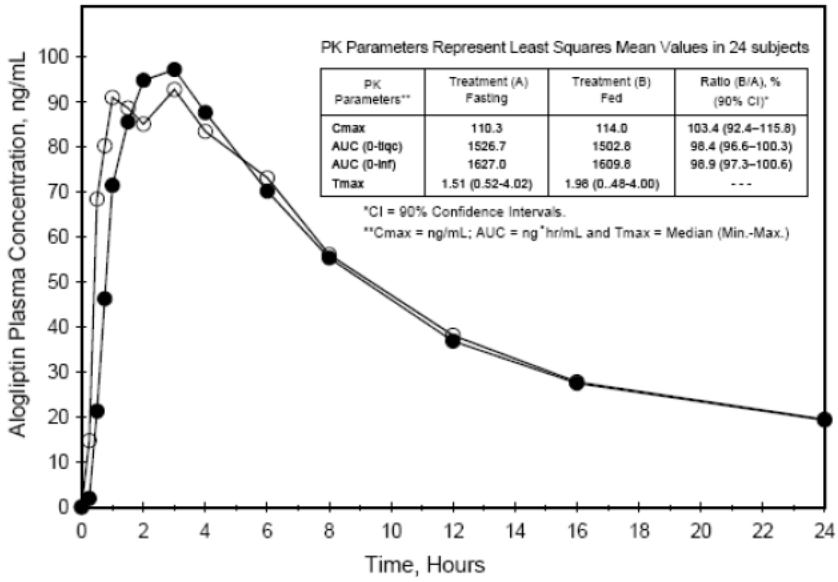


Figure 15 **Alogliptin mean plasma concentration-time profiles following 25 mg under an overnight fasting condition (closed circle) and fed (open circle).**

2.5 General Biopharmaceutics

2.5.1 *What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?*

Commercial formulations [redacted] (b) (4) were bioequivalent to formulations used in the pivotal studies, [redacted] (b) (4) Table 8), at 12.5 mg and 25 mg.

Table 8 **GMR of commercial formulation to clinical formulation (90% CI)**

	AUC_{0-t} (ng hr/mL)	Cmax (ng/mL)
12.5 mg	101.37 (99.67-103.10)	89.20 (81.92-97.14)
25 mg	100.49 (98.64-102.38)	104.75 (98.50-111.38)

Components and composition of commercial formulation are summarized in Table 9 and dissolution study results are shown in Figure 16. Alogliptin tablets were dissolved at a minimum [redacted] (b) (4) in 15 minutes across the range of physiologic pH and 3 specified

dissolution media. Each samples was tested in 900 mL of 0.01M HCl, Apparatus 2 (paddle) at 50 rpm, and 37 °C and sampling time was 5, 10, 15, 20, 30, and 45 minutes.

Table 9 Components and composition of commercial formulation

Component	Reference to Quality Standards	Function	Quantity per Tablet (mg)		
			6.25 mg	12.5 mg	25 mg
Uncoated Tablet					
Alogliptin benzoate (a) (As alogliptin)	In-house standard	Active ingredient	8.5 (6.25)	17 (12.5)	34 (25)
Mannitol	USP	[redacted]			(b) (4)
Microcrystalline cellulose	NF				
Hydroxypropyl cellulose	NF				
Croscarmellose sodium	NF				
Magnesium stearate	NF				
(b) (4)	USP				
Film Coat Solution					
Hypromellose (b) (4)	USP	[redacted]			(b) (4)
Titanium dioxide	USP				
Ferric oxide, yellow	NF				
Ferric oxide, red	NF				
(b) (4)	USP				
Polyethylene glycol (b) (4)	NF				
(b) (4)	USP				
Printing ink gray F1	Manufacturers standard				
(b) (4)	NF				
					(b) (4)

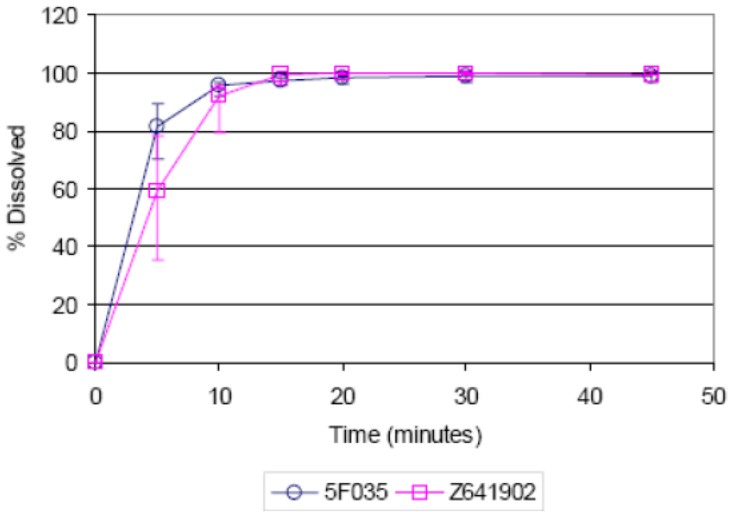


Figure 16 Dissolution profiles

2.6 Analytical Section

2.6.1 *What bioanalytical methods are used to assess concentrations?*

Conventional LC/MS/MS method was used for the quantification of alogliptin and its metabolite in plasma and urine. The individual validation runs were within acceptable specifications including accuracy and precision (Table 10). Lower limit of quantitation was 1.00 ng/mL and 0.100 ng/mL for alogliptin and M1, respectively, and the standard curve was linear up to 1000 ng/mL and 100 ng/mL for alogliptin and M1, respectively.

Table 10 Representative QC statistics

QC statistics for plasma assay (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

Source: LCMS307_4 revision.
(a) Expressed as % difference relative to theoretical concentrations.

QC statistics for urine assay (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

Source: LCMS307_6 validation.
(a) Expressed as % difference relative to theoretical concentrations.

QC statistics for plasma assay (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

Source: LCMS307_4 addendum 2.
(a) Expressed as % difference relative to theoretical concentrations.

QC statistic for plasma assay (validation report for SYR-322/00260)

Analyte	Accuracy (a)	Precision (%CV)
Alogliptin	-1.2 to 4.0	0.8 to 5.8
M-I	-2.0 to 10.0	0.4 to 4.1
M-II	-1.8 to 4.8	1.9 to 7.9

Source: SYR-322/00260.
(a) Expressed as % difference relative to theoretical concentrations.

QC statistic for urine assay (validation report for SYR-322/00260)

Analyte	Accuracy (a)	Precision (%CV)
Alogliptin	-3.6 to 6.0	1.5 to 7.3
M-I	-0.8 to 8.6	1.0 to 8.1
M-II	-8.3 to -2.4	5.1 to 10.2

Source: SYR-322/00262.
(a) Expressed as % difference relative to theoretical concentrations.

3 Detailed Labeling Recommendations

(Please refer attached file for clinical pharmacology labeling comments. ~~Strikethrough~~ indicates deletion and red underlined text indicates addition.)

4 Appendices

4.1 Approvable letter for NDA (b) (4)

(b) (4)

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4.2 Review on the individual study report

4.2.1 Study SYR-322-027 (pivotal BE study): An open-label, randomized, 2-period crossover study to determine the bioequivalence of the Phase 3 tablets (12.5 and 25 mg) with the commercial tablets (12.5 and 25 mg) in healthy adults subjects (n=18 per treatment) under fasting condition

Methods: Subjects were randomized to 12.5 mg or 25 mg group and received the Phase 3 formulation (test) and the commercial tablet in a crossover design under an overnight fasting condition (Table 11). Blood samples were collected up to 72 hours (i.e., predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-dose) following administration of investigational formulations (Table 12). Pharmacokinetic parameters were estimated using the non-compartmental method. Bioequivalence was assessed using GMR and its 90% CI.

Results: Alogliptin plasma concentration-time profiles are shown in Figure 16. Pharmacokinetic parameters and results of statistical analysis for BE assessment are summarized in Table 13. The commercial formulations are BE to the formulations used in the pivotal clinical trials.

Table 11 Summary of study design

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

A=1 SYR-322 12.5 mg phase 3 tablet (reference treatment), B=1 SYR-322 12.5 mg proposed commercial tablet (test treatment), C=1 SYR-322 25 mg phase 3 tablet (reference treatment), D=1 SYR-322 25 mg proposed commercial tablet (test treatment), ET=early termination.
(a) Subjects were confined to the clinic from Day -1 of Treatment Period 1 through Day 4 of Treatment Period 1 and from Day 7 of Treatment Period 1 through Day 4 of Treatment Period 2 and were discharged from the study on Day 4 of Treatment Period 2 after collection of the 72-hour pharmacokinetic blood sample.

Table 12 Summary of investigational products

Drug	Lot Number
SYR-322 12.5 mg proposed commercial tablet	Z6418021
SYR-322 25 mg proposed commercial tablet	Z6419021
SYR-322 12.5 mg phase 3 tablet	5K074
SYR-322 25 mg phase 3 tablet	5K071

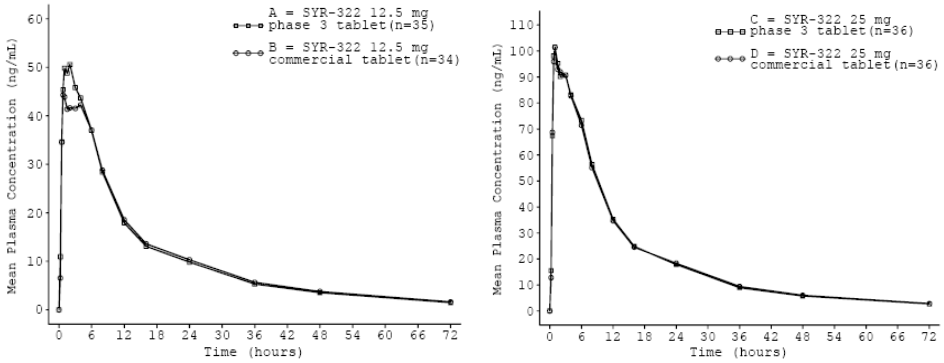


Figure 17 **Mean plasma concentration-time profiles following 12.5 mg (left) and 25 mg (right) administration.**

Table 13 **alogliptin PK parameters following 12.5 (upper) and 25 mg (lower), and GMR (test/reference)**

Parameter (units)	Arithmetic Mean (%CV)		LS Mean (a)		
	Treatment B: SYR-322 12.5 mg Proposed Commercial Tablet (T)	Treatment A: SYR-322 12.5 mg Phase 3 Tablet (R)	Treatment B: SYR-322 12.5 mg Proposed Commercial Tablet (T)	Treatment A: SYR-322 12.5 mg Phase 3 Tablet (R)	Ratio T/R·100 (90% CI) (a)
Plasma	n=33	n=33	n=33	n=33	
AUC(0-tlqc) (ng·hr/mL)	768.84 (17.639)	759.98 (19.118)	756.90	746.64	101.37 (99.67, 103.10)
AUC(0-inf) (ng·hr/mL)	819.80 (17.282)	810.56 (19.029)	807.61	796.49	101.40 (99.62, 103.20)
Cmax (ng/mL)	53.45 (30.390)	60.31 (33.996)	51.12	57.31	89.20 (81.92, 97.14)
Tmax (hr) (b)	1.50 (0.500, 6.000)	1.50 (0.500, 6.000)	1.50	1.50	—
CL/F (L/hr)	15.67 (16.422)	15.92 (17.257)	—	—	—
Urine	n=33	n=33			
Ae(0-24) (mg)	4.76 (24.274)	5.06 (28.017)	—	—	—
CLr (L/hr)	8.79 (26.601)	9.38 (33.879)	—	—	—
Fe (%)	38.09 (24.274)	40.49 (28.017)	—	—	—

Sources: Tables 15.2.1.2, 15.2.1.7, and 15.2.1.12.
— =not applicable, T=test treatment, R=reference treatment.
(a) Ratios and confidence intervals are presented as percentages.
(b) Tmax is presented as median (minimum, maximum); P=0.449.

Parameter (units)	Arithmetic Mean (%CV)		LS Mean (a)		
	Treatment D: SYR-322 25 mg Proposed Commercial Tablet (T)	Treatment C: SYR-322 25 mg Phase 3 Tablet (R)	Treatment D: SYR-322 25 mg Proposed Commercial Tablet (T)	Treatment C: SYR-322 25 mg Phase 3 Tablet (R)	Ratio T/R·100 (90% CI) (a)
Plasma	n=36	n=36	n=36	n=36	
AUC(0-tlqc) (ng·hr/mL)	1447.03 (14.994)	1441.35 (15.478)	1431.56	1424.56	100.49 (98.64, 102.38)
AUC(0-inf) (ng·hr/mL)	1530.52 (15.418)	1525.36 (16.330)	1512.90	1505.58	100.49 (98.73, 102.28)
Cmax (ng/mL)	125.77 (29.051)	118.63 (23.067)	120.95	115.47	104.75 (98.50, 111.38)
Tmax (hr) (b,c)	1.00 (0.500, 6.017)	1.00 (0.500, 6.000)	1.00	1.00	—
CL/F (L/hr)	16.72 (15.727)	16.83 (17.297)	—	—	—
Urine	n=35	n=35			
Ae(0-24) (mg)	8.81 (31.998)	8.67 (36.979)	—	—	—
CLr (L/hr)	8.41 (36.444)	8.13 (40.010)	—	—	—
Fe (%)	35.23 (31.998)	34.67 (36.979)	—	—	—

Sources: Tables 15.2.1.2, 15.2.1.8, and 15.2.1.12.
— =not applicable, T=test treatment, R=reference treatment.
(a) Ratios and confidence intervals are presented as percentages.
(b) Tmax is presented as median (minimum, maximum).
(c) P=0.162

Reviewer's Comments:

- The sponsor proposed 6.25 mg for patients with severe renal impairment. There was no major clinical pharmacology study to evaluate the commercial 6.25 mg strength. A biowaiver should be requested for the approval of 6.25 mg.
- The washout period appears to be reasonable considering more than 5 half-lives. Terminal half-lives (CV) of alogliptin were 19.907 (19.4%), 20.012 (15.8%), 20.220 (18.2%), and 19.473 (16.8%) hours for Treatment A, B, C, and D, respectively.

4.2.2 Study SYR-322-014 (Mass balance study): A phase 1, open-label mass balance and excretion study of [^{14}C]SYR-322 following oral administration in healthy male subjects (n=8)

Methods: Subjects received alogliptin 25 mg aqueous solution containing 100 µCi of ^{14}C under an overnight fasting condition. Blood samples were collected up to 120 hours post-dose. Urinary and fecal excretion samples were collected up to 15 days to obtain at least 90% radioactivity recovery. Alogliptin and its metabolite (M1) pharmacokinetics were estimated using the non-compartmental method.

Results: The mean recovery of radioactivity was 88.53% (75.59% in urine and 12.94% in feces) (Figure 17). Alogliptin was the major component in urine and feces (95% and 88% of total radioactivity, respectively). About 68% of the administered dose of ^{14}C was excreted in the urine as alogliptin by 120 hours post-dose and 56.8% of total radioactivity was recovered in 24 hours.

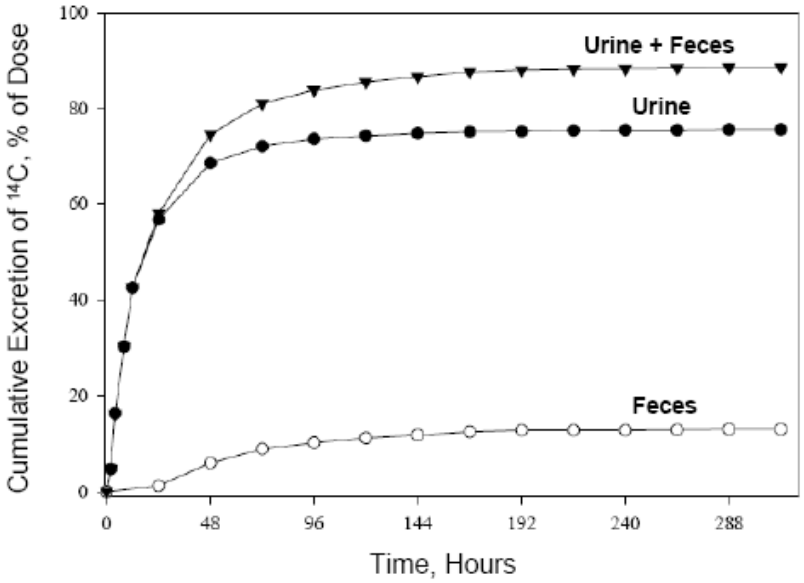
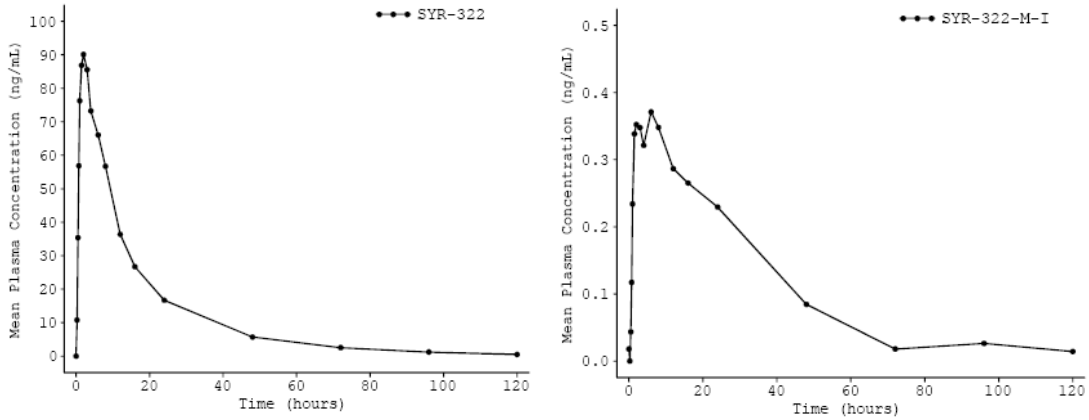


Figure 18 **Mean cumulative profiles of urinary and fecal excretion of radioactivity following 25 mg alogliptin containing 100 µCi of ^{14}C**

Metabolite exposure was less than 1% of alogliptin exposure (Figure 19 and Table 14).



Source: Figure 15.2.1.1.

Source: Figure 15.2.2.1.

Figure 19 **Plasma concentration-time profile of alogliptin (left) and its metabolite (right) following 25 mg oral solution**

Table 14 **Pharmacokinetic parameters for alogliptin and its metabolite following 25 mg oral solution**

	SYR-322			SYR-322 M-I		
Parameter (units)	**n**	**Arithmetic Mean (%CV)**	**Geometric Mean**	**n**	**Arithmetic Mean (%CV)**	**Geometric Mean**
Plasma						
AUC(0-tlqc) (ng·hr/mL)	8	1456.25 (13.467)	1444.37	7	12.49 (63.718)	10.26
AUC(0-inf) (ng·hr/mL)	8	1505.97 (13.315)	1493.74	6	22.26 (88.231)	17.20
Cmax (ng/mL)	8	100.1 (21.9)	97.9	7	0.5 (37.5)	0.4
Tmax (hr) (a)	8	2.00 (1.000, 3.000)	—	7	3.00 (1.000, 24.000)	—
T1/2 (hr)	8	25.61 (43.90)	—	6	37.66 (96.422)	—
MRT (hr)	8	22.72 (23.534)	—	6	55.15 (92.87)	—
CL/F (L/hr)	8	16.88 (14.470)	—		—	
Vz/F (L)	8	609.61 (40.334)	—		—	
Urine						
Ae(0-120) (mg)	8	16.74 (9.116)	—	7	0.25 (44.988)	—

Source: Table 15.2.1.2.
— = not applicable.
(a) Tmax is presented as median (minimum, maximum).

There was no significant radioactivity accumulation in blood cells (Table 15 and Table 16).

Table 15 Radioactivity concentration ratios in whole blood:plasma and whole blood:red blood cells

Collection Time	Whole Blood:Plasma Ratio N=8 Mean (SD)	Whole Blood:Red Blood Cell Ratio N=8 Mean (SD)
0.25	0.850 (—)	—
0.5	0.854 (0.065)	—
0.75	0.874 (0.048)	—
1	0.882 (0.053)	—
1.5	0.857 (0.048)	—
2	0.876 (0.048)	1.11 (0.04)
3	0.856 (0.028)	—
4	0.866 (0.055)	—
6	0.920 (0.040)	1.06 (0.03)
8	0.893 (0.034)	—
12	0.914 (0.027)	1.16 (0.06)
16	0.926 (0.046)	—
24	0.918 (0.084)	—

Source: Appendix 16.6: Covance Radioactivity Report, Tables 5 and 6.
— = not applicable.

Table 16 Whole blood and plasma pharmacokinetic parameters based on radioactivity

	Whole Blood N=8		Plasma N=8	
Parameter (units)	Arithmetic Mean (%CV)	Geometric Mean	Arithmetic Mean (%CV)	Geometric Mean
AUC(0-tlqc) (ng Eq·hr/mL)	1418.43 (13.742)	1407.65	1816.07 (22.191)	1778.01
Cmax (ng Eq/mL)	131.15 (21.778)	128.36	150.88 (22.163)	147.71
Tmax (hr) (a)	2.00 (1.000, 6.000)	—	2.50 (1.000, 3.000)	—

Source: Table 15.2.1.4.
— = not applicable.
(a) Tmax is presented as median (minimum, maximum).

Reviewer's Comments:

The following major conclusions are acceptable.

- The mean total radioactivity recovery of 88.53% is close to the target recovery (90%) with low variability (CV of 2.3%).
- Alogliptin major elimination pathway is the urinary excretion with 68% of dose recovery in urine as alogliptin.
- The metabolite exposure is insignificant compared to that of alogliptin.

4.2.3 Study SYR-322-014 (Single dose pharmacokinetic study): A randomized, double-blind, placebo-controlled, single-dose, dose-ascending study of the safety, tolerability, and pharmacokinetic and pharmacodynamic effects of SYR110322 in healthy volunteers

Methods: Subject received 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, or 800 mg as a combination of 25 mg, 100 mg and 200 mg capsule(s) following an overnight fasting condition. Blood samples were collected up to 72 hours for alogliptin and its metabolite in plasma and urine. Pharmacokinetics and pharmacodynamics (*ex vivo* DPP IV inhibition and plasma GLP-1 levels) were assessed using the non-compartmental analysis. A power model used for the dose proportionality assessment:
Log_e(parameter) = a + b*Log_e(dose) + error; where, a is the intercept and b is the slope.

Results: Mean alogliptin concentration-time profiles, mean DPP-4 inhibition-time profiles and mean GLP-1-time profiles are shown in Figure 20 and Figure 21. Pharmacokinetic and pharmacodynamic parameters are summarized in Table 17 and Table 18. The sponsor concluded that alogliptin exposure was linear to doses but AUC_{0-t} and Cmax did not meet the statistical proportionality criteria because 90% confidence interval of slope did not include 1; 1.010-1.095 for AUC_{0-t} and 1.150-1.278 for Cmax (Table 19).

Conventional Emax model characterized well the relationship between DPP-4 inhibition and plasma alogliptin concentrations (Figure 22). The sponsor estimated exposure of both N-acetylated metabolite (M2) and an optical isomer ((S)-SYR-322) in plasma and M2 in urine (001 Addendum for the post-hoc analysis). Plasma exposure of M2 was 2% to 4% of alogliptin exposure and the urinary excretion of M2 was 2% to 5% of alogliptin. The plasma exposure of (S)-SYR-322 was 0.7% of alogliptin exposure following 800 mg.

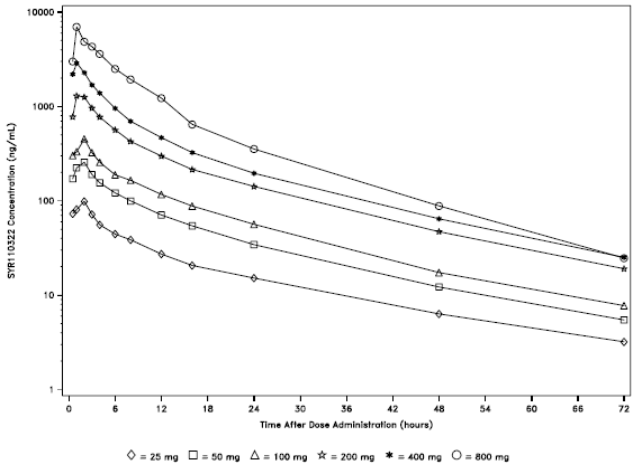


Figure 20 Mean alogliptin plasma concentration-time profiles by doses

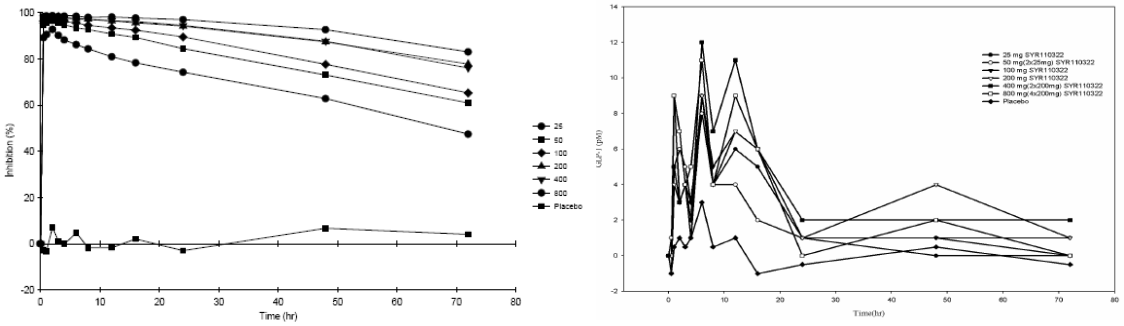


Figure 21 **Pharmacodynamic measures: ex vivo plasma DPP-4 inhibition over time (left) and plasma GLP-1 changes from the baseline over time (right)**

Table 17 **Alogliptin pharmacokinetic parameters following 25, 50, 100, 200, 400, or 800 mg**

	Arithmetic Mean (%CV)					
Parameter (units)	**Alogliptin 25 mg N=5**	**Alogliptin 50 mg N=5**	**Alogliptin 100 mg N=5**	**Alogliptin 200 mg N=5**	**Alogliptin 400 mg N=5**	**Alogliptin 800 mg N=5**
Alogliptin Plasma						
AUC(0-inf) (ng·hr/mL)	1327 (10.3)	3139 (21.4)	5040 (15.3)	13711 (13.0)	22816 (14.6)	49595 (6.5)
Cmax (ng/mL)	110 (23.7)	256 (24.6)	483 (26.9)	1548 (23.4)	3096 (28.2)	6994 (13.3)
Tmax (hr) (a)	2.0 (0.50, 2.00)	2.0 (2.00, 2.00)	2.0 (0.50, 2.00)	2.0 (0.50, 2.00)	1.0 (1.00, 2.00)	1.0 (1.00, 1.00)
T1/2,z (hr)	21.4 (20.8)	18.1 (10.2)	16.4 (19.3)	16.5 (10.0)	16.6 (12.8)	12.4 (14.2)
CL/F (L/hr)	19.0 (11.5)	16.5 (19.0)	20.3 (18.6)	14.8 (13.4)	17.8 (12.7)	16.2 (6.5)
Alogliptin Urine						
Ae(0-72)	16 (6.3)	30 (5.4)	65 (10.6)	142 (1.6)	269 (16.0)	533 (24.2)
Fe%(0-72)	63 (6.3)	60 (5.4)	65 (10.6)	71 (1.6)	67 (16.0)	67 (24.2)
CLr (L/h)	12.1 (14.5)	9.8 (20.3)	13.1 (13.5)	10.5 (12.8)	12.1 (21.1)	10.9 (27.6)

Sources: Study 001 and Study 001 Addendum.
(a) Tmax is presented as median (minimum, maximum).

Table 18 **Pharmacodynamic parameters: ex vivo DPP-4 inhibition (upper) and baseline corrected GLP-1 (lower)**

	Arithmetic Mean (%CV)						
Parameter (units)	**Alogliptin 25 mg N=5**	**Alogliptin 50 mg N=5**	**Alogliptin 100 mg N=5**	**Alogliptin 200 mg N=5**	**Alogliptin 400 mg N=5**	**Alogliptin 800 mg N=5**	**Placebo N=6**
DPP-4 Inhibition							
Emax (% inhibition)	93.3 (1.5)	96.4 (0.71)	97.2 (0.71)	98.3 (0.2)	98.2 (0.2)	98.8 (0.1)	12.2 (70.0)
Tmax (hr) (a)	2.0 (0.5, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	3.0 (1.0, 3.1)	3.0 (2.0, 3.0)	2.0 (2.0, 4.0)	6.0 (2.0, 72.0)
E24 (% inhibition)	74.3 (2.4)	84.4 (3.4)	89.5 (1.6)	94.1 (0.4)	94.5 (0.7)	97.0 (0.1)	-3.0 (-140.7)
E72 (% inhibition)	47.5 (28.5)	60.9 (3.4)	65.3 (12.1)	77.8 (2.6)	76.0 (6.0)	83.0 (4.1)	4.0 (213.2)
GLP-1 (b)							
AUE(0-t) (pM·h)	196.8 (85.8)	154.7 (59.2)	196.9 (57.0)	252.6 (29.0)	240.2 (57.7)	197.2 (57.4)	64.7 (119.9)
Emax (pM)	14.2 (87.3)	8.4 (35.3)	14.0 (77.4)	13.0 (72.0)	12.2 (21.2)	15.2 (50.4)	4.7 (87.5)

Sources: Study 001 and Study 001 Addendum.
(a) Tmax is presented as median (minimum, maximum).
(b) Baseline-corrected active GLP-1 levels.

Table 19 **Results of dose proportionality assessment using a power model: alogliptin (SYR110322) and its metabolite (SYR110324)**

Parameter	Parameter	Slope	Standard Error	90% CI	*P* value
SYR110322	AUC_{0-t}	1.052	0.025	1.010-1.095	0.046
	$AUC_{0-\infty}$	1.035	0.026	0.991-1.078	0.185
	C_{max}	1.214	0.038	1.150-1.278	<0.001
SYR110324	AUC_{0-t}	1.308	0.230	0.916-1.699	0.192
	$AUC_{0-\infty}$	0.855	0.166	0.571-1.140	0.393
	C_{max}	1.223	0.142	0.982-1.465	0.127

Source: Table 14.2.3

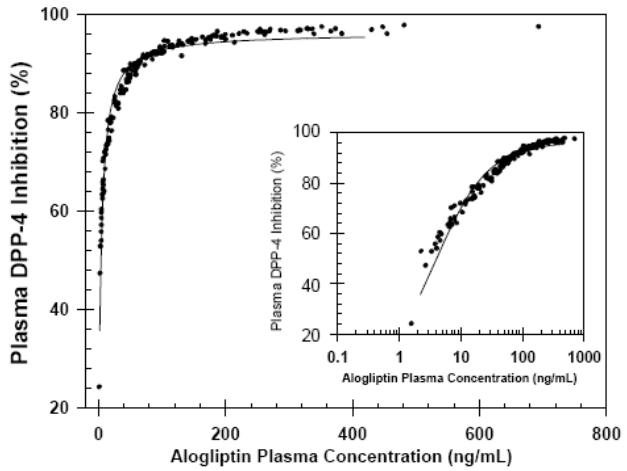


Figure 22 Plasma DPP-4 inhibition vs. alogliptin plasma concentration following single doses

Reviewer's comments:

Alogliptin pharmacokinetics is linear with doses but not proportional to doses based on a statistical perspective in a power model. Alogliptin exposure increased more than proportional to doses but the degree of increase was not significant (Figure 23).

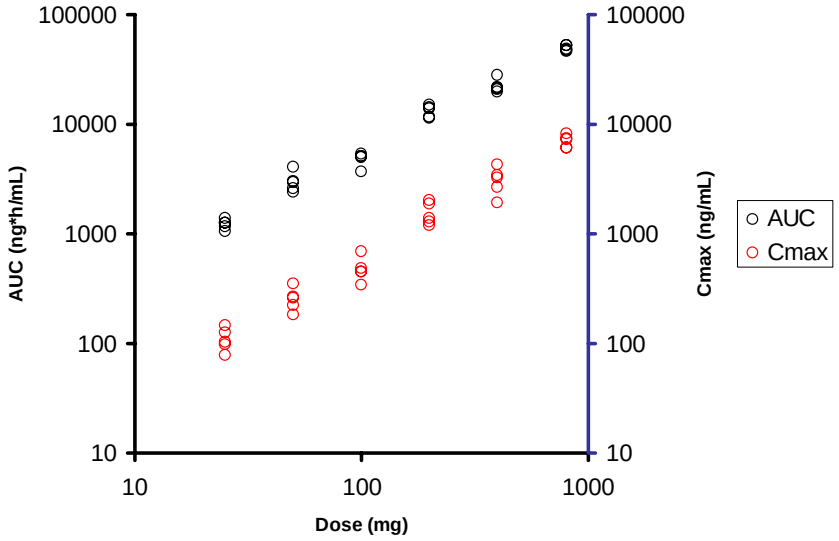


Figure 23 Alogliptin AUC or Cmax vs. doses

4.2.4 Study SYR-322-CPH-001 (Single dose pharmacokinetic study in Japan): A double-blind, randomized, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of single dose of SYP-322 in an ascending dose regimen in healthy male subjects

Methods: The Japanese subjects received single dose of alogliptin (6.25 mg, 12.5 mg, 25 mg, 50 mg, 100 mg as 2x50 mg tablets, or 200 mg as 4x50 mg tablets) following an overnight fasting condition. Plasma pharmacokinetics and urinary excretion of alogliptin, its metabolites, and an optical isomer was estimated. DPP-4 inhibition and plasma GLP-1 was measured as pharmacodynamic endpoints. Pharmacokinetic and pharmacodynamic parameters were estimated using non-compartmental analysis. PK/PD relationship was assessed using a conventional direct model with simultaneous fitting of plasma alogliptin concentrations to 2-compartment model and the DPP-4 inhibition to a sigmoid Emax PD model. Both of a power model and ANOVA for dose normalized exposure were used for the dose proportionality assessment (power model: Log_e(parameter) = a + b*Log_e(dose) + error; where, a is the intercept and b is the slope).

Results: Single dose alogliptin and its metabolite pharmacokinetic and pharmacodynamic parameters are summarized in Table 20 and Table 21. Alogliptin pharmacokinetics after multiple doses was simulated using a two-compartmental model and steady-state was reached by day 5 according to the prediction by the modeling. The values of EC_{50} for DDP-4 inhibition were estimated to be ranging from 1.350ng/mL to 2.818 ng/mL of alogliptin in plasma. The EC_{50} for baseline corrected GLP-1 AUC_{0-24} was 786.41 ng*hr/mL of alogliptin AUC (Figure 24). Alogliptin exposure was linear to doses. However, dose-exposure relationship did not meet the proportionality because 90% CI of slopes did not include 1; slopes (90% CI) of 0.942 (0.917-0.967) and 1.074 (1.018-1.129) for AUC and Cmax, respectively (Table 22). ANOVA results indicate dose-exposure is proportional between 25 mg and 200 mg (Table 23).

Table 20 Alogliptin pharmacokinetic and pharmacodynamic parameters following single doses in Japanese

	Arithmetic Mean (SD)					
Parameter (units)	Alogliptin 6.25 mg N=7	Alogliptin 12.5 mg N=8	Alogliptin 25 mg N=8	Alogliptin 50 mg N=8	Alogliptin 100 mg N=8	Alogliptin 200 mg N=8
Plasma						
AUC(0-inf) (ng·hr/mL)	460.50 (29.944)	850.88 (95.090)	1604.63 (178.002)	2996.96 (384.016)	5768.39 (920.316)	12417.14 (747.163)
Cmax (ng/mL)	52 (16.104)	96.50 (20.128)	193.25 (32.473)	448.00 (95.247)	1013.88 (488.308)	2019.63 (514.644)
Tmax (hr) (a)	1.5 (0.75, 2.0)	1.0 (0.5, 1.5)	1.25 (0.75, 1.5)	1.25 (0.75, 1.5)	0.875 (0.5, 2.0)	0.875 (0.5, 1.25)
T1/2 (hr)	21.80 (2.183)	16.66 (2.398)	17.13 (1.966)	14.29 (1.371)	13.40 (1.708)	12.66 (2.318)
Urine						
Fe%(0-72)	61.575 (11.487)	68.355 (4.5159)	67.771 (2.4728)	77.591 (4.3327)	78.465 (8.8496)	72.560 (6.4295)
CLr (L/h)	8.64 (1.651)	10.19 (1.648)	10.70 (1.298)	13.10 (1.518)	13.83 (2.287)	11.71 (1.245)

Source: Study CPH-001.
(a) Tmax is presented as median (minimum, maximum).

Table 20 (continue)

Parameter (units)	Arithmetic Mean (SD)						
	Alogliptin 6.25 mg	Alogliptin 12.5 mg	Alogliptin 25 mg	Alogliptin 50 mg	Alogliptin 100 mg	Alogliptin 200 mg	Placebo
DPP-4 Inhibition	N=8	N=8	N=8	N=5	N=8	N=8	N=10
Emax (% inhibition)	88.91 (3.153)	93.15 (1.694)	96.38 (0.648)	98.52 (0.327)	99.08 (0.433)	99.20 (0.120)	16.03 (4.252)
E24 (% inhibition)	64.73 (5.818)	70.26 (6.099)	80.65 (1.932)	85.54 (2.955)	90.68 (1.302)	94.23 (0.845)	1.84 (4.703)
E72 (% inhibition)	27.78 (7.160)	34.38 (13.546)	53.76 (7.681)	58.94 (8.484)	69.69 (4.233)	74.35 (6.352)	-0.65 (5.916)
GLP-1 (b)	N=8	N=8	N=8	N=8	N=8	N=8	N=12
AUC(0-24) (pM·h/L)	25.69 (16.275)	38.42 (19.404)	54.89 (26.546)	40.78 (14.210)	59.52 (20.137)	61.01 (32.136)	10.03 (6.092)
Cmax(0-24) (pM/L)	3.66 (1.48)	7.35 (4.28)	8.44 (3.04)	5.04 (1.43)	7.34 (2.55)	8.54 (4.93)	3.26 (1.29)

Source: Study CPH-001.
(a) Tmax is presented as median (minimum, maximum).
(b) Baseline-Corrected active GLP-1 levels.

Table 21 Alogliptin metabolites and the optical isomer pharmacokinetic parameters following single doses in Japanese

Parameter (units)	Arithmetic Mean (SD)					
	Alogliptin 6.25 mg N=7	Alogliptin 12.5 mg N=8	Alogliptin 25 mg N=8	Alogliptin 50 mg N=8	Alogliptin 100 mg N=8	Alogliptin 200 mg N=8
			Plasma			
M-I						
AUC(0-72) (ng·hr/mL)	2.08 (2.661)	5.65 (2.760)	13.39 (9.926)	19.63 (7.065)	57.66 (31.205)	93.94 (44.093)
Cmax (ng/mL)	0.11 (0.069)	0.25 (0.120)	0.50 (0.441)	1.15 (0.457)	4.44 (2.871)	7.01 (3.017)
T1/2 (hr)	59.343 (17.89051)	38.1361 (18.07645)	56.5176 (55.41416)	21.2264 (2.61390)	17.7644 (1.91234)	16.3781 (2.78911)
M-II						
AUC(0-72) (ng·hr/mL)	10.76 (4.883)	26.81 (6.606)	75.26 (27.170)	101.16 (38.388)	216.25 (75.972)	535.69 (171.599)
Cmax (ng/mL)	1.34 (0.577)	2.91 (0.544)	7.69 (2.454)	12.89 (5.288)	31.10 (13.983)	62.15 (16.967)
T1/2 (hr)	5.9274 (1.3839)	7.8524 (2.6232)	11.7501 (3.3094)	10.5054 (3.1461)	14.9144 (6.3089)	12.0213 (3.1848)
(S)-SYR-322						
AUC(0-72) (ng·hr/mL)					15.26 (3.4)	24.04 (4.905)
Cmax (ng/mL)					1.91 (0.788)	2.98 (0.625)
T1/2 (hr)					14.2726 (4.3542)	11.4244 (3.4216)
	Alogliptin 6.25 mg N=7	**Alogliptin 12.5 mg N=8**	**Alogliptin 25 mg N=8**	**Alogliptin 50 mg N=8**	**Alogliptin 100 mg N=8**	**Alogliptin 200 mg N=8**
			Urine			
Fe%(0-72)						
M-I	0.361 (0.252)	0.470 (0.2022)	0.616 (0.5658)	0.600 (0.2378)	1.060 (0.5605)	0.788 (0.3784)
M-II	2.459 (0.9761)	2.928 (0.8638)	3.458 (0.8502)	2.864 (1.1449)	2.845 (0.8058)	3.094 (0.8234)
(S)-SYR-322	0.278 (0.0587)	0.211 (0.0344)	0.116 (0.0169)	0.259 (0.0387)	0.303 (0.0453)	0.310 (0.0273)

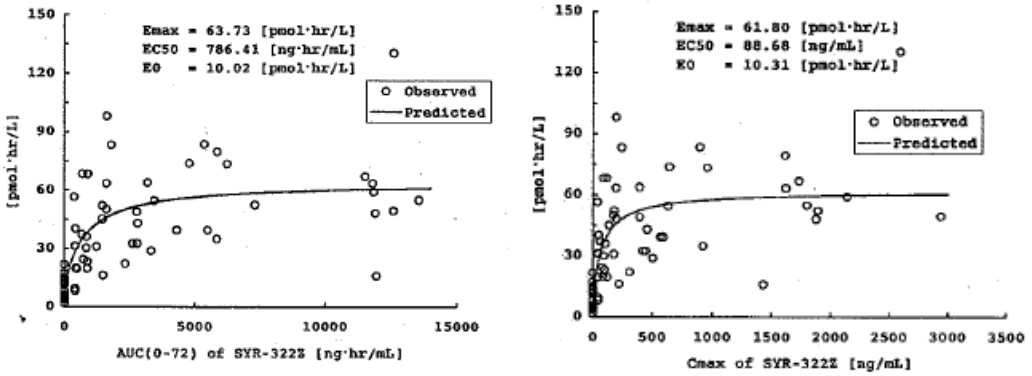


Figure 24 **Baseline corrected GLP-1 (AUC0-24) vs. dose (upper), alogliptin AUC0-24 (lower left), and alogliptin Cmax (lower right)**

Table 22 **Assessment of dose proportionality using a power model**

Power Model 3.1.8.1.1_1

Dependent	$Y=A\times DOSE^B$	Point estimate	95% CI Lower	95% CI Upper	90% CI Lower	90% CI Upper
AUCinf (ng·hr/mL)	A	78.315	70.021	87.590	71.336	85.976
	B	0.942	0.912	0.971	0.917	0.967

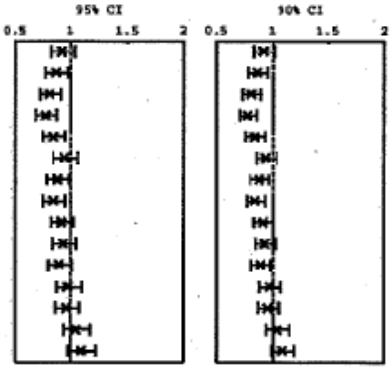
Power Model 3.1.8.1.4_1

Dependent	$Y=A\times DOSE^B$	Point estimate	95% CI Lower	95% CI Upper	90% CI Lower	90% CI Upper
Cmax (ng/mL)	A	6.506	5.054	8.373	5.271	8.029
	B	1.074	1.007	1.141	1.018	1.129

Table 23 **Assessment of dose proportionality using ANOVA for natural log-transformed alogliptin AUC and Cmax normalized by dose**

3.1.9.1.1

Parameter	Pair of Groups*1 A	Pair of Groups*1 B	Point Estimate*2	95% CI*2 Lower	95% CI*2 Upper	90% CI*2 Lower	90% CI*2 Upper
AUCinf (ng·hr/mL)	6.25	12.5	0.920	0.818	1.036	0.834	1.016
	6.25	25	0.868	0.771	0.977	0.786	0.959
	6.25	50	0.809	0.719	0.911	0.733	0.893
	6.25	100	0.776	0.689	0.873	0.703	0.856
	6.25	200	0.843	0.749	0.949	0.764	0.930
	12.5	25	0.943	0.841	1.057	0.857	1.037
	12.5	50	0.879	0.784	0.986	0.799	0.967
	12.5	100	0.843	0.752	0.945	0.766	0.927
	12.5	200	0.916	0.817	1.027	0.833	1.007
	25	50	0.932	0.832	1.045	0.849	1.025
	25	100	0.894	0.797	1.002	0.813	0.983
	25	200	0.971	0.866	1.089	0.883	1.068
	50	100	0.959	0.855	1.075	0.872	1.054
	50	200	1.042	0.929	1.168	0.947	1.146
	100	200	1.087	0.969	1.218	0.988	1.195



*1:Dose(mg)

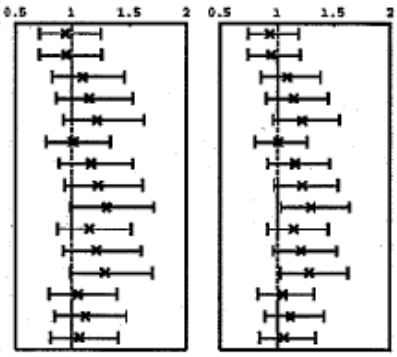
*2:Ratio of dose - normalized PK parameters between A and B (B/A)

The antilogs of the Point Estimates and the Confidence Intervals obtained were presented.

Table 23 (continue)

3.1.5.1.4

Parameter	Pair of Groups*1 A	Pair of Groups*1 B	Point Estimate*2	95% CI*2 Lower	95% CI*2 Upper	90% CI*2 Lower	90% CI*2 Upper
Cmax(ng/mL)	6.25	12.5	0.937	0.705	1.247	0.739	1.189
	6.25	25	0.947	0.712	1.259	0.746	1.201
	6.25	50	1.090	0.820	1.450	0.860	1.383
	6.25	100	1.148	0.863	1.527	0.905	1.456
	6.25	200	1.220	0.917	1.621	0.962	1.547
	12.5	25	1.010	0.767	1.330	0.803	1.271
	12.5	50	1.163	0.883	1.533	0.925	1.464
	12.5	100	1.225	0.930	1.614	0.974	1.541
	12.5	200	1.301	0.988	1.714	1.034	1.637
	25	50	1.152	0.875	1.517	0.916	1.449
	25	100	1.213	0.921	1.598	0.964	1.526
	25	200	1.289	0.978	1.697	1.024	1.621
	50	100	1.053	0.799	1.387	0.837	1.325
	50	200	1.119	0.849	1.473	0.889	1.407
	100	200	1.062	0.807	1.399	0.844	1.337



*1:Dose(mg)

*2:Ratio of dose - normalized PK parameters between A and B (B/A)

The antilogs of the Point Estimates and the Confidence Intervals obtained were presented.

Reviewer's comments:

Alogliptin pharmacokinetic and pharmacodynamic parameters were comparable between US study (001) and Japanese study (CPH-001) and there was no significant difference in study designs between the studies (Figure 25). It indicates that there is no apparent ethnic difference between Japanese and US (primarily Caucasian) in alogliptin pharmacokinetics and pharmacodynamics.

Metabolites and the optical isomer exposure were significantly lower than that of alogliptin: 0.361-1.060% dose for M1, 2.459-3.458 % dose for M2 and 0.116-0.310% dose for the optical isomer compared to 64.6-82.7% dose for alogliptin in urine.

Alogliptin $AUC_{0\text{-}inf}$ was slightly less proportional to dose in the Japanese study and the $AUC_{0\text{-}inf}$ was proportional to dose in US study. Sample size may play a role for the difference; n=5 for US study and n=8 for Japanese study

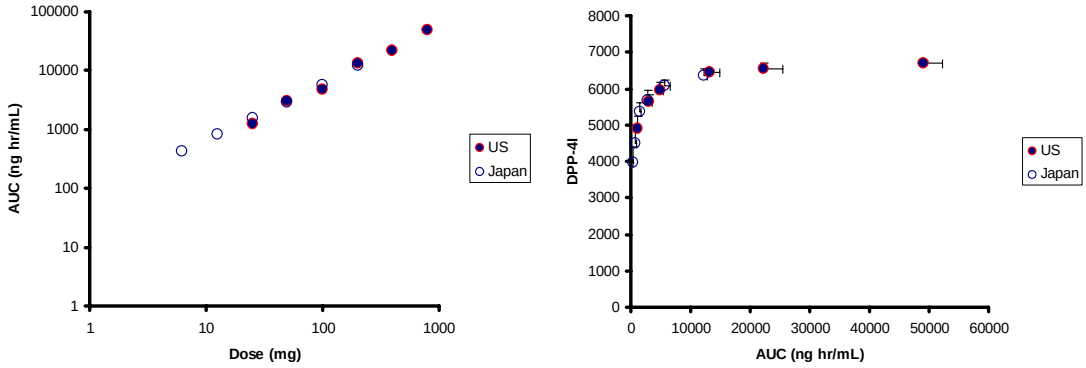


Figure 25 AUC vs. dose (left) and DPP-4 inhibition vs. AUC (right)

There was no apparent hysteresis between alogliptin plasma concentrations and DPP-4 inhibition and it indicates that there is no delay for the alogliptin inhibition on DPP-4. In addition, clear maximum inhibition was observed (Figure 26).

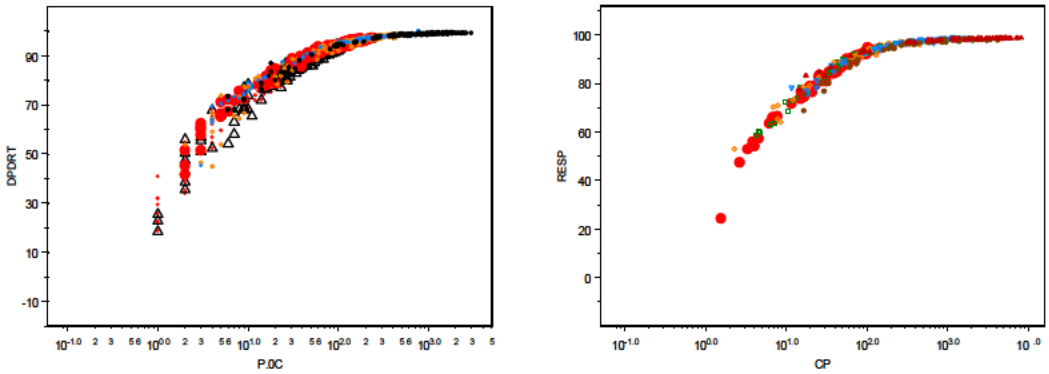


Figure 26 **Relationship between alogliptin plasma concentrations (P.0C) and DPP-4 inhibition (DPDRT) by treatment: open red circle – 6.25 mg, open triangle – 12.5 mg, closed red – 25 mg, and close black circle – 200 mg in Japanese (CPH-001, left), closed red circle – 25 mg, closed brown triangle – 800 mg, other symbols are intermediate doses in Caucasian (001, right).**

4.2.5 Study SYR-322-CPH-002 (multiple dose pharmacokinetic study in Japan): A double-blind, randomized, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of SYR-322 in an ascending dose regimen in healthy male subjects

Methods: Alogliptin pharmacokinetics were estimated following 25 mg, 50 mg or 100 mg (2x50 mg tablets) QD for 7 days in healthy Japanese subjects. Dose was administered 30 minutes before breakfast for 7 days. Blood and urine samples were collected as follows. Pharmacokinetic and pharmacodynamic parameters were estimated using non-compartmental analysis.

PK sampling

- predose, and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2,5, 3, 4, 6, 8, 12, and 24 hours post-dose at Day 1,
- prior to dosing at Day 3, 4, 5, and 6,
- prior to dosing, and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2,5, 3, 4, 6, 8, 12, 24, 48, and 72 hours post-dose at Day 7

DPP-4 inhibition

- predose, 1, 2, 11, 15 and 24 hours post-dose at Day 1,
- prior to and 1 hour after dosing at Day 3, and 5,
- prior to, 1, 2, 11, 15, 24, 48 and 72 hours post-dose at Day 7

Urine sampling

- 12 hours just before administration, 0 to 24 hours post-dose, at Day1
- 0 to 24 hours post-dose at Day 2, 3, 4, 5, and 6
- 0-24, 24-48, 48-72 hours post dose

Results: Alogliptin plasma concentration-time profiles and relationship between alogliptin plasma concentration and DPP-4 inhibition are shown in Figure 27. Pharmacokinetic and pharmacodynamic parameters are summarized in Table 24. There was about 1.3-fold accumulation for both AUC and Cmax after 25mg QD (Table 25).

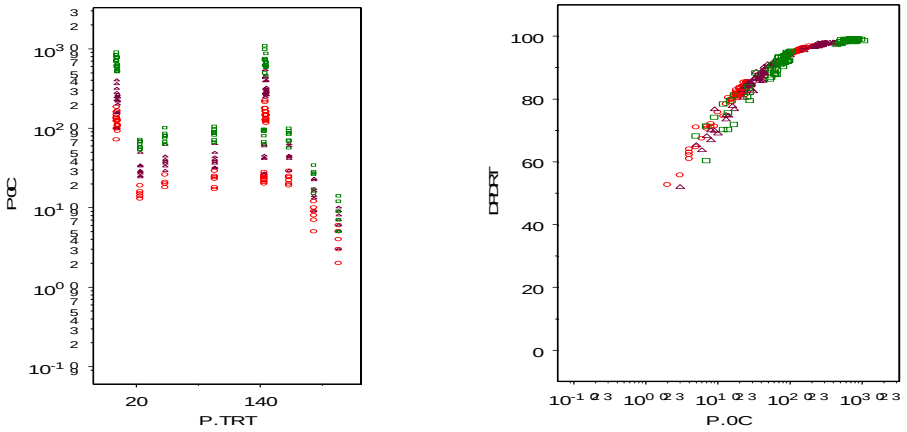


Figure 27 **Alogliptin plasma concentration-time profiles (left) and alogliptin plasma concentration-DPP-4 inhibition (right); red circle – 25 mg, brown triangle 50 mg, and green square – 100 mg**

Table 24 **Alogliptin pharmacokinetic and pharmacodynamic parameters following multiple doses**

Parameter (units)	Arithmetic Mean (SD)					
	Day 1			Day 7		
	Alogliptin 25 mg N=6	Alogliptin 50 mg N=8	Alogliptin 100 mg N=6	Alogliptin 25 mg N=6	Alogliptin 50 mg N=8	Alogliptin 100 mg N=6
Alogliptin Plasma						
AUC(0-24) (ng·hr/mL)	1050.62 (72.914)	2225.53 (69.918)	5284.10 (644.348)	1374.95 (128.181)	3052.40 (349.081)	6210.18 (399.603)
AUC(0-inf) (ng·hr/mL)	1280.83 (118.769)	2678.68 (243.741)	6102.92 (670.020)	N/A	N/A	N/A
Cmax (ng/mL)	142.83 (21.830)	317.88 (115.782)	876.67 (236.587)	180.17 (17.747)	431.50 (114.424)	1069.83 (198.005)
Tmax (hr)(a)	1.125 (0.50, 2.0)	1.25 (0.75, 4.0)	0.875 (0.75, 2.0)	1.00 (0.75, 1.50)	0.750 (0.75, 2.00)	0.875 (0.75, 1.50)
T1/2 (hr)	10.05 (1.190)	9.62 (2.234)	9.06 (0.628)	17.10 (3.641)	16.99 (1.523)	14.84 (2.544)
Alogliptin Urine						
CLr (L/h)	13.43 (2.412)	13.53 (1.370)	12.27 (1.204)	13.60 (0.976)	12.59 (1.554)	13.52 (1.871)

Source: Study CPH-002.
N/A=Not applicable.
(a)Tmax is presented as median (minimum, maximum).

Parameter (units)	Arithmetic Mean (SD)							
	Day 1				Day 7			
	Alogliptin 25 mg N=8	Alogliptin 50 mg N=8	Alogliptin 100 mg N=8	Placebo N=6	Alogliptin 25 mg N=8	Alogliptin 50 mg N=8	Alogliptin 100 mg N=8	Placebo N=6
Emax(0-24) (%inhibition)	95.81 (0.790)	97.24 (0.852)	98.58 (0.292)	3.77 (2.594)	96.20 (0.460)	97.84 (0.233)	98.60 (0.532)	4.62 (1.664)
Tmax(0-24) (hr) (a)	1.0 (1, 2)	1.0 (1, 2)	1.0 (1, 2)	15.0 (11, 24)	1.0 (1, 2)	1.0 (1, 2)	1.0 (1, 2)	15.0 (0, 15)
E24 (%inhibition)	79.65 (0.950)	85.75 (2.663)	89.79 (2.290)	1.37 (3.658)	83.50 (1.429)	88.36 (2.242)	91.96 (2.339)	1.93 (1.389
E72 (%inhibition)	N/A	N/A	N/A	N/A	62.15 (5.867)	66.45 (7.050)	71.00 (5.443)	0.75 (2.331)

Source: Study CPH-002.
N/A=not applicable.
(a) Tmax is presented as median (minimum, maximum).

Table 25 Accumulation ratios

Variable	Treatment	Summary Statistics									95% Confidence Interval	
		N	Mean	SD	SE	Min	Q1	Median	Q3	Max	Lower	Upper
R(AUC)	25mg	6	1.313	0.1528	0.0624	1.12	1.200	1.315	1.370	1.56	1.1530	1.4737
	50mg	8	1.373	0.1530	0.0541	1.23	1.265	1.315	1.470	1.65	1.2446	1.5004
	100mg	6	1.185	0.1159	0.0473	1.02	1.160	1.170	1.210	1.38	1.0634	1.3066
R(Cmax)	25mg	6	1.285	0.2171	0.0886	1.03	1.080	1.265	1.500	1.57	1.0571	1.5129
	50mg	8	1.486	0.5753	0.2034	0.84	1.085	1.255	1.965	2.44	1.0053	1.9672
	100mg	6	1.285	0.4334	0.1769	0.93	0.940	1.220	1.290	2.11	0.8302	1.7398
AI(AUC)	25mg	6	1.077	0.1152	0.0470	0.98	1.000	1.040	1.110	1.29	0.9558	1.1975
	50mg	8	1.139	0.0624	0.0221	1.04	1.120	1.130	1.155	1.26	1.0866	1.1909
	100mg	6	1.023	0.0898	0.0367	0.90	1.010	1.010	1.030	1.18	0.9291	1.1176
AI(T1/2)*	25mg	6	1.138	0.1886	0.0770	0.93	1.040	1.065	1.290	1.44	0.9404	1.3363
	50mg	8	1.101	0.2443	0.0864	0.84	1.005	1.050	1.095	1.67	0.8970	1.3055
	100mg	6	1.020	0.1168	0.0477	0.86	0.940	1.015	1.110	1.18	0.8974	1.1426

* T1/2 were estimated from data up to 24hrs on each day

4.2.6 Study SYR-322-002 (multiple dose pharmacokinetic study in T2D): A Multicenter, Randomized, Double-Blind, Placebo-Controlled Repeat-Dose Study to Determine the Safety, Pharmacokinetic and Pharmacodynamic Effects, and Efficacy of SYR110322 in Patients with Type 2 Diabetes Who are Either Newly Diagnosed or Managed with Diet and Exercise Alone for the Past 3 Months

Method: The subjects received 25mg , 100 mg and 400 mg once daily for 14 days before breakfast. Pharmacokinetic blood samples were collected on Days 1 and 14 prior to dosing (0 hour) and at 0.5, 0.75, 1, 1.25, 1.5, 2.5, 4.5, 6.5, 8.5,10.5, 10.75, 11.0, 11.25, 11.5, 12.5, 14.5 and 24 hours after dosing. On Day 13, blood sample was collected prior to dosing (0 hour) to obtain trough levels for assessment of steady state plasma levels. Pharmacodynamic blood sampling was collected as follows:

- Day 1 and 14: Blood samples were collected predose (0 hour), and at 0.5, 0.75, 1.0, 1.25, 1.5, 2.5, 4.5, 6.5, 8.5, 10.5, 10.75, 11.0, 11.25, 11.5, 12.5, 14.5, and 24 (Day 2) hours after administration of study drug.
- Days 16, 17, and 21: blood samples were collected prior to dosing on Days 16, 17, and 21.

Results: Alogliptin plasma concentration-time profiles and DPP-4 inhibition-time profiles are shown in Figure 28 and Figure 29. Pharmacokinetic and pharmacodynamic parameters are summarized in **Error! Reference source not found.**. Exposure was proportional to dose following multiple doses in T2D (Table 27).

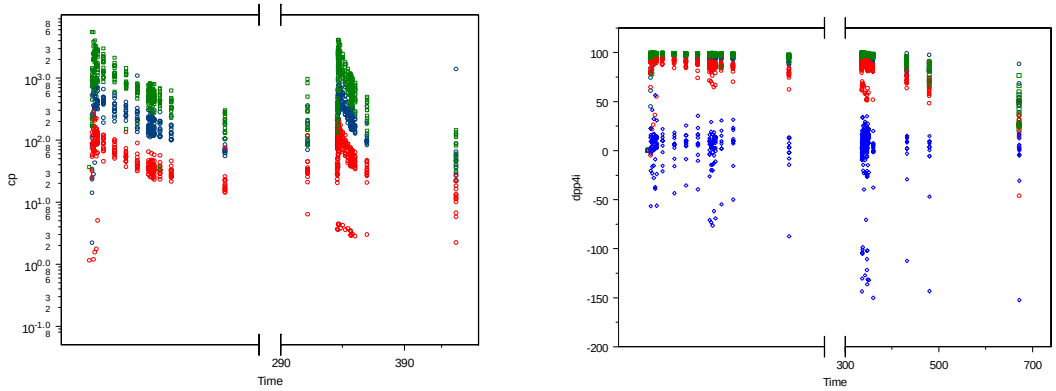


Figure 28 plasma concentration-time profiles (left) and DPP-4-time profiles (right); red for 25 mg, blue for 100 mg, green for 400 mg and light blue in right for placebo.

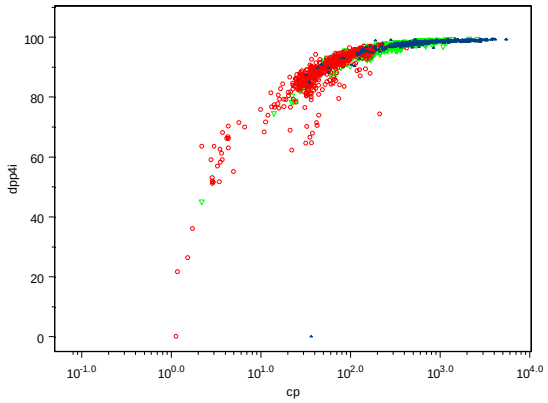


Figure 29 **Relationship between CP and DPP-4 inhibition in T2D following once daily; red circle – 25 mg QD, green triangle – 100 mg QD, and blue triangle – 400 mg QD**

Table 26 **Pharmacokinetic and pharmacodynamic parameters on Day 14 following multiple doses**

Parameter (units)	Alogliptin Dose	Geometric Mean N	Day 1 (R)	N	Day 14 (T)	Ratio T/R·100 (90% CI) (a)
AUC(0-24) (ng·hr/mL)	25 mg	13	1068	13	1430	134 (128, 140)
	100 mg	14	4801	14	6428	134 (128, 140)
	400 mg	15	15093	14	20207	134 (128, 140)
Cmax (ng/mL)	25 mg	13	135.7	13	148.2	109 (99, 121)
	100 mg	14	578.5	14	631.8	109 (99, 121)
	400 mg	15	2219	14	2423	109 (99, 121)

Parameter (units)	Arithmetic Mean (%CV) Alogliptin 25 mg Day 1 N=13	Alogliptin 25 mg Day 14 N=13	Alogliptin 100 mg Day 1 N=13	Alogliptin 100 mg Day 14 N=14	Alogliptin 400 mg Day 1 N=15	Alogliptin 400 mg Day 14 N=14
CLr (L/hr)	9.93 (31)	10.49 (24)	10.06 (41)	10.24 (41)	15.23 (30)	13.27 (35)
Fe (%)	41.27 (29)	60.83 (22)	46.96 (30)	62.93 (32)	57.12 (19)	63.38 (18)
Ae (mg)	10.32 (29)	15.21 (22)	46.96 (30)	62.93 (32)	228.5 (19)	253.5 (18)

Source: Study 002.
R=reference treatment, T=test treatment.
(a) Ratios and CIs are presented as percentages.

Parameter (units)	Arithmetic Mean (%CV) Placebo Day 1 N=11	Placebo Day 14 N=11	Alogliptin 25 mg Day 1 N=15	Alogliptin 25 mg Day 14 N=15	Alogliptin 100 mg Day 1 N=14	Alogliptin 100 mg Day 14 N=14	Alogliptin 400 mg Day 1 N=16	Alogliptin 400 mg Day 14 N=14
Emax (% inhibition)	25.34 (53.42)	20.77 (68.44)	94.70 (2.02)	93.76 (7.01)	97.79 (0.66)	98.00 (0.61)	98.84 (0.23)	98.91 (0.28)
Tmax (hr) (a)	1.5 (0.5, 24.0)	6.5 (1.3, 14.5)	1.0 (0.6, 12.5)	1.0 (0.5, 4.5)	1.3 (0.5, 6.5)	2.5 (0.8, 4.6)	1.4 (0.7, 4.5)	2.0 (0.5, 6.4)
E(24) (% inhibition)	-5.46 (-523.42)	-13.57 (-349.18)	78.28 (6.72)	81.83 (10.95)	91.01 (2.59)	94.00 (2.41)	95.70 (1.69)	96.70 (1.09)
E(72) (% inhibition)	N/A	-13.85 (-332.10)	N/A	66.28 (16.21)	N/A	78.12 (12.00)	N/A	81.58 (8.67)
E(168) (% inhibition)	N/A	-13.67 (-348.24)	N/A	20.54 (104.33)	N/A	44.52 (46.28)	N/A	45.63 (36.07)

Source: Study 002.
(a) Tmax is expressed as median (minimum, maximum).

Table 27 **dose proportionality**

Analyte	Parameter	Slope	90% CI	*P* value
SYR110322	ln AUC_{0-24}	0.9520	0.91-1.00	0.094
	ln C_{max}	1.0080	0.94-1.07	0.835

Source: Table 14.3.8.5

4.2.7 Study SYR-322-004: An Evaluator-Blinded, Active- and Placebo-Controlled, Multiple-Dose, Crossover Study to Assess the Effects of SYR110322 on the QTc Interval in Healthy Subjects (additional pharmacokinetic information)

The subjects received 100 mg (2x50 mg tablets) or 400 mg (8x5 0mg tablets) once a day for 6 days in the morning. Blood samples were collected prior to dosing (0 hour) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16 and 24 hours postdose on Days 1 and 6. Additional blood samples were collected within 30 minutes prior to dosing (0 hour) on Days 2 through 5 to evaluate trough levels of SYR-322.

Alogliptin pharmacokinetic parameters are summarized in Table 28. A formal QT analysis was not conducted for this study because of study design flaw.

Table 28 Pharmacokinetic parameters on Day 1 and Day 6 following 100 mg or 400 mg QD for 6 days

	Arithmetic Mean (SD)			
	Day 1		Day 6	
Parameter (units)	Alogliptin 100 mg N=46	Alogliptin 400 mg N=46	Alogliptin 100 mg N=46	Alogliptin 400 mg N=46
AUC(0-t) (ng·hr/mL)	5192 (1362.8)	21,752 (5379.1)	N/A	N/A
AUC(0-inf) (ng·hr/mL)	6277 (1804.3)	24,791 (6266.4)	N/A	N/A
AUC(0-24) (ng·hr/mL)	N/A	N/A	6184 (1419.0)	27,405 (12,109.4)
Cmax (ng/mL)	657.0 (183.09)	3104.1 (963.82)	714.4 (225.22)	3592.2 (1329.69)
Tmax (hr) (a)	1.6 (0.58, 6.08)	0.6 (0.58, 6.08)	1.1 (0, 6.08)	0.6 (0.58, 4.08)
CL/F (L/hr)	16.85 (3.607)	16.94 (3.513)	20.27 (26.684)	15.78 (3.430)
Vz/F (L)	252.7 (64.52)	220.3 (53.59)	307.9 (217.44)	219.9 (56.58)
T1/2,z (hr)	10.43 (1.705)	9.01 (1.138)	11.63 (2.395)	9.65 (1.265)

Source: Study 004.
(a) Median (minimum, maximum).

4.2.8 Study SYR-322-019: A Single-Blind, Randomized, Parallel Trial to Define the ECG Effects of SYR-322 Using a Clinical and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women (additional pharmacokinetic information)

The subjects received 50 mg (1x50 mg) or 400 mg (8x50 mg) for 7 days in the morning. Blood samples were collected predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours postdose on Days 1 and 7. In addition, blood samples were collected within 0.5 hours before dosing on Days 5 and 6 for the measurement of trough plasma concentrations.

Alogliptin pharmacokinetic parameters are summarized in

Table 29.

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Table 29 Pharmacokinetic parameters on Day 1 and Day 7 following 50mg or 400mg QD for 7 days

Parameter (units)	SYR-322 50 mg Day 1 n=64	SYR-322 400 mg Day 1 n=64	SYR-322 50 mg Day 7 n=63	SYR-322 400 mg Day 7 n=64
SYR-322				
AUC(0-23.5) (ng·hr/mL)	2301.76 (13.902)	20161.56 (15.693)	2909.88 (13.844)	23646.49 (17.332)
Cmax (ng/mL)	269.77 (25.095)	2794.22 (26.664)	301.33 (22.835)	2844.06 (25.943)
Cmin(0) (ng/mL)	---	---	47.37 (19.349)	282.56 (26.964)
Tmax (hr) (a)	1.10 (0.60-5.10)	1.10 (0.60-3.22)	1.10 (0.60-4.13)	1.10 (0.60-4.10)
CL/F (L/hr)	---	---	17.51 (13.733)	17.44 (18.501)
M-I				
AUC(0-23.5) (ng·hr/mL)	17.75 (65.137)	164.76 (66.703)	29.33 (60.828)	212.60 (64.213)
Cmax (ng/mL)	1.22 (71.715)	14.01 (68.935)	1.92 (64.857)	16.69 (66.598)
Cmin(0) (ng/mL)	---	---	0.75 (61.785)	4.24 (65.193)
Tmax (hr) (a)	3.10 (0.60-8.10) (b)	2.10 (0.60-6.10)	3.100 (0.60-6.10) (c)	2.100 (0.60-6.15)

Source: Tables 15.2.1.3.
--- = not applicable.
(a) Median (minimum, maximum).
(b) n=60.
(c) n=59.

4.2.9 Study SYR-322-022: A Phase 1, Single-Blind, Placebo-Controlled, Randomized, Parallel-Group Study to Evaluate the Possible Effects of Age, Gender, and Race on the Safety and Pharmacokinetics of Single and Multiple Doses of SYR-322 in Healthy Adult Subjects

Methods: The subjects received 25 mg tablet once daily under overnight fasting condition for 8 days (Table 30). Pharmacokinetic sampling schemes are summarized in Table 31. Pharmacokinetics of alogliptin, its metabolites and optical isomer were assessed at Day 1 and Day 8. Alogliptin pharmacodynamics was assessed following the first dose. Age range was 18 to 45 for young and 65 to 85 for elderly subjects. Alogliptin pharmacokinetics were estimated 25mg QD for 8 days and the effect of age, gender and race on alogliptin exposure was estimated using PK parameters at Day 8 with least square mean ratio.

Results: LSM ratios by treatments are shown in Figure 30 LSM AUC by and pharmacokinetic parameters and LSM ratios are summarized in Table 32.

Major conclusions were as follows:

- Elderly subjects had 28% higher in AUC_{0-24} than that of young subjects and Cmax in the elderly subjects was not significantly different to that of young subjects.
- Women had 19% and 22% higher for AUC_{0-24} and Cmax, respectively than those of men.

- White subjects had 28% and 20% higher for AUC_{0-24} and Cmax, respectively than those of Black subjects.
- The sponsor concluded that the alogliptin PK changes in each sub-groups were not clinically meaningful. Exposure of alogliptin metabolites were less than 4% of alogliptin. Therefore, metabolites exposure changes were not considered clinically important.

Table 30 Treatment groups

Treatment Group	Population			Number of Subjects		
	Age (a)	Gender	Race	SYR-322	Placebo	Total
I	Young	Female	Black	6	2	8
II	Elderly	Female	Black	6	2	8
III	Young	Male	Black	6	2	8
IV	Elderly	Male	Black	6	2	8
V	Young	Female	White	6	2	8
VI	Elderly	Female	White	6	2	8
VII	Young	Male	White	6	2	8
VIII	Elderly	Male	White	6	2	8
Total	—	—	—	**48**	**16**	**64**

Black=Black or African American.
(a) Elderly subjects were 65 to 85 years of age, inclusive; young subjects were 18 to 45 years of age, inclusive.

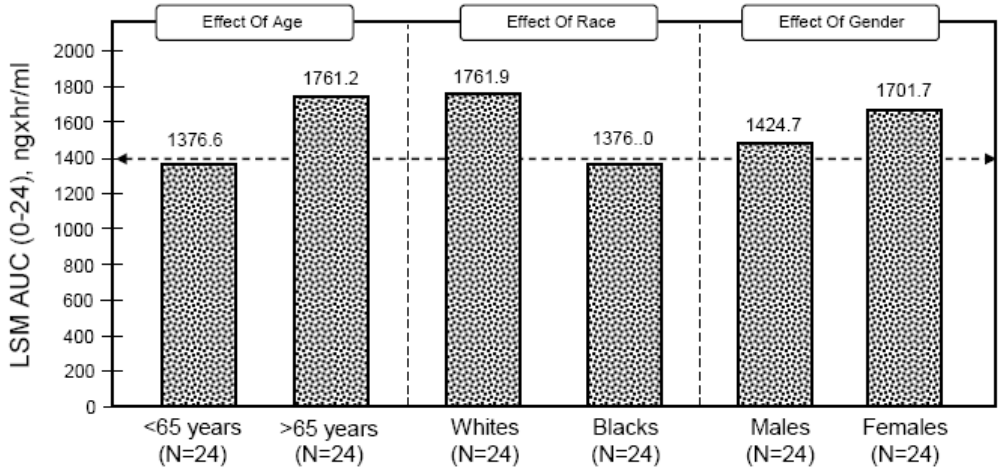
Table 31 Samples for pharmacokinetic and pharmacodynamic assessment

Study Day	Scheduled Time	
	Pharmacokinetics (SYR-322, its Metabolites M-I and M-II, and the S-isomer of SYR-322)	**Pharmacodynamics (DPP-IV Inhibition)**
1	Predose (within 0.25 hour prior to dosing) and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, and 12 hours after Day 1 dose	0, 2, 4, 8, and 12 hours after Day 1 dose
2	16, 24, and 36 hours after Day 1 dose	24 hours after Day 1 dose
3	48 hours after Day 1 dose	48 hours after Day 1 dose
4	72 hours after Day 1 dose	NA
6 and 7	Predose (within 0.25 hour prior to dosing)	NA
8	Predose (within 0.25 hour prior to dosing) and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, and 12 hours after Day 8 dose	NA
9	16 and 24 hours after Day 8 dose	NA

NA=not applicable.

Table 31 (continue) Urine samples

Study Day	Scheduled Time
-1 to 1	From -24 to 0 hours before Day 1 dose
1 to 2	From 0 to 24 hours after Day 1 dose
2 to 3	From 24 to 48 hours after Day 1 dose
3 to 4	From 48 to 72 hours after Day 1 dose
8 to 9	From 0 to 24 hours after Day 8 dose



Source: Study 022.

Figure 30 LSM AUC by sub-groups

Table 32 Pharmacokinetic parameters and LSM by sub-groups

Analyte	Parameter (units)	n		LS Mean		
		R	T	Young R	Elderly T	Ratio (T/R)·100 (90% CI) (a)
Day 1						
SYR-322	Cmax (ng/mL)	24	24	146.0	153.0	104.8 (92.78, 118.38)
	AUC(0-tlqc) (ng·hr/mL)	24	24	1417.1	1742.7	123.0 (116.72, 129.57)
	AUC(0-inf) (ng·hr/mL)	23	23	1496.6	1896.0	126.7 (119.69, 134.10)
SYR-322 M-I (b)	Cmax (ng/mL)	20	21	0.5	0.5	90.8 (63.79, 129.26)
	AUC(0-tlqc) (ng·hr/mL)	20	21	10.1	11.5	113.9 (61.32, 211.66)
SYR-322 M-II	Cmax (ng/mL)	24	24	3.1	3.6	113.2 (75.47, 169.83)
	AUC(0-tlqc) (ng·hr/mL)	24	24	31.4	47.7	151.7 (102.22, 225.11)
	AUC(0-inf) (ng·hr/mL)	22	19	38.7	65.0	168.2 (111.68, 253.44)
Day 8						
SYR-322	Cmax (ng/mL)	24	24	176.5	176.7	100.1 (89.81, 111.59)
	AUC(0-24) (ng·hr/mL)	24	24	1376.6	1761.2	127.9 (120.84, 135.46)
SYR-322 M-I	Cmax (ng/mL)	20	22	0.9	1.0	111.6 (82.09, 151.80)
	AUC(0-24) (ng·hr/mL)	20	22	12.7	16.7	131.6 (95.62, 181.14)
SYR-322 M-II	Cmax (ng/mL)	24	24	3.4	4.2	123.7 (84.25, 181.46)
	AUC(0-24) (ng·hr/mL)	24	24	33.0	54.4	164.8 (114.57, 237.17)

R=reference group, T=test group.
(a) Ratios and CIs are presented as percentages.
(b) AUC(0-inf) was not analyzed due to insufficient data.

Analyte	Parameter (units)	n		LS Mean		
		R	T	Male R	Female T	Ratio (T/R)·100 (90% CI) (a)
Day 1						
SYR-322	Cmax (ng/mL)	24	24	133.0	167.9	126.2 (110.86, 143.76)
	AUC(0-tlqc) (ng·hr/mL)	24	24	1469.8	1680.2	114.3 (108.12, 120.86)
	AUC(0-inf) (ng·hr/mL)	22	24	1578.3	1797.9	113.9 (107.27, 120.96)
SYR-322 M-I (b)	Cmax (ng/mL)	21	20	0.5	0.5	95.9 (65.21, 140.93)
	AUC(0-tlqc) (ng·hr/mL)	21	20	11.3	10.3	90.5 (46.02, 177.89)
SYR-322 M-II	Cmax (ng/mL)	24	24	3.2	3.5	112.0 (72.69, 172.62)
	AUC(0-tlqc) (ng·hr/mL)	24	24	36.5	41.0	112.4 (73.79, 171.24)
	AUC(0-inf) (ng·hr/mL)	19	22	51.6	48.7	94.5 (61.40, 145.29)
Day 8						
SYR-322	Cmax (ng/mL)	24	24	159.9	195.0	122.0 (108.65, 136.96)
	AUC(0-24) (ng·hr/mL)	24	24	1424.7	1701.7	119.5 (112.39, 126.95)
SYR-322 M-I	Cmax (ng/mL)	21	21	1.1	0.9	80.9 (57.88, 113.12)
	AUC(0-24) (ng·hr/mL)	21	21	16.1	13.2	81.6 (57.59, 115.57)
SYR-322 M-II	Cmax (ng/mL)	24	24	3.5	4.2	119.6 (79.45, 180.05)
	AUC(0-24) (ng·hr/mL)	24	24	39.7	45.2	113.8 (77.20, 167.71)

R=reference group, T=test group.
(a) Ratios and CIs are presented as percentages.
(b) AUC(0-inf) was not analyzed due to insufficient data.

Pharmacokinetic Parameters of SYR-322 and its Metabolites M-I and M-II by Race:

Analyte	Parameter (units)	n		LS Mean		
		R	T	Black (a) R	White T	Ratio (T/R)·100 (90% CI) (a)
Day 1						
SYR-322	Cmax (ng/mL)	24	24	150.4	148.5	98.7 (87.20, 111.78)
	AUC(0-tlqc) (ng·hr/mL)	24	24	1436.8	1718.8	119.6 (113.42, 126.17)
	AUC(0-inf) (ng·hr/mL)	23	23	1518.5	1868.6	123.1 (116.15, 130.38)
SYR-322 M-I (b)	Cmax (ng/mL)	21	20	0.5	0.6	131.6 (91.91, 188.53)
	AUC(0-tlqc) (ng·hr/mL)	21	20	7.8	14.9	190.3 (101.32, 357.34)
SYR-322 M-II	Cmax (ng/mL)	24	24	3.7	3.0	81.0 (53.55, 122.41)
	AUC(0-tlqc) (ng·hr/mL)	24	24	41.3	36.3	87.8 (58.74, 131.34)
	AUC(0-inf) (ng·hr/mL)	23	18	47.5	52.9	111.3 (72.85, 170.01)
Day 8						
SYR-322	Cmax (ng/mL)	24	24	161.4	193.2	119.7 (107.17, 133.72)
	AUC(0-24) (ng·hr/mL)	24	24	1376.0	1761.9	128.0 (120.80, 135.72)
SYR-322 M-I	Cmax (ng/mL)	22	20	0.8	1.2	155.2 (113.55, 212.02)
	AUC(0-24) (ng·hr/mL)	22	20	11.2	18.9	168.1 (121.49, 232.50)
SYR-322 M-II	Cmax (ng/mL)	24	24	4.0	3.6	88.5 (59.88, 130.88)
	AUC(0-24) (ng·hr/mL)	24	24	43.1	41.7	96.7 (66.71, 140.04)

Black=Black or African American, R=reference group, T=test group.
(a) Ratios and CIs are presented as percentages.
(b) AUC(0-inf) was not analyzed due to insufficient data.

Reviewer's Comments:

There was a total of 8 treatment sub-groups for the effect of age, sex, and race on alogliptin exposure (Table 30). The sponsor pooled sub-groups by age, sex and race. For example, young Black men, young White men, young Black women, White women groups were pooled for young age groups. However, there was statistically significant effect of age (e.g., young White women vs. elderly White women), sex and race on alogliptin exposure. Furthermore, there was interaction among age, sex and race. For example, alogliptin AUC in elderly White women was 97% higher than that of young White men and it may not induced from the pooled data analysis of apparent sex (28-29%) and age (52-54%) effect on alogliptin exposure. Therefore, the sponsor's pooled data analysis is not acceptable. Age related alogliptin AUC increase (Figure 32) may be related renal function decrease with age.

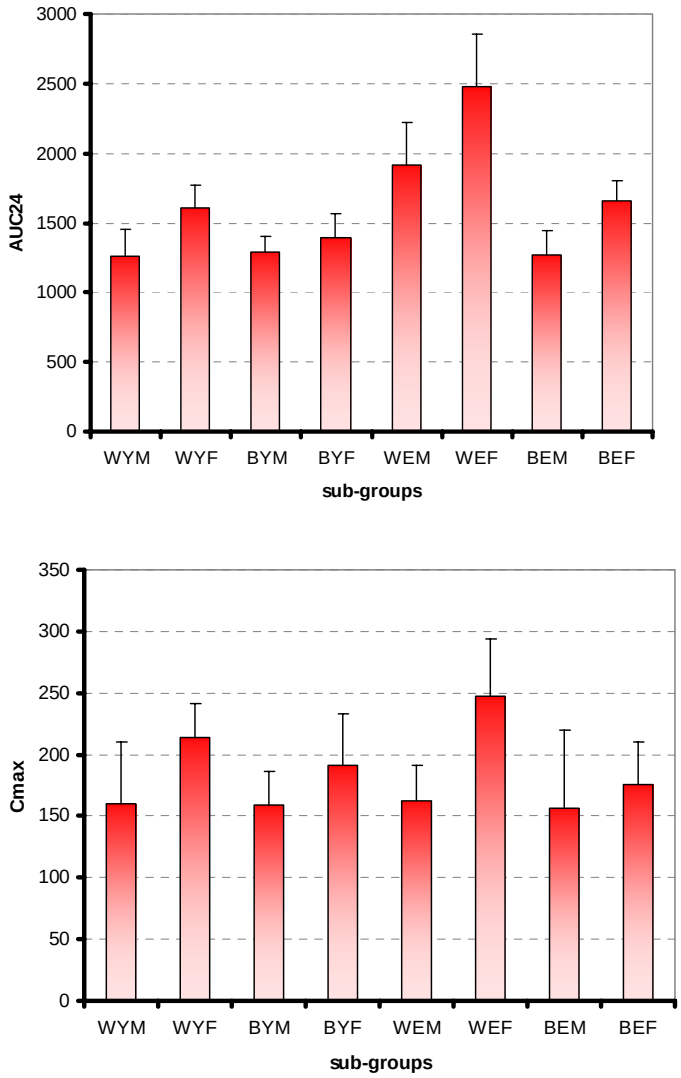


Figure 31 Mean(SD) AUC (upper) and Cmax (lower) by study groups

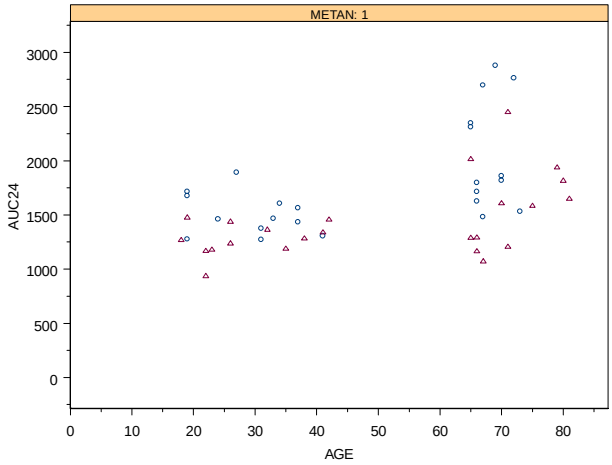


Figure 32 Alogliptin AUC vs. Age by sex (circle for female and triangle for male)

4.2.10 Study SYR-322-006: An Open-Label, Parallel-Group Comparison Study of Single-Dose Pharmacokinetics of SYR110322 in Subjects with Mild or Moderate Renal Impairment and Healthy Volunteers

Methods: Subjects received 50mg tablet following an overnight fast except subjects receiving hemodialysis for 2 hours fasting before dosing. Treatments groups were as follows:
Group A: 24 healthy subjects (creatinine clearance [CrCl] > 80 mL/min)
Group B: 6 subjects with mild renal impairment (CrCl 51-80 mL/min)
Group C: 6 subjects with moderate renal impairment (CrCl 30-50 mL/min)
Group D: 6 subjects with severe renal impairment (CrCl <30 mL/min but not on dialysis).
Group E: 6 subjects with end-stage renal disease (ESRD) on hemodialysis with no or negligible urine output.

Glomerular filtration rate (CrCl) was estimated using the Cockcroft-Gault formula:
CrCl (mL/min) = c * (140-Age(yrs)*Weight(kg)) / 72*Serum creatinine (mg/dL)
where c = 0.85 for female and 1 for male subjects

Pharmacokinetic sampling scheme are summarized in Table 33. Pharmacokinetic parameters were estimated conventional method including trapezoidal rule for AUC. Exposure changes were assessed by LSM ratios.

Results: There was clear association between AUC and CrCl (Figure 33). AUC_{0-t} was increase by 69%, 108%, 219% and 281% in subjects with mild, moderate, severe and ESRD, respectively, compared to that of healthy control subjects (Table 34). Cmax was increased by 13%, 42%, 27%, and 32% in subjects with mild, moderate, severe and ESRD, respectively, compared to that of healthy control subjects (Table 34). The sponsor proposed dose adjustment based on renal function:

- 12.5 mg for creatinine clearance ≥ 30 to < 50 mL/min,

- 6.25 mg for creatinine < 30 mL/min

Metabolites exposure was significantly increased with renal impairment. However, it may be clinically meaningful because that exposure was significantly lower than that of alogliptin.

Table 33 Pharmacokinetic sampling scheme

Day	Hour before and after dosing	Pharmacokinetic Sample Plasma
1 (a)	Immediately before dosing (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 hours after dosing	X
2	24 hours after dosing	X
3	48 hours after dosing	X
4	72 hours after dosing	X
5	96 hours after dosing	X
6	120 hours after dosing	X
8	Approximately 168 hours after dosing	X
14	Approximately 312 hours after dosing	X
Day	**Hour before and after dosing**	**Urine (b)**
1	Immediately before dosing and for the 0 to 12 hour interval after dosing	X
2	12-to-24-hour interval after dosing	X
3	24-to-48-hour interval after dosing	X
4	48-to-72-hour interval after dosing	X
5	72-to-96-hour interval after dosing	X
6	96-to-120-hour interval after dosing	X

(a) Additional blood samples to evaluate plasma protein binding were collected at 1 and 4 hours after dosing. For subjects receiving hemodialysis, arterial samples (from the outgoing line on the dialyzer) were collected while subjects were on hemodialysis on Day 1 before dosing and at 1, 2, and 3 hours (if the subject was still on hemodialysis) after dosing. Additionally, for subjects receiving hemodialysis, dialysate samples were collected at 1, 2, and 3 hours after dosing and within 10 minutes before the end of hemodialysis.
(b) Subjects on hemodialysis were excluded from the urine sample collection.

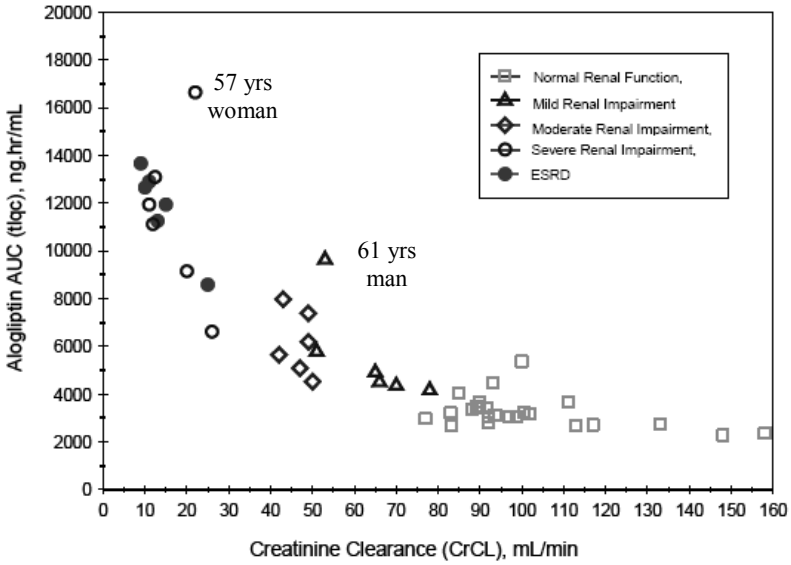


Figure 33 AUC_{0-t} vs. CrCl by renal status

Table 34 Pharmacokinetic parameters and LSMs

	Arithmetic Mean (%CV)		Geometric Least Squares Means		Ratio (T/R) *100 (b) 90% CI (%) (c) Impairment Group Difference (P-Value) (d)
Parameter (units)	**Mild N=6**	**Healthy N=6**	**Mild N=6**	**Healthy N=6**	
AUC(0- tlqc) (ng.hr/mL)	5554.08 (37)	3198.66 (11)	5348.65	3156.46	169.45 (134.497, 213.488) 0.002
AUC(0-inf) (ng.hr/mL)	5738.80 (39)	3261.24 (10)	5506.56	3216.92	171.175 (134.835, 217.310) 0.003
Cmax (ng/mL)	327.50 (26)	285.83 (29)	313.34	278.22	112.622 (82.60, 153.553) 0.500
Tmax (hr)	1.667 (75)	1.475 (120)	1.25(a)	0.68 (a)	n/a 0.368 (e)
CL/F(L/hr)	9.53 (27)	15.48 (11)	n/a	n/a	n/a
Vz/F(L)	549.41 (27)	624.15 (18)	n/a	n/a	n/a
T1/2(hr)	40.41 (12)	27.89 (14)	n/a	n/a	n/a
	Moderate N=6	**Healthy N=6**	**Moderate N=6**	**Healthy N=6**	
AUC(0- tlqc) (ng.hr/mL)	6133.30 (22)	3108.60 (19)	6189.05	2978.05	207.822 (167.622, 257.664) <0.001
AUC(0-inf) (ng.hr/mL)	6369.03 (24)	3178.59 (19)	6430.03	3034.01	211.932 (170.010, 264.192) <0.001)
Cmax (ng/mL)	355.67 (27)	227.00 (30)	326.58	229.60	142.239 (102.663, 197.071) 0.079
Tmax (hr)	1.50 (70)	1.58 (61)	1.25 (a)	1.25 (a)	n/a >0.999 (e)
CL/F(L/hr)	8.21 (23)	16.19 (18)	n/a	n/a	n/a
Vz/F(L)	465.21 (20)	591.57 (18)	n/a	n/a	n/a
T1/2(hr)	40.01 (18)	25.61 (17)	n/a	n/a	n/a

Parameter (units)	Arithmetic Mean (%CV) Severe N=6	Arithmetic Mean (%CV) Healthy N=6	Geometric Least Squares Means Severe N=6	Geometric Least Squares Means Healthy N=6	Ratio (T/R) *100 (b) 90% CI (%) (c) Impairment Group Difference (P-Value) (d)
AUC(0- tlqc) (ng.hr/mL)	11427.76 (30)	3547.25 (26)	11006.97	3455.08	318.573 (234.663, 432.488) <0.001
AUC(0-inf) (ng.hr/mL)	12911.24 (32)	3614.01 (25)	12342.82	3521.24	350.524 (252.909, 485.816) <0.001
Cmax (ng/mL)	318.17 (25)	258.50 (37)	309.12	243.31	127.052 (87.500, 184.482) 0.269
Tmax (hr)	2.67 (58)	1.67 (72)	2.75(a)	1.51(a)	n/a 0.259(e)
CL/F(L/hr)	4.30 (39)	14.43 (20)	n/a	n/a	n/a
Vz/F(L)	357.89 (23)	466.42 (33)	n/a	n/a	n/a
T1/2(hr)	60.92 (24)	23.12 (35)	n/a	n/a	n/a
	ESRD N=6	**Healthy N=6**	**ESRD N=6**	**Healthy N=6**	
AUC(0- tlqc) (ng.hr/mL)	11834.86 (15)	3177.87 (25)	11757.03	3089.51	380.547 (308.661, 469.174) <0.001
AUC(0-inf) (ng.hr/mL)	15280.93 (20)	3242.62 (24)	15037.05	3154.58	476.674 (373.107, 608.990) <0.001
Cmax (ng/mL)	265.50 (21)	203.67 (22)	261.87	198.84	131.702 (106.780, 162.441) 0.039
Tmax (hr)	2.39 (45)	2.50 (62)	2.00 (a)	2.75 (a)	n/a 0.871(e)
CL/F(L/hr)	3.42 (27)	16.15 (23)	n/a	n/a	n/a
Vz/F(L)	382.64 (11)	661.45 (23)	n/a	n/a	n/a
T1/2(hr)	80.04 (16)	28.65 (14)	n/a	n/a	n/a

Footnotes for Table 11.a are on the following page.

Parameter (units)	Arithmetic Mean (%CV) Mild N=6	Healthy N=6	Moderate N=6	Healthy N=6
Ae (0-120) (mg)	29.82 (14)	32.72 (12)	26.34 (36)	30.31 (13)
Fe (0-120) (%)	59.64 (14)	65.44 (12)	52.68 (36)	60.62 (13)
CLr (L/hr)	5.74 (30)	10.14 (17)	4.54 (53)	9.71 (16)
	Severe N=6	**Healthy N=6**	**ESRD N=6**	**Healthy N=6**
Ae (0-120) (mg)	12.14 (34)	30.53 (9)	n/a	n/d
Fe (0-120) (%)	24.28 (34)	61.05 (9)	n/a	n/d
CLr (L/hr)	0.99 (31)	8.80 (23)	n/a	n/d

Source: Table 15.2.5.1.
n/a=not available or not applicable.
n/d=not done.

4.2.11 Study SYR-322-023: An Open-Label Evaluation of the Single Dose Pharmacokinetics of SYR-322 in Subjects With and Without Hepatic Impairment

Methods: Subjects received 25 mg tablet following an overnight fasting condition. Moderate hepatic impairment was defined by Child-Pugh classification system. Pharmacokinetic blood sampling schemes are summarized in Table 35. Pharmacokinetic parameters were estimated conventional method including trapezoidal rule for AUC. Exposure changes were assessed by LSM ratios.

Results: Alogliptin exposure was decreased by 10% and 9% for AUC_{0-t} and Cmax, respectively, in subjects with moderate hepatic impairment compared to those of healthy control subjects (Table 36).

Table 35 Pharmacokinetic blood sampling

Plasma

Study Day	Scheduled Time
1	Predose (at 0 hour) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 16 hours postdose
2	24 and 36 hours postdose
3	48 hours postdose
4	72 hours postdose

urine **Urine Sampling Schedule for SYR-322 and its Metabolite M-I**

Study Day	Scheduled Time
-1 to 1	Predose
1 to 2	0 to 24 hours after the Day 1 dose
2 to 3	24 to 48 hours after the Day 1 dose
3 to 4	48 to 72 hours after the Day 1 dose

Table 36 Pharmacokinetic parameters

Alogliptin

Parameter (units)	Arithmetic Mean (%CV)		LS Mean		
	Moderate Hepatic Impairment (T) n=8	Healthy (R) n=8	Moderate Hepatic Impairment (T) n=8	Healthy (R) n=8	Ratio T/R·100 (90% CI) (a)
SYR-322 Plasma					
AUC(0-tlqc) (ng·hr/mL)	1240.63 (19.611)	1531.89 (23.216)	1281.27	1424.40	89.95 (73.41, 110.22)
AUC(0-inf) (ng·hr/mL)	1321.30 (19.852)	1607.04 (22.848)	1362.28	1497.11	90.99 (74.19, 111.60)
Cmax (ng/mL)	110.23 (37.984)	139.60 (28.000)	113.52	122.94	92.34 (68.27, 124.90)
Tmax (hr) (b)	2.00 (0.750, 4.000)	1.50 (0.500, 2.000)	2.00	1.50	—
T1/2 (hr)	20.75 (16.147)	18.32 (12.194)	—	—	—
MRT (hr)	21.90 (16.614)	20.55 (16.961)	—	—	—
CL/F (L/hr)	19.63 (21.047)	16.26 (22.435)	—	—	—
CL/F/70 kg (L/hr)	15.32 (18.383)	14.81 (21.099)	—	—	—
Vz/F (L)	583.76 (24.547)	430.86 (25.480)	—	—	—
Vz/F/70 kg (L)	457.29 (23.604)	389.91 (22.510)	—	—	—
SYR-322 Urine					
Fe(0-24) (%)	37.92 (29.532)	43.36 (24.701)	—	—	—
Fe(0-48) (%)	47.70 (28.297)	52.26 (24.667)	—	—	—
Fe(0-72) (%)	50.98 (28.424)	55.16 (23.788)	—	—	—
Ae(0-24) (mg)	9.48 (29.532)	10.84 (24.701)	—	—	—
Ae(0-48) (mg)	11.92 (28.297)	13.06 (24.667)	—	—	—
Ae(0-72) (mg)	12.74 (28.424)	13.79 (23.788)	—	—	—

Source: Tables 15.2.1.2, 15.2.1.3, and 15.2.1.5.
T=test group=subjects with moderate hepatic impairment, R=reference group=healthy subjects.
(a) Ratios and CIs are presented as percentages.
(b) Tmax is presented as median (minimum, maximum). P= 0.091.

Metabolite (M1)

Parameter (units)	Arithmetic Mean (%CV)		LS Mean		
	Moderate Hepatic Impairment (T) n=5 (a)	Healthy (R) n=7 (b)	Moderate Hepatic Impairment (T) n=5 (a)	Healthy (R) n=7 (b)	Ratio T/R·100 (90% CI) (c)
SYR-322 M-I Plasma					
AUC(0-tlqc) (ng·hr/mL)	11.23 (79.291)	14.63 (42.211)	8.50	11.84	71.79 (26.72, 192.86)
AUC(0-inf) (a,b) (ng·hr/mL)	24.43 (13.212)	22.05 (24.512)	24.50	21.54	113.72 (72.79, 177.64)
Cmax (ng/mL)	0.62 (73.039)	0.58 (43.972)	0.54	0.49	110.91 (53.26, 230.95)
Tmax (hr) (d)	2.00 (1.500, 4.000)	3.00 (1.500, 8.000)	2.00	3.00	—
λz (1/hr)	0.03 (25.814)	0.04 (35.815)	—	—	—
T1/2 (hr)	24.10 (30.091)	21.48 (38.289)	—	—	—
MRT (hr) (a,b)	33.78 (33.099)	29.28 (40.490)	—	—	—
SYR-322 M-I Urine	n=8	n=8	n=8	n=8	
Ae(0-24) (mg)	0.07 (83.719)	0.11 (61.848)	—	—	—
Ae(0-48) (mg)	0.09 (82.182)	0.15 (56.661)	—	—	—
Ae(0-72) (mg)	0.10 (86.284)	0.17 (55.720)	—	—	—

Source: Tables 15.2.1.2, 15.2.1.3, and 15.2.1.5.
T=test group=subjects with moderate hepatic impairment, R=reference group=healthy subjects.
(a) n=2 for AUC(0-inf) and for MRT, and n=3 for λz and T1/2 for subjects with moderate hepatic impairment, where applicable.
(b) n=3 for AUC (0-inf) and MRT for healthy subjects, where applicable.
(c) ratios and CIs are presented as percentages.
(d) Tmax is presented as median (minimum, maximum). P=1.000.

4.2.12 Study SYR-322-015: An Open-Label, Multiple-Dose Study to Assess the Drug-Drug Interaction Between SYR-322 and Caffeine, Tolbutamide, Dextromethorphan, Midazolam, and Fexofenadine Administered Concomitantly to Healthy Adult Subjects

Methods: Subjects received caffeine, tolbutamide, dextromethorphan, midazolam and fexofenadine as a single dose cocktail for probes of CYP1A2, 2C9, 2D6, 3A4 and P-gp, respectively. Subjects received the single dose cocktail on Day 1, 100mg alogliptin QD on Day 4 through 10 and the single dose cocktail with alogliptin on Day 10. Formulations of probes were as follows:

- Caffeine was supplied (b) (4) in cartons containing 40 tablets each (over-the-counter medication)
- Tolbutamide (b) (4) was supplied as 500 mg tablets in bottles containing 100 tablets each
- Dextromethorphan hydrobromide was supplied (b) (4) in cartons containing 30 gelcaps each (over-the-counter medication)
- Midazolam hydrochloride (b) (4) was supplied as a 2 mg/mL syrup in bottles containing 118 mL
- Fexofenadine hydrochloride was supplied (b) (4) in bottles containing 100 tablets each

Pharmacokinetic sampling schedule for the probe substrates and alogliptin are summarized in Table 37. The following metabolite pharmacokinetics of probe substrates were also assessed; 1,7-paraxanthine (caffeine), 4-hydroxytolbutamide, carboxytolbutamide (tolbutamide), dextrorphan (dextromethorphan), and 1-hydroxymidazolam (midazolam). Exposure change was assessed by LMS ratios.

Results: Pharmacokinetic parameters for probe substrate, those metabolites and alogliptin are summarized in Table 38. Alogliptin 10 0mg QD for 7 days did not affect significantly probe substrates pharmacokinetics of CYP1A2 (caffeine), 2C9 (tolbutamide), and 3A4/5 (midazolam). Alogliptin did not affect significantly metabolite pharmacokinetics of above mentioned probe substrates.

Alogliptin 100 mg QD for 7 days increased AUC_{0-t} and Cmax of CYP2D6 substrate (dextromethorphan) by 26% and 32%, respectively. Alogliptin did not affect dextromethorphan metabolite pharmacokinetics.

Alogliptin 100 mg QD for 7 days increased fexofenadine AUC_{0-t} and Cmax by 32% and 17%, respectively.

Drugs concentrations in plasma and urine were measured by HPLC/MS with the following validated concentration ranges:

- SYR-322 in plasma: 1.0 to 1000 ng/mL.
- Caffeine and 1,7-paraxanthine in plasma: 25 to 25,000 ng/mL.

- Caffeine in urine: 50 to 50,000 ng/mL.
- 1,7-Paraxanthine in urine: 120 to 50,100 ng/mL.
- Tolbutamide in plasma: 0.10 to 100 µg/mL.
- 4-Hydroxytolbutamide in plasma: 0.0025 to 2.50 µg/mL.
- Carboxytolbutamide in plasma: 0.005 to 5.00 µg/mL.
- Tolbutamide in urine: 5.0 to 1000 ng/mL.
- 4-Hydroxytolbutamide in urine: 0.3 to 150 µg/mL
- Carboxytolbutamide in urine: 0.6 to 300 µg/mL.
- Dextromethorphan in plasma: 0.05 to 50.0 ng/mL.
- Dextrorphan in plasma: 0.8 to 800 ng/mL.
- Dextromethorphan in urine: 0.001 to 1.00 µg/mL.
- Dextrorphan in urine: 0.02 to 20.0 µg/mL.
- Midazolam and 1-hydroxymidazolam in plasma: 0.1 to 100 ng/mL.
- Midazolam in urine: 0.05 to 50 ng/mL.
- Hydroxymidazolam in urine: 1.0 to 1000 ng/mL.
- Fexofenadine in plasma: 0.5 to 500 ng/mL.
- Fexofenadine in urine: 0.05 to 10 µg/mL.

Reviewer's Comments:

Alogliptin dose was 100mg QD in the cocktail study and the proposed dosing is 25 mg QD. The observed alogliptin effect on dextromethorphan exposure (i.e., 26-32% exposure increase) may be lower at the proposed dosing assuming competitive inhibition. Therefore, the alogliptin effect on CYP2D6 seems to be not clinically significant at the proposed dosing.

Table 37 Sampling schedule

Probe substrates

Study Day	Scheduled Time
1	Predose (within 0.5 hour prior to dosing) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the Day 1 dose
2	16, 24, and 36 hours after the Day 1 dose
3	48 hours after the Day 1 dose
4	72 hours after the Day 1 dose
10	Predose (within 0.5 hour prior to dosing) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the Day 10 dose
11	16, 24, and 36 hours after the Day 10 dose
12	48 hours after the Day 10 dose
13	72 hours after the Day 10 dose

Alogliptin

Study Day	Scheduled Time
4, 7, 8, and 9	Predose (within 0.5 hour prior to dosing)
10	Predose (within 0.5 hour prior to dosing) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the Day 10 dose
11	16, 24, and 36 hours after the Day 10 dose
12	48 hours after the Day 10 dose
13	72 hours after the Day 10 dose

Urinary sampling schedule

Day	Scheduled Time
1-2	Predose (0 hour) and 0-24 hours after the Day 1 dose
2-3	24-48 hours after the Day 1 dose
3-4	48-72 hours after the Day 1 dose
10-11	0-24 hours after the Day 10 dose
11-12	24-48 hours after the Day 10 dose
12-13	48-72 hours after the Day 10 dose

Table 38 Pharmacokinetic parameters of probe substrates and metabolites

		Arithmetic Mean (%CV)		Geometric Mean		
Analyte/ Parameter (units)	n	SYR-322 + Drug Cocktail (T) Day 10	Drug Cocktail (R) Day 1	SYR-322 + Drug Cocktail (T) Day 10	Drug Cocktail (R) Day 1	Ratio (T/R)*100 (90% CI) (%)
Caffeine						
Plasma						
AUC(0-tlqc) (ng·hr/mL)	18	48085.68 (35.822)	46196.61 (40.232)	45249.03	43133.39	104.90 (92.47, 119.01)
AUC(0-inf) (ng·hr/mL)	18	48683.33 (35.335)	46624.51 (39.805)	45893.03	43589.76	105.28 (93.06, 119.12)
Cmax (ng/mL)	18	5308.33 (24.07)	5386.11 (18.68)	5164.82	5293.40	97.57 (91.77, 103.74)
Tmax (hr) (a,b)	18	1.33 (0.500, 3.000)	1.22 (0.250, 3.000)	---	---	---
T1/2 (hr)	18	5.36 (24.147)	5.32 (27.824)	---	---	---
CL/F (L/hr)	18	4.62 (35.165)	4.90 (38.107)	---	---	---
Urine						
Ae(0-72) (µg)	18	7166.35 (75.122)	6048.22 (49.798)	5750.57	5481.25	104.91 (88.15, 124.86)
UMR	18	0.35 (76.654)	0.27 (37.444)	0.29	0.26	112.58 (94.21, 134.54)
1,7-Paraxanthine						
Plasma						
AUC(0-tlqc) (ng·hr/mL)	18	27499.63 (20.825)	28273.64 (28.110)	26931.00	27258.14	98.80 (91.67, 106.49)
AUC(0-inf) (ng·hr/mL)	18	28367.75 (21.109)	28991.00 (27.961)	27773.84	27944.33	99.39 (92.08, 107.28)
Cmax (ng/mL)	18	1303.72 (19.42)	1337.56 (22.08)	1281.99	1308.00	98.01 (93.92, 102.28)
Tmax (hr) (a,c)	18	8.00 (3.000, 16.000)	7.00 (2.000, 12.000)	---	---	---
T1/2 (hr)	18	6.94 (24.291)	6.92 (27.986)	---	---	---
Urine						
Ae(0-72) (µg)	18	19523.31 (36.474)	20550.98 (28.037)	18422.0	19768.7	93.19 (84.17, 103.18)

Sources: Tables 15.2.1.6.1, 15.2.1.7.1, and 15.2.1.20.1.
T=test treatment, R=reference treatment, --- =not applicable.
(a) Tmax is presented as median (minimum, maximum).
(b) P=0.487.
(c) P=0.078.

Analyte/ Parameter (units)	n	Arithmetic Mean (%CV)		Geometric Mean		
		SYR-322 + Drug Cocktail (T) Day 10	Drug Cocktail (R) Day 1	SYR-322 + Drug Cocktail (T) Day 10	Drug Cocktail (R) Day 1	Ratio (T/R)*100 (90% CI) (%)
Tolbutamide						
Plasma						
AUC(0-tlqc) (µg·hr/mL)	18	684.48 (36.741)	700.77 (34.829)	655.74	673.16	97.41 (93.07, 101.96)
AUC(0-inf) (µg·hr/mL)	18	691.43 (38.261)	711.11 (37.448)	660.78	680.25	97.14 (92.87, 101.60)
Cmax (µg/mL)	18	51.44 (19.541)	51.27 (14.572)	50.55	50.77	99.58 (95.76, 103.54)
Tmax (hr) (a,b)	18	3.00 (1.500, 6.000)	3.00 (2.000, 4.000)	---	---	---
T1/2 (hr)	18	7.09 (30.417)	8.38 (31.741)	---	---	---
CL/F (L/hr)	18	0.78 (22.615)	0.76 (22.293)	---	---	---
Urine						
Ae(0-72) (µg)	18	611.71 (49.722)	606.32 (47.139)	560.86	566.79	98.95 (89.11, 109.88)
UMR	18	0.00 (51.432)	0.00 (57.842)	0.00	0.00	102.84 (94.02, 112.49)
4-Hydroxytolbutamide						
Plasma						
AUC(0-tlqc) (µg·hr/mL)	18	7.74 (22.263)	8.13 (22.078)	7.58	7.96	95.32 (91.79, 98.98)
AUC(0-inf) (µg·hr/mL)	18	7.87 (21.341)	8.27 (21.667)	7.72	8.11	95.25 (91.84, 98.80)
Cmax (µg/mL)	18	0.61 (27.856)	0.63 (27.772)	0.59	0.60	97.73 (92.45, 103.30)
Tmax (hr) (a,c)	18	4.00 (3.000, 6.000)	4.00 (3.000, 6.000)	---	---	---
T1/2 (hr)	18	8.42 (27.883)	9.31 (32.057)	---	---	---
Urine						
Ae(0-72) (µg)	18	61453.75 (20.162)	65340.14 (14.064)	60355.79	64720.96	93.26 (88.51, 98.26)
Carboxytolbutamide						
Plasma						
AUC(0-tlqc) (µg·hr/mL)	18	23.33 (18.965)	23.79 (16.792)	22.94	23.48	97.67 (94.73, 100.71)
AUC(0-inf) (µg)g·hr/mL)	18	23.58 (18.551)	24.05 (16.302)	23.20	23.752	97.68 (94.77, 100.68)
Cmax (µg/mL)	18	1.97 (31.030)	1.98 (26.252)	1.87	1.91	98.04 (92.27, 104.18)
Tmax (hr) (a,d)	18	4.00 (3.000, 6.000)	4.00 (4.000, 6.000)	---	---	---
T1/2 (hr)	18	8.02 (24.549)	8.95 (29.290)	---	---	---
Urine						
Ae(0-72) (µg)	18	370226.10 (11.988)	381345.85 (8.771)	367476.25	379955.76	96.72 (92.22, 101.43)

Footnotes for Table 11.b are on the next page.

Analyte/ Parameter (units)	n	Arithmetic Mean (%CV)		Geometric Mean		
		SYR-322 + Drug Cocktail (T) Day 10	Drug Cocktail (R) Day 1	SYR-322 + Drug Cocktail (T) Day 10	Drug Cocktail (R) Day 1	Ratio (T/R)*100 (90% CI) (%)
Dextromethorphan						
Plasma						
AUC(0-tlqc) (ng·hr/mL)	18	167.51 (214.516)	162.75 (221.327)	17.69	14.04	125.97 (107.82, 147.17)
AUC(0-inf) (ng·hr/mL)	13	14.98 (70.807)	11.54 (78.330)	11.00	8.67	126.92 (103.68, 155.37)
Cmax (ng/mL)	18	6.24 (173.709)	5.57 (186.351)	2.11	1.60	132.02 (113.81,153.14)
Tmax (hr) (a,b)	18	3.50 (2.000, 6.000)	3.00 (2.000, 6.000)	---	---	---
T1/2 (hr)	18	13.09 (123.346)	14.17 (126.136)	---	---	---
CL/F (L/hr)	13	3022.47 (107.792)	3347.66 (72.373)	---	---	---
Urine						
Ae(0-72) (µg)	18	835.67 (215.562)	862.26 (217.544)	84.66	90.66	93.38 (72.49, 120.28)
UMR (d)	18	0.84 (278.238)	0.81 (266.858)	0.01	0.01	84.37 (65.67, 108.40)
Dextrorphan						
Plasma						
AUC(0-tlqc) (ng·hr/mL)	18	1606.39 (44.596)	1601.14 (42.877)	1276.72	1270.92	100.46 (96.92, 104.12)
AUC(0-inf) (ng·hr/mL)	15	1900.38 (17.654)	1894.24 (12.679)	1875.16	1880.73	99.70 (96.10, 103.45)
Cmax (ng/mL)	18	381.86 (53.521)	377.64 (50.829)	226.19	224.07	100.94 (95.43, 106.78)
Tmax (hr) (a,c)	18	2.00 (1.500, 4.000)	2.00 (1.500, 4.000)	---	---	---
T1/2 (hr)	18	12.03 (156.575)	14.97 (185.653)	---	---	---
Urine						
Ae(0-72) (µg)	18	9400.15 (47.009)	8307.66 (46.301)	7325.42	6618.92	110.67 (99.48, 123.13)

Sources: Tables 15.2.1.9.1, 15.2.1.10.1, and 15.2.1.20.1.
T=test treatment, R=reference treatment,--- =not applicable.
(a) Tmax is presented as median (minimum, maximum).
(b) P=0.688.
(c) P=0.883.

Analyte/ Parameter (units)	n	Arithmetic Mean (%CV)		Geometric Mean		
		SYR-322 + Drug Cocktail (T) Day 10	Drug Cocktail (R) Day 1	SYR-322 + Drug Cocktail (T) Day 10	Drug Cocktail (R) Day 1	Ratio (T/R)*100 (90% CI) (%)
Midazolam						
Plasma						
AUC(0-tlqc) (ng·hr/mL)	18	50.80 (28.633)	47.03 (28.675)	48.89	45.46	107.55 (97.88, 118.19)
AUC(0-inf) (ng·hr/mL)	18	52.56 (28.712)	48.81 (27.723)	50.58	47.25	107.05 (97.16, 117.95)
Cmax (ng/mL)	18	22.72 (28.32)	19.91 (26.340)	21.80	19.35	112.68 (101.70, 124.84)
Tmax (hr) (a,b)	18	0.50 (0.250, 1.000)	0.75 (0.250, 1.500)	---	---	---
T1/2 (hr)	18	5.70 (23.138)	5.80 (18.167)	---	---	---
CL/F (L/hr)	18	82.11 (27.696)	87.18 (23.776)	---	---	---
Urine						
Ae(0-72) (µg)	18	7.12 (41.555)	7.86 (33.926)	6.65	7.41	89.80 (76.66, 105.20)
UMR (e)	18	0.00 (40.688)	0.00 (36.461)	0.00	0.00	79.70 (67.81, 93.67)
1-Hydroxymidazolam						
Plasma						
AUC(0-tlqc) (ng·hr/mL)	18	19.69 (33.494)	19.11 (38.834)	18.59	17.83	104.24 (94.42, 115.08)
AUC(0-inf) (ng·hr/mL)	17	20.91 (32.090)	20.31 (37.563)	19.82	19.02	104.21 (93.85, 115.72)
Cmax (ng/mL)	18	9.64 (32.620)	8.98 (47.373)	9.09	8.15	111.45 (96.60, 128.59)
Tmax (hr) (a,c)	18	0.50 (0.500, 1.000)	0.75 (0.500, 1.500)	---	---	---
T1/2 (hr)	18	4.84 (68.525)	3.86 (29.778)	---	---	---
Urine						
Ae(0-72) (µg)	18	2905.22 (15.701)	2574.74 (14.355)	2871.58	2548.65	112.67 (102.12, 124.31)

Sources: Tables 15.2.1.15, 15.2.1.16, and 15.2.1.20.1.
T=test treatment, R=reference treatment, --- =not applicable.
(a) Tmax is presented as median (minimum, maximum).
(b) P=0.153.
(c) P=0.020.

Analyte/ Parameter (units)	n	Arithmetic Mean (%CV)		Geometric Mean		
		SYR-322 + Drug Cocktail (T) Day 10	Drug Cocktail (R) Day 1	SYR-322 + Drug Cocktail (T) Day 10	Drug Cocktail (R) Day 1	Ratio (T/R)*100 (90% CI) (%)
Fexofenadine						
Plasma						
AUC(0-tlqc) (ng·hr/mL)	18	714.58 (30.438)	577.59 (52.591)	676.85	512.56	132.05 (110.78, 157.41)
AUC(0-inf) (ng·hr/mL)	15	742.03 (29.254)	587.84 (49.063)	704.62	527.24	133.64 (112.27, 159.09)
Cmax (ng/mL)	18	116.53 (40.736)	108.44 (63.806)	107.72	91.70	117.47 (95.38, 144.67)
Tmax (hr) (a,b)	18	1.50 (0.750, 4.000)	1.25 (0.750, 2.000)	---	---	---
T1/2 (hr)	17	21.53 (55.524)	35.31 (115.205)	---	---	---
Urine						
Ae(0-72) (µg)	18	2320.14 (27.927)	1799.15 (39.277)	2234.71	1669.46	133.86 (110.67, 161.91)

Sources: Tables 15.2.1.12, 15.2.1.13, and 15.2.1.20.1.
T=test treatment, R=reference treatment, --- =not applicable.
(a) Tmax is presented as median (minimum, maximum).
(b) P=0.033.

Parameter (units)	SYR-322 + Drug Cocktail Day 10 (N=18) Arithmetic Mean (%CV)
SYR-322	
AUC(0-tau) (ng·hr/mL)	5403.56 (18.734)
Cmax (ng/mL)	546.22 (23.429)
Tmax (hr) (a)	1.5 (0.500, 4.000)
Ctrough (ng/mL)	73.62 (18.44)

Source: 15.2.1.4.
(a) Tmax is presented as median (minimum, maximum).

4.2.13 Study SYR-322-018: An Open-Label Study to Assess the Effect of SYR-322 on Glyburide in Healthy Adult Subjects

Methods: Subjects received glyburide (Diaβeta®), a representative sulfonylurea and a CYP2C9 substrate, 5 mg tablet on Day 1, alogliptin 25 mg tablet QD for 8 days (Day 3-10), and glyburide (Diaβeta®) 5mg tablet on Day 10 with alogliptin following an overnight fasting condition.

Pharmacokinetic sampling schedules are summarized in Table 39. Pharmacokinetic parameters were estimated using the conventional method including trapezoidal rule for AUC. The drug concentrations in human plasma were measured by HPLC/MS with validated concentration ranges of 1.00 to 1000 ng/mL for alogliptin, 0.100 to 100 ng/mL for its metabolite (M-I), and 1.00 to 500 ng/mL for glyburide. Statistical significant was assessed for natural logarithms of AUC and Cmax of glyburide using a paired t-test on within-subject difference. The effect of alogliptin on glyburide exposure was assessed using LSM ratios.

Results: Alogliptin 25 mg QD for 8 days did not significantly change glyburide AUC but increased glyburide Cmax 15% (Table 40 and Table 41).

Table 39 Sampling schedule

alogliptin

Study Day	Scheduled Time
1, 7, 8, and 9	Predose (within 0.25 hour prior to dosing)
10	Predose (within 0.25 hour prior to dosing), and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours after the Day 10 dose
11	24, 28, 32, and 36 hours after the Day 10 dose
12	48 hours after the Day 10 dose

glyburide

Study Day	Scheduled Time
1	Predose (within 0.25 hour prior to dosing), and 0.25, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 10, 12, and 16 hours after the Day 1 dose
2	24 and 36 hours after the Day 1 dose
3	48 hours after the Day 1 dose
10	Predose (within 0.25 hour prior to dosing), and 0.25, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 10, 12, and 16 hours after the Day 10 dose
11	24 and 36 hours after the Day 10 dose
12	48 hours after the Day 10 dose

Table 40 alogliptin pharmacokinetic parameters on Day 10

Parameter (units)	n	Arithmetic Mean (%CV)		Geometric Mean		
		SYR-322 25 mg + Glyburide 5 mg (T) Day 10	Glyburide 5 mg (R) Day 1	SYR-322 25 mg + Glyburide 5 mg (T) Day 10	Glyburide 5 mg (R) Day 1	Ratio T/R·100 (90% CI)
AUC(0-tlqc) (ng·hr/mL)	24	792.46 (37.481)	809.22 (48.024)	745.36	749.88	99.40 (93.14, 106.08)
AUC(0-inf) (ng·hr/mL)	23	831.76 (35.696)	880.49 (46.090)	786.58	817.12	96.26 (89.21, 103.87)
Cmax (ng/mL)	24	123.32 (30.496)	109.26 (40.400)	118.39	102.63	115.36 (105.98, 125.57)
Tmax (hr) (a,b)	24	2.50 (2.000, 4.000)	2.00 (1.000, 6.000)	—	—	—
T1/2 (hr)	24	8.88 (50.499)	12.57 (57.800)	—	—	—
CL/F (L/hr)	23	6.69 (31.097)	6.48 (31.495)	—	—	—

Sources: Tables 15.2.1.2 and 15.2.1.3.
T=test treatment, R=reference treatment, — =not applicable.
(a) Tmax is presented as median (minimum, maximum).
(b) P=0.406.

Table 41 alogliptin pharmacokinetic parameters on Day 10

Parameter (units)	SYR-322 25 mg + Glyburide 5 mg Day 10 Arithmetic Mean (%CV)	
	SYR-322 n=24	SYR-322 M-I n=23
AUC(0-24) (ng·hr/mL)	1293.34 (15.569)	14.01 (53.970)
Cmax (ng/mL)	148.13 (24. 659)	0.91 (47.153)
Cmin (ng/mL)	20.67 (21.461)	0.39 (61.770)
Tmax (hr) (a)	1.00 (0.500, 1.500)	1.50 (0.500, 16.000)

Source: 15.2.1.5.
(a) Tmax is presented as median (minimum, maximum).

4.2.14 Study SYR-322-021: SYR-322-021: A Randomized, Single-Blind, Placebo-Controlled Assessment of the Pharmacokinetics and Pharmacodynamics of Warfarin in the Presence of Multiple Doses of SYR-322 in Healthy Male and Female Subjects

Methods: Subjects received either placebo+a stable warfarin dose QD (Treatment A) or alogliptin 25 mg tablet+a stable dose of warfarin QD (Treatment B) following an overnight fasting condition (Figure 34).

Pharmacokinetics of S-warfarin (CYP2C9 substrate), R-warfarin (CYP1A2, 2C19 and 3A4 substrate) and alogliptin were assessed. Prothrombin time (PT) and International Normalized Ratio (INR) were estimated for warfarin pharmacodynamic parameters. Pharmacokinetic and pharmacodynamic sampling schemes are summarized in

Table 42. The drug concentrations in human plasma and urine were measured using HPLC/MS with validated concentration ranges of 1.00 ng/mL to 1000 ng/mL for alogliptin in human plasma, 0.100 ng/mL to 100 ng/mL for M1 in human plasma, 5.00 to 5000 ng/mL for alogliptin and its metabolite M1 in human urine, and 5.00 to 1500 ng/mL for warfarin (R- and S- enantiomers) in human plasma. The effect of alogliptin multiple dose on warfarin pharmacokinetics was analyzed using an analysis of covariance (ANCOVA).

Results: warfarin plasma concentration-time profiles are shown in Figure 35. wafarin pharmacokinetic and pharmacodynamic parameters are summarized in

Table 43 and

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Table 44. There was no significant effect of alogliptin on warfarin pharmacokinetics and pharmacodynamics.

Figure 34 Schematic of study design

Pretreatment (a)		Treatment Period (a)				Posttreatment (a)	
Screening	Baseline	Warfarin Titration Period		Coadministration Period			Study Exit/ET (e)
Days -28 to -10	Day -9 (b)	Day -8	Days -7 to -1 (c)		Days 1 to 7 (d)	Days 8 to 9	Day 10
	≥67 kg: warfarin 6 mg or <67 kg: 5 mg	≥67 kg: warfarin 4 mg or <67 kg: 3 mg	Warfarin 1-10 mg to stable dose		Treatment A n=18		
					Treatment B n=18		

ET=early termination; Treatment A=placebo + stable dose of warfarin QD; Treatment B=SYR-322 25 mg + stable dose of warfarin QD.

(a) INR was monitored throughout the study.

(b) For subjects who achieved 3 consecutive days of target INR values at a stable warfarin dose a day early, the Baseline day was recalculated as Day -8.

(c) Subjects were required to have at least 3 consecutive days of target (1.2 to 1.8, inclusive) INRs at a stable dose prior to Day -1 to be eligible for the Coadministration Period. Subjects who had 3 consecutive days of target INRs at a stable warfarin dose by Day -4 or Day -3 were permitted to begin the Day -1 (24-hour Baseline warfarin pharmacokinetic sampling) after the third consecutive day that target INRs were achieved, and then continue with the Coadministration Period. Subjects who did not achieve a stable warfarin dose during Warfarin Titration (Day -8 to Day -1) were withdrawn from the study and were not replaced.

(d) Subjects were randomized on Day 1.

(e) Subjects were not discharged from the study until INR was ≤1.2 or at level considered by the investigator to be safe for discharge.

Table 42 Pharmacokinetic and pharmacodynamic sampling schemes

Plasma sampling

Day	Scheduled Time	Pharmacokinetic Sample SYR-322 (a)	Pharmacokinetic Sample Warfarin (b)
-9 through -2	Predose (-15 minutes)		X
-1	Predose (-15 minutes) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose		X
1	Predose (-15 minutes)	X	
2 and 3	Predose (-15 minutes)		X
4 through 6	Predose (-15 minutes)	X	X
7	Predose (-15 minutes) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose	X	X

(a) Blood was collected from subjects who received placebo as well as from subjects who received SYR-322 in order to maintain the treatment blind.
(b) The 24-hour postdose blood sample for Day -1 was drawn prior to dosing with SYR-322 on Day 1.

Urine sampling

Day	Scheduled Time
-9 and -8	24 hours starting at admission to the clinic
7 and 8	0 to 24 hours postdose

PT and INR sampling

Day	Scheduled Time
-9	Immediately following Check-in
-8 through -1	Predose (-15 minutes) and 5 and 12 hours postdose
1 through 7	Predose (-15 minutes) and 12 hours postdose
8 and 9	Approximately the same time as the predose and 12-hour postdose collections on previous days

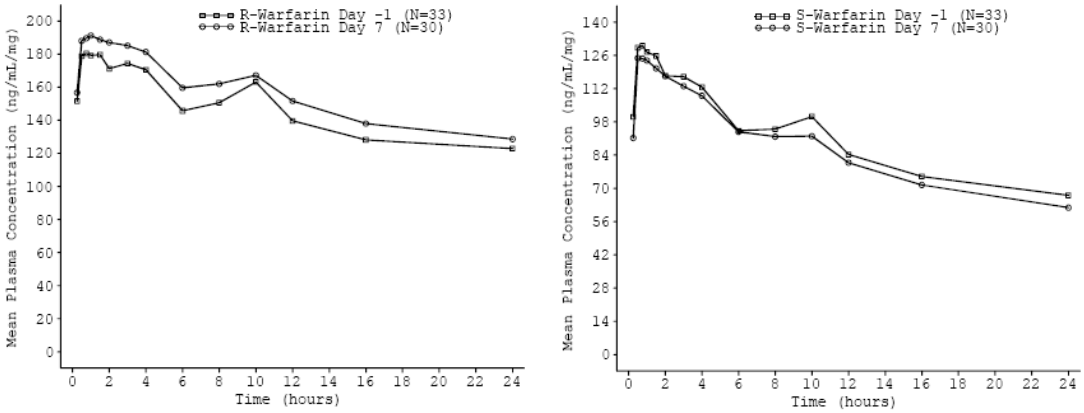


Figure 35 Plasma concentration-time profiles of R-warfarin (left) and S-warfarin (right)

Table 43 Pharmacokinetic parameters of R-warfarin, S-warfarin and alogliptin

Parameter (units)	Arithmetic Mean (%CV)		LS Mean		
	SYR-322 + Warfarin (Test)	Placebo + Warfarin (Reference)	SYR-322 + Warfarin (Test)	Placebo + Warfarin (Reference)	Ratio (T/R) of Least Squares Mean (90% CI) (a)
R-warfarin	n=15	n=15 (b)	n=15	n=15 (b)	n=15
AUC(0-24) (ng·hr/mL/mg)	3632.61 (17.03)	3743.21 (20.28)	3605.32	3649.05	98.80 (94.2, 103.60)
Cmax (ng/mL/mg)	204.5 (15.4)	210.5 (18.5)	203.2	206.1	98.56 (92.03, 105.56)
Cmin (ng/mL/mg)	121.2 (21.2)	128.1 (22.9)	123.0	120.6	101.98 (95.26 , 109.18)
Tmax (hr) (c)	0.50 (0.250, 6.000)	1.00 (0.500, 4.000)	0.50	1.00	—
S-warfarin	n=15	n=15 (b)	n=15	n=15 (b)	n=15
AUC(0-24) (ng·hr/mL/mg)	2104.19 (18.293)	1970.77 (23.951)	2003.98	1982.40	101.09 (97.22, 105.11)
Cmax (ng/mL/mg)	140.00 (17.71)	135.90 (17.92)	135.67	136.01	99.75 (92.11, 108.02)
Cmin (ng/mL/mg)	62.30 (22.53)	59.26 (30.62)	59.92	57.51	104.20 (98.28, 110.47)
Tmax (hr) (c)	0.75 (0.500, 6.000)	0.75 (0.500, 4.000)	0.75	0.75	—

Source: Tables 15.2.1.9 and 15.2.1.10.
T=test; R=reference.
(a) Ratios and CIs were presented as percentages. Ratios are LS means from test treatment divided by LS means from reference treatment.
(b) Data from Subject 006, who discontinued early and had pharmacokinetic samples collected on Day 4 instead of Day 7, were not included in pharmacokinetic analyses (Appendix 16.2.1.3 and Appendix 16.2.3.1).
(c) Median (minimum, maximum) values are presented for Tmax; P=0.305 (R-warfarin), P=0.587 (S-warfarin).

Parameter (units)	Arithmetic Mean (%CV)	
	SYR-322	SYR-322 M-I
	n=15	n=14 (a)
AUC(0-24) (ng·hr/mL)	1359.58 (14.153)	15.45 (70.248)
Cmax (ng/mL)	131.55 (21.044)	0.91 (67.394)
Cmin (ng/mL)	21.68 (30.091)	0.40 (70.663)
Tmax (hr) (a)	2.00 (1.000, 4.000)	4.00 (0.750, 12.000)

Source: Table 15.2.1.4.
(a) Data from Subject 003 were excluded because SYR-322 M-I concentrations were BLQ at all time points (Appendix 16.2.6.5).
(b) Median (minimum, maximum) values are presented for Tmax.

Table 44 Pharmacodynamic parameters

	LS Means				
	SYR-322 + Warfarin (Test)	Placebo + Warfarin (Reference)	Difference in LS Means	95% CI for Mean Difference	P-value
PT (sec)					
Predose	14.21	15.19	-0.98	(-2.70, 0.74)	0.254
12 hours postdose	14.45	15.33	-0.88	(-2.87, 1.11)	0.373
INR					
Predose	1.50	1.60	-0.10	(-0.29 , 0.10)	0.317
12 hours postdose	1.51	1.51	0.00	(-0.17, 0.17)	0.972
	LS Means of Changes from Predose				
	SYR-322 + Warfarin (Test)	Placebo + Warfarin (Reference)	Mean Difference	95% CI for Mean Difference	P-value
PT (sec)	-0.02	0.39	-0.41	(-1.37 , 0.55)	0.390
INR	-0.04	-0.04	0.00	(-0.06 , 0.07)	0.928

Source: Table 15.2.2.2 and Table 15.2.2.3.
Test: SYR-322 25 mg + stable dose of warfarin QD (Treatment B).
Reference: placebo + stable dose of warfarin QD (Treatment A).
Note: N=15 for test and reference groups. Subject 006 (placebo + warfarin group) was excluded from all analyses of PT and INR data. This subject discontinued during the Coadministration Period because of a high INR value (Appendix 16.2.1.3 and Appendix 16.2.3.1).

4.2.15 Study SYR-322-024: The Effect of SYR-322 on the Pharmacokinetics and Pharmacodynamics of Ethinyl Estradiol and Norethindrone (Ortho-Novum® 1/35) in Healthy Adult Female Subjects

Methods: Subjects received either placebo+Ortho-Novum® QD or alogliptin 25 mg tablet+Ortho-Novum® QD for 21 days in the crossover study design following an overnight fasting condition (Figure 35). Ortho-Novum® contains norethindrone 1 mg and ethinyl estradiol 35 µg. Pharmacokinetic and pharmacodynamic sampling schemes are summarized in Table 45 and Table 46. Drug concentrations in plasma and urine were measured by HPLC/MS with validated concentration ranges of 1.00 to 1000 ng/mL for alogliptin in plasma, 0.100 to 100 ng/mL for M-I in plasma, 2.00 to 500 pg/mL for ethinyl estradiol in plasma (truncated to 2.00 to 250 pg/mL), 50.0 to 25,000 pg/mL for norethindrone in plasma, and 5.0 to 5000 ng/mL for alogliptin and its metabolite M-I in urine. Statistical significant was assessed for natural logarithms of AUC and Cmax. The effect of alogliptin on ethinyl estradiol and norethindrone exposure was assessed using LSM ratios.

Results: ethinyl estradiol and norethindrone pharmacokinetic and pharmacodynamic parameters are summarized in Table 47 and Table 48. Alogliptin and its metabolite pharmacokinetic parameters are summarized in Table 49. Alogliptin 25mg co-administration with Ortho-Novum® QD for 21 days did not significantly affect ethyl estradiol and norethindrone pharmacokinetics and pharmacodynamics.

Figure 36 Schematic of study design

Pretreatment Period (a,b)			Period 1 (a,b,c)		Period 2 (a,b)	
Days -28 to -2	Day -1	Sequence	Days 1 to 21 Dosing	Days 22 to 28	Days 1 to 21 Dosing	Day 22
Screening	Check-in for Period 1	1 n=14	Placebo + Ortho-Novum 1/35	Washout	SYR-322 25 mg + Ortho-Novum 1/35	Final Visit
		2 n=14	SYR-322 25 mg+ Ortho-Novum 1/35		Placebo+ Ortho-Novum 1/35	

Placebo + Ortho-Novum 1/35=reference treatment (Treatment A), SYR-322 + Ortho-Novum 1/35=test treatment (Treatment B).
(a) Subjects were confined to the clinic overnight on Days -1, 20, and 21 of Period 1, and Days 20 and 21 of Period 2.
(b) Blood and urine samples for pharmacokinetic and pharmacodynamic analyses were collected at designated time points throughout the study.
(c) Check-in for Treatment Period 2 was Day 28 of Period 1.

Table 45 Pharmacokinetic sampling schemes

Treatment Period	Day	Scheduled Time
1 and 2	1, 19-20	Predose (0 hour)
	21 (a)	Predose (0 hour), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose

(a) When subjects received placebo, blood for SYR-322 analysis was only collected at 4 hours postdose on Day 21.

Treatment Period	Day	Scheduled Time (a)
1	-1 to 1	-24 to 0 hours predose
2	21 to 22	0 to 24 hours postdose

(a) Urine collected from subjects who were receiving placebo was to be discarded; urine was collected to maintain the study blind.

Table 46 Pharmacodynamic sampling for LH, FSH, E2, progesterone, and SHBG

Treatment Period	Day	Scheduled Time
1 and 2	1, 14, and 21	Predose (-0.5 hour)

Table 47 Ethinyl estradiol and norethindrone pharmacokinetic parameters

Analyte/ Parameter (units)	Arithmetic Mean (%CV) SYR-322 + Ortho-Novum (T) n=25	Arithmetic Mean (%CV) Placebo + Ortho-Novum (R) n=25	LS Mean SYR-322 + Ortho-Novum (T) n=25 (e,f)	LS Mean Placebo + Ortho-Novum (R) n=25 (e,f)	Ratio (T/R) ·100 (90% CI) (a)
Ethinyl estradiol					
AUC(0-24) (pg·hr/mL)	1273.74 (25.749)	1291.01 (27.362)	1238.41	1256.17	98.59 (94.92, 102.40)
Cmax (pg/mL)	154.40 (24.944)	165.17 (23.031)	148.88	162.51	91.62 (86.77, 96.73)
Cmin (pg/mL)	22.70 (31.003)	23.13 (31.327)	21.76	22.26	97.79 (92.49, 103.39)
Tmax (hr) (b,c)	1.50 (0.500, 2.000)	1.50 (1.000, 2.000)	1.50	1.50	—
Norethindrone					
AUC(0-24) (pg·hr/mL)	194995.98 (31.66)	182740.69 (29.27)	184257.16	179791.82	102.48 (99.51, 105.55)
Cmax (pg/mL)	25980.0 (20.8)	24688.0 (19.4)	25162.6	24417.0	103.05 (97.73, 108.66)
Cmin (pg/mL)	2721.7 (47.4)	2518.4 (48.3)	2397.5	2365.5	101.35 (97.54, 105.31)
Tmax (hr) (b,d)	1.00 (0.500, 2.000)	1.00 (0.500, 2.000)	1.000	1.000	—

Source: Tables 15.2.1.4 and 15.2.1.5.
R=reference treatment, T=test treatment.
(a) Ratios and CIs are presented as percentages.
(b) Median (minimum, maximum) values are presented for Tmax.
(c) P=0.286.
(d) P=0.568.
(e) 27 unique subjects analyzed.
(f) n=23 for Tmax.

Table 48 Ethinyl estradiol and norethindrone pharmacodynamic parameters

Analyte (units) Study Day	n (T)	n (R)	LS Means SYR-322 + Ortho-Novum (T)	LS Means Placebo + Ortho-Novum (R)	Within Day Pairwise Treatment Comparison P-value	Overall Treatment Effect P-value	Day by Treatment Interaction P-value
LH (mIu/mL)							
1	21	18	5.11	4.56	0.281	0.734	0.367
14	19	17	2.25	1.98	0.602	—	—
21	18	13	0.94	1.43	0.397	—	—
FSH (mIu/mL)							
1	23	22	8.65	8.22	0.606	0.986	0.785
14	20	20	1.89	1.93	0.965	—	—
21	19	18	1.55	1.97	0.651	—	—
E2 (pg/mL)							
1	9	9	66.50	78.73	0.855	0.843	0.767
14	9	7	140.50	87.52	0.461	—	—
21	4	5	28.43	41.79	0.891	—	—
Progesterone (ng/mL)							
1	25	25	1.49	1.51	0.947	0.240	0.438
14	24	24	1.91	1.52	0.095	—	—
21	25	25	1.31	1.22	0.669	—	—
SHBG (nmol/L)							
1	24	24	113.97	111.41	0.567	0.651	0.877
14	23	23	132.84	131.20	0.720	—	—
21	24	24	139.30	139.83	0.906	—	—

Source: Table 15.2.1.13
T=test treatment=SYR-322 + Ortho-Novum (Treatment B), R=reference treatment=placebo + Ortho-Novum (Treatment A).

Table 49 alogliptin and its metabolite pharmacokinetic parameters

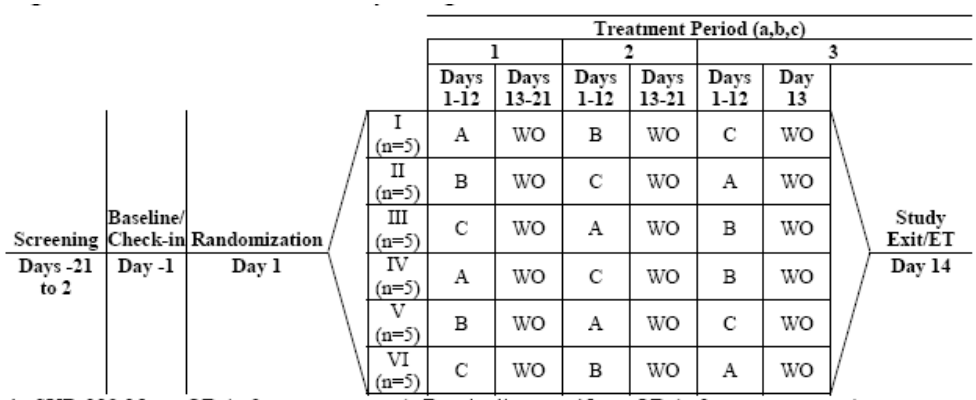
Parameter (units)	Arithmetic Mean (%CV)			
	n	SYR-322	n	SYR-322 M-I
AUC(0-24) (ng·hr/mL)	25	1472.61 (14.090)	24	14.41 (48.809)
Cmax (ng/mL)	25	174.28 (23.723)	24	1.03 (45.848)
Cmin (ng/mL)	25	22.27 (17.088)	24	0.35 (65.433)
Tmax (hr) (a)	25	2.00 (0.500, 3.000)	24	2.00 (0.500, 24.000)
Ae(0-24)	25	15.95 (13.879)	25	0.22 (56.507)
CLr(0-24)	25	10.97 (16.00)	24	15.80 (18.939)
Fe(0-24)	25	63.81 (13.879)	25	1.24 (56.507)

Source: Table 15.2.1.7 and 15.2.1.11.
(a) Median (minimum, maximum) values are presented for Tmax.

4.2.16 Study SYR-322-017: A Phase 1, Open-Label, Randomized, Multiple-Dose, Crossover Study to Assess the Drug-Drug Interaction of SYR-322 and Pioglitazone

Methods: Subjects received alogliptin 25mg QD for 12 days, pioglitazone 45 mg QD for 12 days, and alogliptin 25 mg+pioglitazone 45 mg QD for 12 days in the crossover design (Figure 37). Pioglitazone is mainly metabolized by CYP2C8 and to a lesser extent by CYP3A4, 1A1, and other enzymes. Pharmacokinetic sampling schemes are summarized in Table 50. Statistical significant was assessed for natural logarithms of AUC and Cmax. The drug interaction was assessed using LSM ratios.

Results: pioglitazone, alogliptin and alogliptin metabolite pharmacokinetic parameters are summarized in Table 51 and Table 52. There was no significant pharmacokinetic interaction between alogliptin and pioglitazone at steady-state.



A=SYR-322 25 mg QD (reference treatment), B= pioglitazone 45 mg QD (reference treatment), C=SYR-322 25 mg + pioglitazone 45 mg QD (test treatment), ET=Early termination, WO=washout.
(a) Subjects were confined to the clinic from the evening prior to dosing (Check-in/Day -1 of Treatment Period 1 and Day 21 of Treatment Periods 1 and 2) through Day 14 of each treatment period.
(b) Subjects were dosed on Days 1-12 of each treatment period.
(c) Pharmacokinetic blood samples were collected on Days 1 and 9-14 of each treatment period and pharmacokinetic urine samples were collected on Days 1-3 and 12-14 of each treatment period; urine samples were collected only during Treatments A and C.

Figure 37 Schematic of study design

Table 50 Pharmacokinetic sampling for drugs

plasma sampling

Study Day	Scheduled Time (a)
1	Predose (within 0.25 hour prior to dosing)
9	Predose (within 0.25 hour prior to dosing)
10	Predose (within 0.25 hour prior to dosing)
11	Predose (within 0.25 hour prior to dosing)
12	Predose (within 0.25 hour prior to dosing) and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 hours after the Day 12 dose
13	24 and 36 hours after the Day 12 dose
14	48 hours after the Day 12 dose

(a) Sample sizes for SYR-322 and pioglitazone were 10 mL and 6 mL, respectively.

urine sampling

Study Day	Scheduled Time
1	Predose for 10 hours (from -10 to 0 hour) and from 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours after the Day 1 dose
2-3	24 to 48 hours after the Day 1 dose
12	0 to 4, 4 to 8, and 8 to 12 hours after the Day 12 dose
12-13	12 to 24 hours after the Day 12 dose
13-14	24 to 48 hours after the Day 12 dose

Table 51 Pioglitazone and its metabolites pharmacokinetics on Day 12

	Arithmetic Mean (%CV)		LS Mean (a)		
Parameter (units)	SYR-322 25 mg QD + Pioglitazone 45 mg QD (T) n=27	Pioglitazone 45 mg QD (R) n=28	SYR-322 25 mg QD + Pioglitazone 45 mg QD(T) n=28	Pioglitazone 45 mg QD (R) n=28	Ratio T/R·100 (90% CI) n=28 (b)
Pioglitazone					
AUC(0-24) (ng·hr/mL)	15871.86 (34.488)	14804.45 (27.735)	14889.02	14075.09	105.78 (97.49, 114.78)
AUC(0-48) (ng·hr/mL)	18164.08 (33.088)	17383.07 (26.958)	17186.07	16590.32	103.59 (96.61, 111.08)
Cmax (ng/mL)	1796.63 (31.47)	1739.82 (31.65)	1709.07	1625.69	105.13 (92.34, 119.68)
Cmin (ng/mL)	167.02 (41.27)	183.79 (36.39)	152.21	168.41	90.38 (83.83, 97.44)
Ctrough (ng/mL)	213.67 (40.28)	224.53 (38.08)	197.67	208.06	95.01 (85.67, 105.37)
Tmax (hr) (c,d)	1.000 (0.500, 4.067)	1.008 (0.500, 4.117)	1.00	1.00	—
CL/F (L/hr)	3.12 (30.922)	3.32 (37.663)	—	—	—
Pioglitazone M-III					
AUC(0-24) (ng·hr/mL)	12663.70 (38.545)	12637.17 (34.307)	11840.83	11923.576	99.31 (93.26, 105.75)
AUC(0-48) (ng·hr/mL)	20852.40 (40.841)	20830.57 (35.635)	19390.42	19590.24	98.98 (93.26, 105.06)
Cmax (ng/mL)	639.44 (36.66)	629.75 (31.52)	603.58	599.66	100.65 (93.24, 108.66)
Cmin (ng/mL)	422.52 (33.62)	438.61 (37.16)	399.68	410.26	97.42 (91.46, 103.77)
Ctrough (ng/mL)	504.81 (37.11)	493.14 (35.97)	473.76	465.21	101.84 (93.97, 110.36)
Tmax (hr) (c,e)	6.00 (0.000, 12.000)	5.00 (0.000, 12.000)	6.00	6.00	—
Pioglitazone M-IV					
AUC(0-24) (ng·hr/mL)	34054.24 (25.35)	33688.13 (26.70)	32738.43	32570.01	100.52 (94.14, 107.33)
AUC(0-48) (ng·hr/mL)	54421.79 (26.81)	54125.23 (27.16)	52213.26	52253.56	99.92 (93.90, 106.34)
Cmax (ng/mL)	1701.1 (26.7)	1637.3 (26.4)	1632.8	1583.8	103.10 (95.75, 111.01)
Cmin (ng/mL)	1103.2 (26.2)	1123.7 (26.8)	1062.0	1085.7	97.82 (91.65, 104.39)
Ctrough (ng/mL)	1214.2 (29.1)	1228.0 (28.9)	1167.9	1192.3	97.96 (90.12, 106.47)
Tmax (hr) (c,f)	8.00 (0.000, 12.017)	8.000 (0.000, 12.067)	8.00	8.00	—

Sources: Tables 15.2.1.9 and 15.2.1.10.
T=test treatment=treatment C, R=reference treatment=treatment B, —=not applicable.
(a) n=27 for LS median Tmax.
(b) Ratios and confidence intervals are presented as percentages.
(c) Tmax is presented as median (minimum, maximum).
(d) P=0.833
(e) P=0.378
(f) P=0.753

Table 52 Alogliptin, its metabolites, and optical isomer pharmacokinetics on Day 12

Parameter (units)	Arithmetic Mean (%CV) (a)		LS Mean (b)		
	SYR-322 25 mg QD + Pioglitazone 45 mg QD (T) n=27 (a)	SYR-322 25 mg QD (R) n=28 (a)	SYR-322 25 mg QD + Pioglitazone 45 mg QD(T) n=28	SYR-322 25 mg QD (R) n=28	Ratio T/R·100 (90% CI) n=28 (c)
SYR-322					
Plasma (Day 12)					
AUC(0-24) (ng·hr/mL)	1656.82 (18.452)	1511.20 (18.979)	1644.57	1492.05	110.22 (107.75, 112.75)
AUC(0-48) (ng·hr/mL)	2108.68 (19.193)	1904.56 (19.199)	2087.22	1877.46	111.17 (108.94, 113.45)
Cmax (ng/mL)	178.56 (29.497)	164.86 (30.503)	174.16	158.83	109.65 (102.55, 117.25)
Cmin (ng/mL)	28.919 (28.347)	25.33 (25.508)	28.05	24.57	114.16 (110.42, 118.03)
Ctrough (ng/mL)	29.76 (27.896)	26.29 (25.548)	28.68	25.38	112.98 (108.99, 117.12)
Tmax (hr) (d,e)	2.00 (0.500, 3.000)	2.50 (0.500, 3.000)	2.00	2.50	—
CL/F (L/hr)	15.58 (18.187)	17.13 (18.936)	—	—	—
Urine (Day 12)					
Ae(0-24) (mg)	15.97 (14.619)	15.40 (13.874)	—	—	—
Ae(0-48) (mg)	19.90 (14.970)	18.92 (14.312)	—	—	—
CLr(0-24) (L/hr)	9.87 (19.088)	10.49 (20.202)	—	—	—
CLr(0-48) (L/hr)	9.67 (18.071)	10.22 (19.887)	—	—	—
Fe(0-24) (%)	63.88 (14.619)	61.61 (13.874)	—	—	—
Fe(0-48) (%)	79.591 (14.970)	75.70 (14.312)	—	—	—
SYR-322 M-I					
Plasma (Day 12)					
AUC(0-24) (ng·hr/mL)	16.39 (47.680)	13.467 (46.072)	14.34	11.84	121.13 (116.90, 125.50)
AUC(0-48) (ng·hr/mL)	24.37 (51.708)	19.93 (50.282)	20.75	16.98	122.20 (116.77, 127.88)
Cmax (ng/mL)	1.03 (40.530)	0.85 (39.899)	0.92	0.77	119.63 (114.40, 125.09)
Cmin (ng/mL)	0.46 (55.659)	0.38 (51.900)	0.38	0.31	122.78 (118.43, 127.28)
Ctrough (ng/mL)	0.48 (53.791)	0.41 (49.070)	0.42	0.35	118.01 (113.01, 123.22)
Tmax (hr) (d,f)	2.50 (0.750, 4.067)	2.51 (0.750, 8.000)	2.50	2.51	—
Urine (Day 12)					
Ae(0-24) (μg)	217.22 (51.113)	178.53 (53.392)	—	—	—
Ae(0-48) (μg)	310.85 (55.128)	252.24 (57.693)	—	—	—
CLr(0-24) (L/hr)	14.17 (21.866)	14.55 (19.138)	—	—	—
CLr(0-48) (L/hr)	13.67 (20.522)	14.15 (18.670)	—	—	—
Fe(0-24) (%)	1.23 (51.113)	1.01 (53.392)	—	—	—
Fe(0-48) (%)	1.76 (55.128)	1.43 (57.693)	—	—	—

Parameter (units)	Arithmetic Mean (%CV) (a)		LS Mean (b)		
	SYR-322 25 mg QD + Pioglitazone 45 mg QD (T) n=27 (a)	SYR-322 25 mg QD (R) n=28 (a)	SYR-322 25 mg QD + Pioglitazone 45 mg QD(T) n=28	SYR-322 25 mg QD (R) n=28	Ratio T/R·100 (90% CI) n=28 (c)
SYR-322 M-II					
Plasma (Day 12)					
AUC(0-24) (ng·hr/mL)	51.26 (57.667)	45.93 (61.247)	38.53	35.50	108.53 (104.62, 112.60)
AUC(0-48) (ng·hr/mL)	63.42 (56.185)	57.46 (61.076)	48.33	44.97	107.47 (103.42, 111.68)
Cmax (ng/mL)	5.27 (62.527)	4.52 (60.399)	3.86	3.47	111.12 (104.23, 118.46)
Cmin (ng/mL)	0.82 (64.221)	0.74 (69.622)	0.62	0.58	106.37 (99.40, 113.84)
Ctrough (ng/mL)	0.91 (59.300)	0.83 (64.669)	0.71	0.67	107.32 (100.68, 114.40)
Tmax (hr) (d,g)	2.50 (1.500, 4.000)	2.50 (1.500, 4.050)	2.50	2.50	—
Urine (Day 12)					
Ae(0-24) (μg)	612.30 (59.431)	561.95 (58.938)	—	—	—
Ae(0-48) (μg)	756.91 (58.557)	694.84 (58.365)	—	—	—
CLr(0-24) (L/hr)	11.87 (21.314)	12.43 (22.498)	—	—	—
CLr(0-48) (L/hr)	11.80 (19.835)	12.33 (23.339)	—	—	—
Fe(0-24) (%)	2.96 (59.431)	2.72 (58.938)	—	—	—
Fe(0-48) (%)	3.66 (58.557)	3.36 (58.365)	—	—	—
SYR-322 S-isomer	All concentration data were BLQ.				

Sources: Tables 15.2.1.4, 15.2.1.5 and 15.2.1.12.
T=test treatment=treatment C, R=reference treatment=treatment A, — =not applicable.
(a) n=26 for arithmetic mean AUC(0-24), AUC(0-48), Cmin (SYR-322 + pioglitazone only), Tmax (median), and CLr for SYR-322 M-I; n=25 for Cmin for SYR-322 M-I (SYR-322 alone).
(b) n=29 for LS mean Ctrough for SYR-322 and SYR-322 M-II; n=27 for Tmax (median) for SYR-322 and SYR-322 M-II; n=26 for all parameters for M-I except Ctrough (n=27).
(c) Ratios and confidence intervals are presented as percentages.
(d) Tmax is presented as median (minimum, maximum).
(e) P=0.048.
(f) P=0.016.
(g) P=0.092.

4.2.17 Study SYR-322-025: A Phase 1, Open-Label, Randomized, Multiple-Dose, Crossover Study to Assess the Drug-Drug Interaction of SYR-322 and Atorvastatin

Methods: Subjects received alogliptin 25 mg QD for 7 days, atorvastatin 80mg QD for 7 days and alogliptin 25 mg+atorvastatin 80 mg QD for 7 days by the randomized crossover design under an overnight fasting condition (Figure 38). Pharmacokinetic sampling schemes are summarized in Table 53. Statistical significant was assessed for natural logarithms of AUC and Cmax. The drug interaction was assessed using LSM ratios.

Results: Alogliptin 25 mg QD for 7 days increased atorvastatin AUC and Cmax by 14% and 13%, respectively. Alogliptin increased 2-OH-atorvastatin AUC by 12% and 4-OH-atorvastatin AUC and Cmax by 11% and 23%, respectively (Table 54 and Table 55).

Pretreatment			Treatment Periods (a,b,c,d)					
			1		2		3	
		Sequence	Days 1-7	Days 8-14	Days 1-7	Days 8-14	Days 1-7	
Screening Days -28 to -2	Baseline/ Check-in Day -1	I (n=8)	A	WO	B	WO	C	Study Exit/ET Day 8
		II (n=8)	B	WO	C	WO	A	
		III (n=8)	C	WO	A	WO	B	

A=SYR-322 25 mg QD (reference treatment), B=atorvastatin 80 mg QD (reference treatment), C=SYR-322 25 mg + atorvastatin 80 mg QD (test treatment), ET=Early termination, WO=washout.
(a) Subjects were randomized on Day 1 of Treatment Period 1.
(b) Subjects were confined to the clinic from the evening prior to dosing (Day -1 of Treatment Period 1 and Day 14 of Treatment Periods 1 and 2) through Day 8 of each treatment period.
(c) Subjects were dosed on Days 1-7 of each treatment period.
(d) Blood samples for pharmacokinetic analyses were collected on Days 1 and 4-8 of each treatment period and urine samples for pharmacokinetic analyses were collected on Days -1 to 1 of Treatment Period 1 and Days 7-8 of each treatment period; urine samples were collected only during Treatments A and C. Blood samples for possible pharmacodynamic analysis were collected on Days 7-8 of each treatment period.

Figure 38 Schematic of study design

Table 53 Pharmacokinetic sampling for drugs

plasma

Period	Study Day	Scheduled Time	Pharmacokinetics	HMG-CoA Reductase Inhibition
1, 2, 3	1, 4-6	Predose (-15 minutes)	X	
	7	Predose (-15 minutes) and 2, 4, and 12 hours postdose		X
	7	Predose (-15 minutes) and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 hours postdose	X	
	8	16 and 24 hours postdose	X	X

urine

Period	Study Day	Scheduled Time
1	-1 to 1	Predose from -12 to 0 hour
1 and 2, 2 and 3, or 1 and 3	7 to 8	0-4, 4-8, 8-12, and 12-24 hours after the Day 7 dose

Table 54 atorvastatin and its metabolites pharmacokinetics on Day 7

Analyte Parameter (units)	Arithmetic Mean (%CV)		LS Mean		
	SYR-322 25 mg QD + Atorvastatin 80 mg QD (T) n=23	Atorvastatin 80 mg QD (R) n= 24	SYR-322 25 mg QD + Atorvastatin 80 mg QD (T) n=23 (f)	Atorvastatin 80 mg QD (R) n=24 (f,g)	Ratio (T/R)·100 (90% CI) (a)
Atorvastatin					
AUC(0-24) (ng·hr/mL)	275.24 (56.711)	229.93 (48.450)	239.71	209.96	114.17 (101.36, 128.59)
Cmax (ng/mL)	68.30 (75.188)	55.73 (54.949)	55.79	49.52	112.66 (95.43, 133.00)
Cmin (ng/mL)	0.84 (52.774)	0.78 (46.048)	0.75	0.71	105.45 (90.58, 122.76)
Tmax (hr) (b,c)	2.00 (0.500, 6.000)	1.00 (0.500, 4.000)	2.00	1.00	—
2-Hydroxyatorvastatin					
AUC(0-24) (ng·hr/mL)	297.89 (45.319)	249.15 (31.658)	265.96	237.58	111.95 (100.11, 125.18)
Cmax (ng/mL)	57.88 (54.439)	49.35 (32.620)	50.03	46.68	107.19 (91.99, 124.90)
Cmin (ng/mL)	1.20 (53.330)	0.97 (42.728)	1.05	0.90	116.64 (104.79, 129.84)
Tmax (hr) (b,d)	1.50 (0.500, 8.000)	1.50 (0.750, 4.000)	1.50	1.50	—
4-Hydroxyatorvastatin					
AUC(0-24) (ng·hr/mL)	40.80 (85.278)	33.033 (63.239)	32.03	28.86	110.97 (97.73, 126.00)
Cmax (ng/mL)	5.32 (112.442)	3.47 (68.716)	3.51	2.86	122.73 (98.39, 153.11)
Cmin (ng/mL)	0.37 (64.744)	0.32 (58.139)	0.31	0.29	106.06 (95.58, 117.70)
Tmax (hr) (b,e)	3.00 (0.750, 12.000)	4.00 (1.500, 8.000)	3.00	4.00	—

Source: Tables 15.2.1.15 and 15.2.1.16.
T=test treatment (treatment C), R=reference treatment (treatment B).
(a) Ratios and CIs are presented as percentages.
(b) Median (minimum, maximum) values are presented for Tmax.
(c) P=0.084.
(d) P=0.540.
(e) P=0.461.
(f) 24 unique subjects were included in the analysis.
(g) n=23 for Tmax.

Table 55 alogliptin and its metabolite pharmacokinetics on Day 7

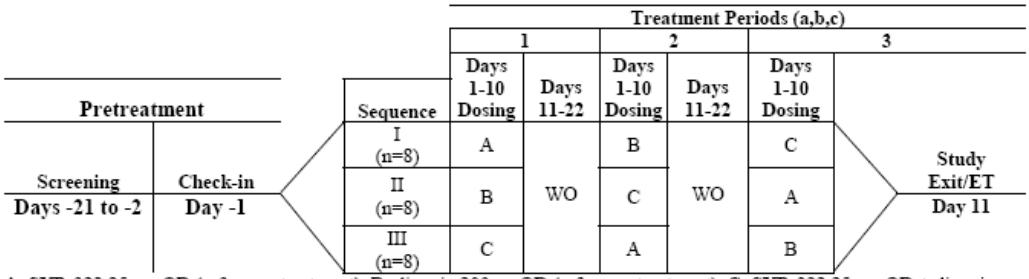
Analyte Parameter (units)	Arithmetic Mean (%CV)		LS Mean		
	SYR-322 25 mg QD + Atorvastatin 80 mg QD (T)	SYR-322 25 mg QD (R)	SYR-322 25 mg QD + Atorvastatin 80 mg QD (T)	SYR-322 25 mg QD (R)	Ratio (T/R)·100 (90% CI) (a)
SYR-322 Plasma	**n=23**	**n=23**	**n=23**	**n=23**	
AUC(0-24) (ng·hr/mL)	1344.87 (19.188)	1340.94 (17.172)	1321.79	1320.86	100.07 (96.35 , 103.94)
Cmax (ng/mL)	162.54 (23.930)	151.39 (29.892)	158.04	145.42	108.68 (96.26 , 122.70)
Cmin (ng/mL)	21.36 (26.109)	20.72 (23.232)	20.68	20.20	102.41 (99.70 , 105.19)
Tmax (hr) (b,c)	0.75 (0.500, 4.000)	1.00 (0.500, 4.000)	0.75	1.00	—
SYR-322 Urine	**n=23**	**n=23**			
Ae(0-24) (mg)	15.05 (18.213)	15.79 (19.212)	—	—	—
CLr(0-24) (L/hr)	11.57 (22.391)	12.11 (24.458)	—	—	—
Fe(0-24) (%)	60.21 (18.213)	63.17 (19.212)	—	—	—
SYR-322 M-I Plasma	**n=22**	**n=22**	**n=22 (e)**	**n=22 (e)**	
AUC(0-24) (ng·hr/mL)	19.24 (75.750)	16.40 (73.866)	14.77	12.37	119.34 (107.35 , 132.67)
Cmax (ng/mL)	1.27 (76.370)	1.09 (66.263)	1.02	0.89	114.47 (102.73 , 127.55)
Cmin (ng/mL)	0.45 (77.087)	0.40 (71.900)	0.39	0.35	112.72 (102.29 , 124.22)
Tmax (hr) (b,d)	1.25 (0.500, 6.000)	2.00 (0.750, 6.000)	1.25	2.00	—
SYR-322 M-I Urine	**n=23 (f)**	**n=23 (f)**			
Ae(0-24) (mg)	0.29 (80.741)	0.26 (82.984)	—	—	—
CLr(0-24) (L/hr)	16.60 (25.859)	17.59 (42.005)	—	—	—
Fe(0-24) (%)	1.66 (80.741)	1.48 (82.984)	—	—	—

Source: Tables 15.2.1.5, 15.2.1.6, and 15.2.1.9.
T=test Treatment (treatment C), R=reference treatment (treatment A).
(a) Ratios and CIs were presented as percentages.
(b) Median (minimum, maximum) values are presented for Tmax.
(c) P=0.015.
(d) P=0.177.
(e) n=21 for Cmin.
(f) n=22 for CLr.

4.2.18 Study SYR-322-029: A Phase 1, Multiple-Dose, Open-Label, Randomized, 3-Period Crossover Study to Evaluate the Effect of SYR-322 on the Pharmacokinetics of Digoxin in Healthy Subjects

Method: Subjects received alogliptin 25 mg QD for 10 days, digoxin 200 µg QD for 10 days, and alogliptin 25 mg+digoxin 200 µg QD for 10 days by the randomized crossover design in the morning (Figure 39). Pharmacokinetic sampling schemes are summarized in Table 56. Alogliptin concentrations in human plasma and urine were measured using HPLC/MS with validated concentration ranges of 1.00 ng/mL to 1000 ng/mL for plasma and 5.00 to 5000 ng/mL for urine. Digoxinconcentrations in human plasma and urine were measured by radioimmunoassay with validated concentration ranges of 0.150 ng/mL to 8.00 ng/mL for plasma and 1.00 ng/mL to 40.0 ng/mL for urine.

Results: There was no significant pharmacokinetic interaction between alogliptin and digoxin at steady-state (Table 57).



A=SYR-322 25 mg QD (reference treatment), B=digoxin 200 µg QD (reference treatment), C=SYR-322 25 mg QD + digoxin 200 µg QD (test treatment), WO=washout, ET=early termination.
(a) Subjects were confined to the clinic from the evening prior to dosing (Day -1 and Day 22 of Period 1 and Day 22 of Period 2) through Day 11 of every period.
(b) Subjects were dosed on Days 1 through 10 of every treatment period.
(c) Blood samples for pharmacokinetic analysis were collected on Day 1 and Days 7 to 11 of each treatment period, and urine samples for pharmacokinetic analysis were collected on Days -1 to 1 and Days 10 to 11.

Figure 39 Schematic of study design

Table 56 Pharmacokinetic sampling for drugs

plasma

Treatment Period	Study Day	Scheduled Time (a)
1, 2, and 3	1	Predose (within 0.50 hour prior to dosing)
	7-9	Predose (within 0.25 hour prior to dosing)
	10	Predose (within 0.25 hour prior to dosing), and 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose
	11	16 and 24 hours post Day 10 dose

(a) Samples sizes were 6 mL for Treatments A and B (reference treatments: SYR-322 alone and digoxin alone), and 2x6 mL for Treatment C (test treatment: SYR-322 + digoxin).

urine

Period	Study Day	Scheduled Time
1	-1 to 1	Predose from -12 to 0 hour
1, 2, and 3	10 to 11	0 to 24 hours after the Day 10 dose

Table 57 digoxin and alogliptin pharmacokinetic parameters

Parameter (units)	Arithmetic Mean (%CV)		LS Mean		
	Treatment C SYR-322 25 mg QD + Digoxin 200 µg QD (T)	Treatment B Digoxin 200 µg QD (R)	Treatment C SYR-322 25 mg QD + Digoxin 200 µg QD (T)	Treatment B Digoxin 200 µg QD (R)	Ratio (T/R)·100 (90% CI) (a)
Digoxin Plasma					
AUC(0-24) (ng·hr/mL)	13.96 (15.814)	14.00 (19.081)	13.76	13.80	99.71 (96.02, 103.55)
Cmax (ng/mL)	1.92 (23.597)	2.05 (28.101)	1.86	1.98	94.16 (85.16, 104.11)
Cmin(0) (ng/mL)	0.41 (20.119)	0.43 (24.309)	0.41	0.42	97.43 (91.34, 103.93)
Tmax (hr) (b)	0.88 (0.500, 1.500)	0.75 (0.500, 24.000)	1.00	0.75	—
CL/F (L/hr)	14.64 (14.501)	14.74 (17.465)	—	—	—
Digoxin Urine					
Ae(0-24) (mg)	0.11 (19.849)	0.11 (17.833)	0.11	0.10	101.15 (96.49, 106.05)
CLr (L/hr)	7.77 (21.671)	7.73 (22.557)	7.66	7.55	101.45 (97.15, 105.93)

Sources: Tables 15.2.1.11, 15.2.1.12, and 15.2.1.14.
— =not applicable, T=test treatment, R=reference treatment.
n=24 for all arithmetic means of the test treatment.
n=23 for all arithmetic means of the reference treatment and for the ANOVA.
(a) Ratios and CIs are presented as percentages.
(b) Tmax is presented as median (minimum, maximum); P=0.614.

Parameter (units)	Arithmetic Mean (%CV)		LS Mean		
	Treatment C SYR-322 25 mg QD + Digoxin 200 µg QD (T)	Treatment A SYR-322 25 mg QD (R)	Treatment C SYR-322 25 mg QD + Digoxin 200 µg QD (T)	Treatment A SYR-322 25 mg QD (R)	Ratio (T/R)·100 (90% CI) (a)
SYR-322 Plasma					
AUC(0-24) (ng·hr/mL)	1523.02 (17.910)	1480.62 (19.310)	1497.57	1456.89	102.79 (99.46, 106.23)
Cmax (ng/mL)	162.08 (23.93)	148.77 (28.71)	158.95	143.48	110.79 (101.61, 120.80)
Cmin(0) (ng/mL)	26.43 (25.47)	26.21 (25.87)	25.61	25.52	100.36 (97.10, 103.73)
Tmax (hr) (b)	1.00 (0.500, 4.000)	1.00 (0.750, 4.000)	1.00	1.00	—
CL/F (L/hr)	16.92 (18.039)	17.53 (20.711)	—	—	—
SYR-322 Urine					
Ae(0-24) (mg)	13.80 (25.716)	13.94 (23.437)	13.45	13.65	98.58 (90.72, 107.12)
CLr (L/hr)	9.20 (26.819)	9.59 (23.025)	8.98	9.37	95.90 (87.63, 104.97)

Sources: Tables 15.2.1.4, 15.2.1.5, and 15.2.1.7.
— =not applicable, T=test treatment, R=reference treatment.
n=24 for all arithmetic means of the test treatment.
n=23 for all arithmetic means of the reference treatment and for the ANOVA.
(a) Ratios and CIs are presented as percentages.
(b) Tmax is presented as median (minimum, maximum); P=0.025.

4.2.19 Study SYR-322-005: A Randomized, Open-label Study to Evaluate the Pharmacokinetics of SYR-322 When Administrated with Food and When Coadministered with Metformin or Cimetidine

NDA22271, SYR-322/005 Study date April 7 to June 1 2005
A Randomized, Open-label Study to Evaluate the Pharmacokinetics of SYR-322 When Administrated with Food and When Coadministered with Metformin or Cimetidine

Background: Results from phase 1 study (SYR-322-001) in healthy volunteers showed that 60% to 71% of the SYR-322 dose was excreted unchanged in the urine at the dose range of 25 to 800 mg of SYR-322. In addition, the renal clearance of SYR-322 exceeded the glomerular filtration rate (GFR), suggesting that SYR-322 undergoes active renal tubular secretion. It is hypothesized that SYR-322 is likely secreted through the cationic transporter systems of the proximal renal tubule. This study was aimed to investigate the potential drug-drug interaction between SYR-322 and other renally excreted compounds.

The biguanide metformin is a highly cationic compound and it undergoes active renal secretion via the proximal tubular system. As a DPP4 inhibitor, SYR-322 reduces plasma glucose by a different mechanism of action as compared to metformin. The combination of SYR-322 and metformin may potentially be used to improve the glycemic control in patients with type 2 diabetic mellitus. Thereby, the drug-drug interaction between SYR-322 and metformin is evaluated in this drug-drug interaction study. This study also evaluates drug-drug interaction between SYR 322 and cimetidine as the later is known to affect the pharmacokinetics or renally excreted cationic compounds.

Objectives:

1. To assess the effect of food administration on the pharmacokinetics of SYR-322.
2. To evaluate the effect of metformin or cimetidine on the steady-state pharmacokinetics of SYR-322 in healthy volunteers.
3. To evaluate the effect of SYR-322 on the steady-state pharmacokinetics of metformin or cimetidine in healthy volunteers.

Study Design:

This was a randomized, open-label, single-center, 2-phase, single-dose and multiple-dose study conducted in healthy male and female subjects. The study dose was administered orally with 240 mL of water in the morning after at least 8 hour fast. Subjects were required to continue fasting for 1 hour post dose.

Single-dose phase: In the first phase of the study, a 2-period crossover design was used to examine the effect of food on the pharmacokinetics of SSYR-322 after a single oral dose. There was 96 hour washout between the two periods.

Period 1: All subjects received a single oral dose of SYR-322 after an overnight fast of at least 10 hours (fast condition) or immediately after consuming a standard high-fat meal (fed condition).

Period 2: All subjects received a single oral dose of SYR-322 under the alternate conditions.

Multiple-dose Phase: In the second phase of the study, a three-way crossover study design was used to assess the drug-drug interaction between SYR-322 and metformin or cimetidine. Subjects were randomized into metformin arm or cimetidine arm. In each arm, subjects received three treatments listed below in a crossover fashion.

Metformin arm:

- SYR-322 100 mg QD for 6 days
- Metformin 1000 mg BID for 6 days.
- SYR-322 100 mg QD + Metformin 1000 mg BID for 6 days

Cimetidine arm:

- SYR-322 100 mg QD for 6 days
- Cimetidine 400 mg QD for 6 days.
- SYR-322 100 mg QD + Cimetidine 400 mg QD for 6 days

A 96 hour washout period separated each of the three periods. Plasma and urine samples were collected over 96 hours post dose on day 6 in each period for the determination of plasma drug concentration of SYR-322 and metformin or cimetidine.

Food content for the breakfast: Subjects were provided a standard high-fat meal that was consumed within 30 minutes. Subjects received the SYR-322 dose immediately after completing the meal. The standard high-fat meal consists 2 eggs (fried in butter), 2 strips of beacon, slices of toast with butter, 4 oz of hash brown potatoes (fried with butter), and 8 oz (240 mL) of whole milk.

PK sampling: Blood samples were collected at predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72 and 96 hours post dose on days 1 of both periods for the single dose phase. Samples were collected prior to dosing (for the measurement of the trough level) at Days 4, 5 and 6, and then on Day 6 at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72 and 96 hours post dose.

Urine samples were collected immediately prior to dose (0 hour) and at the interval of 0 to 4, 4 to 8, 8 to 12, 12 to 16, 16 to 24, 24 to 48, 48 to 72 and 72 to 96 hours after dosing for both the single dose and multiple dose phase.

PK analysis: Plasma PK data were analyzed using noncompartmental (NCA) analysis. AUCt in single dose study, AUCτ in multiple dose study, AUCinf, Cmax, Tmax, $T_{1/2}$, CL/F, Vz/F, accumulated urine excretion $XU_{0\text{-}96\ hr}$ were calculated.

Statistical Analysis: Descriptive statistics were applied to summarize the PK parameters. An analysis of variance (ANOVA) was performed on log-transformed PK parameters to evaluate the food effect and to assess the drug-drug interactions. The geometric mean ratios and 90% confidence intervals (CIs) of AUCinf for single dose study or AUCτ for multiple dose study and Cmax of SYR100322 and the interacting drugs were estimated.

If the 90% CI fell within 80% to 125% for AUC and Cmax, then the presence of food effect or drug-drug interactions were excluded.

Results:

1. Food effect. PK parameters and summary statistics of SYR-322 were listed in Table 58. Table 59 provides the geometric mean ratios (GMRs) of AUCτ and Cmax of SYR-322 in healthy volunteers receiving a single dose of SYR-322 100 mg under fasted and fed conditions. The 90% confidence interval (CI) of GMR (SYR-322 fed/SYR-322 fasted) of AUCτ of plasma SYR-322 fell within the boundary of 80% to 125%; while 90% CI of GMR of Cmax was slightly out of the range of 80% to 125%.

- Plasma AUCτ and Cmax of SYR-322 had 4.7% and 14.4% reduction in GMR.
- The 90% CI for AUC was 93.8% to 96.8%.
- The 90% CI for Cmax was 79.8% to 91.7%.

These results suggested that food has no effect on the extent of absorption of SYR-322 and may have minor effect on the rate of absorption of SYR-322.

Table 58 PK parameters of SYR-322 following a single oral dose of SYR-322 100 mg under fast or fed conditions in healthy subjects.

Parameter/ Statistic	SYR110322 100 mg Fasted (N = 36)	SYR110322 100 mg Fed (N = 36)
AUC_{0-t} (ng•h/mL)		
Mean	6917	6577
CV%	16	16
AUC_{0-inf} (ng•h/mL)		
Mean	7056	6723
CV%	16	16
C_{max} (ng/mL)		
Mean	607.9	526.9
CV%	26	35
T_{max} (h)		
Median	2.00	2.51
Min, Max	0.5, 6.0	0.3, 6.1
$t_{1/2,z}$ (h)		
Mean	20.96	20.50
CV%	16	16
CL/F (L/h)		
Mean	14.51	15.23
CV%	15	15
V_z/F (L)		
Mean	440	449
CV%	23	20
XU_{0-96} (mg)		
Mean	73.82	74.78
CV%	14	12
$Fe\%_{0-96}$		
Mean	73.82	74.78
CV%	14	12
CLr (L/h)		
Mean	10.66	11.30
CV%	19	15

Source: Tables 14.2.1.2 and 14.2.1.5

Table 59 **Geometric mean, GM ratios and 90% CI of SYR-322 in healthy subjects following a single oral dose of SYR-322 100 mg under fast or fed conditions.**

Table 7. Analysis of Food-Effect on the Single-Dose Pharmacokinetics of SYR110322

Parameter	Treatment	N	Geometric LS means	Ratio of LS Means	90% CI	*P* Values		
						Treatment	Period	Sequence
AUC_{0-inf} (ng•h/mL)	100 mg Fasted	36	6971.27					
	100 mg Fed	36	6643.81	0.953	0.938, 0.968	<0.001	0.243	0.826
C_{max} (ng/mL)	100 mg Fasted	36	587.27					
	100 mg Fed	36	502.46	0.856	0.798, 0.917	<0.001	0.132	0.795

Source: Table 14.2.1.3.1

Note: An ANOVA model was performed on log-transformed parameters. The model included sequence, period, and treatment as fixed effects, and subject nested within sequence as a random effect. Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale.

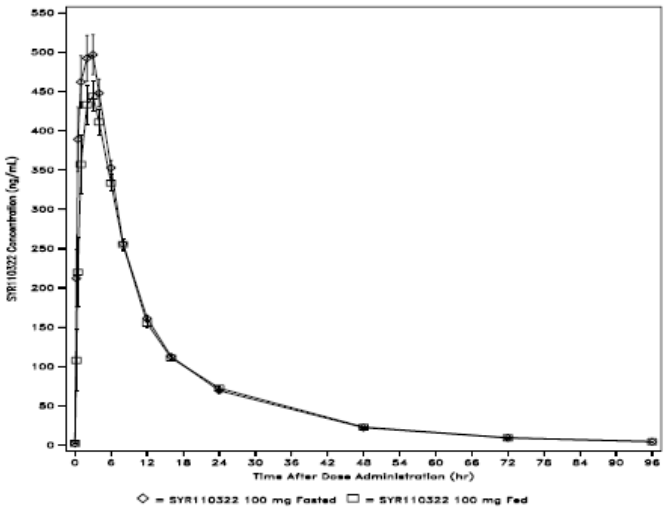


Figure 40 **Average plasma concentration of SYR-322 following a single oral dose of SYR-322 100 mg in healthy male subjects under fast or fed conditions.**

2. Drug-drug interaction between SYR-322 and cimetidine or metformin

PK parameters and summary statistics of SYR-322, cimetidine and metformin were listed in Table 60 to Table 63, respectively. Table 64 provides the geometric mean ratios (GMRs) of AUCτ and Cmax of SYR-322 in healthy volunteers receiving multiple dose of SYR-322 alone and in coadministration of multiple doses of cimetidine. Table 65 and Table 66 provides the geometric mean ratios (GMRs) of AUCτ and Cmax of cimetidine or metformin in healthy volunteers receiving multiple dose of cimetidine or metformin alone and in coadministration of multiple doses of SYR-322.

SYR-322 in the presence of cimetidine

- Plasma AUCτ and Cmax of SYR-322 had 6.5% and 4.8% increase in GMR, respectively.
- The 90% CI for AUCτ was 103.2% to 109.9%.
- The 90% CI for Cmax was 98.4% to 111.6%.

SYR-322 in the presence of metformin

- GMRs of plasma AUCτ and Cmax of SYR-322 had no change and 10.5% reduction, respectively.
- The 90% CI for AUCτ was 97.2% to 102.9%.
- The 90% CI for Cmax was 82.0% to 97.7%.

Cimetidine

- GMRs of AUCτ and Cmax of cimetidine had 4.3% increase and 0.7% reduction, respectively.
- The 90% CI of GMR for AUCτ was 98.2% to 110.7%.
- The 90% CI of GMR for Cmax was 90.7% to 108.7%.

Metformin

- GMRs of AUCτ and Cmax of metformin had 18.9 and 0.4% increase, respectively.
- The 90% CI of GMR for AUCτ was 109.5% to 129.1%.
- The 90% CI of GMR for Cmax was 91.9% to 109.7%.

These results suggested that metformin or cimetidine has no effect on the extent and rate of absorption of SYR-322 at steady state. SYR-322 has no effect on the absorption of cimetidine at steady state. SYR-322 has no effect on the rate but a minor effect on the extent of the absorption of metformin at steady state. Combining no change in Cmax and an increase of 18.9% in AUCτ of metformin, SYR-322 is unlikely to cause a clinical significant effect on metformin.

Table 60 PK parameters of SYR-322 in healthy subjects following multiple oral doses of SYR-322 100 mg QD alone or in coadministration with multiple oral doses of 400 mg cimetidine QD.

	SYR110322 100 mg (Cimetidine Arm) (N=18)	Cimetidine 400 mg QD + SYR110322 100 mg QD (N = 18)
AUC_{0-tau} (ng•h/mL)		
Mean	6946	7397
CV%	18	18
C_{max} (ng/mL)		
Mean	669.8	698.7
CV%	28	26
T_{max} (h)		
Median	3.00	3.00
Min, Max	0.5, 4.0	0.3, 6.0
$t_{1/2,z}$ (h)		
Mean	22.87	21.84
CV%	22	15
CL/F (L/h)		
Mean	14.85	13.94
CV%	18	18
V_z/F (L)		
Mean	486.4	440.2
CV%	24	23
XU_{0-96} (mg)		
Mean	103.82	103.48
CV%	9	14
$Fe\%_{0-96}$		
Mean	103.82	103.48
CV%	9	14
CLr (L/h)		
Mean	10.42	9.84
CV%	14	15

Source: Tables 14.2.2.2.1 and 14.2.2.5.1

Table 61 **PK parameters of SYR-322 in healthy subjects following multiple oral doses of SYR-322 100 mg QD alone or in coadministration with multiple oral doses of 1000 mg metformin BID.**

	SYR110322 100 mg (Metformin Arm) (N=17)	Metformin 1000 mg BID + SYR110322 100 mg QD (N = 17)
AUC_{0-tm} (ng•h/mL) Mean CV%	 6981 17	 6961 16
C_{max} (ng/mL) Mean CV%	 800.0 29	 709.5 23
T_{max} (h) Median Min, Max	 1.00 0.3, 4.0	 1.00 0.3, 6.0
$t_{1/2,z}$ (h) Mean CV%	 21.23 12	 21.99 15
CL/F (L/h) Mean CV%	 14.67 15	 14.71 15
V_z/F (L) Mean CV%	 449.8 20	 463.8 17
XU_{0-96} (mg) Mean CV%	 98.40 11	 97.38 11
$Fe\%_{0-96}$ Mean CV%	 98.40 11	 97.38 11
CLr (L/h) Mean CV%	 10.48 16	 10.15 19

Source: Tables 14.2.2.2.1 and 14.2.2.5.1

Table 62 **PK parameters of cimetidine in healthy subjects following multiple oral doses of 400 mg cimetidine QD alone or in coadministration with multiple oral doses of 100 mg SYR-322 QD.**

Table 11. Multiple-Dose Pharmacokinetic Parameters for Cimetidine

	Cimetidine 400 mg QD (N = 18)	Cimetidine 400 mg QD + SYR110322 100 mg QD (N = 18)
AUC_{0-tm} (µg•h/mL) Mean CV%	 11 22	 11 20
C_{max} (µg/mL) Mean CV%	 2.2 34	 2.1 31
T_{max} (h) Median Min, Max	 2.00 0.5, 3.0	 3.00 1.0, 4.0
$t_{1/2,z}$ (h) Mean CV%	 15.20 77	 10.44 75
CL/F (L/h) Mean CV%	 38.02 19	 36.51 21
V_z/F (L) Mean CV%	 876.2 84	 583.3 91
XU_{0-96} (mg) Mean CV%	 245.36 17	 252.32 15
$Fe\%_{0-96}$ Mean CV%	 61.34 17	 63.08 15
CLr (L/h) Mean CV%	 23.22 23	 22.79 20

Source: Table 14.2.2.2.2 and 14.2.2.5.2

Table 63 **PK parameters of metformin in healthy subjects following multiple oral doses of 1000 mg metformin BID alone or in coadministration with multiple oral doses of 100 mg SYR-322 QD.**

Table 13. Multiple-Dose Pharmacokinetic Parameters for Metformin

	Metformin 1000 mg BID (N =17)	Metformin 1000 mg BID + SYR110322 100 mg QD (N = 17)
$AUC_{0\text{-}tau}$ (ng•h/mL)		
Mean	10449	12393
CV%	25	25
C_{max} (ng/mL)		
Mean	1942.5	1951.9
CV%	26	27
T_{max} (h)		
Median	1.03	2.00
Min, Max	0.5, 2.1	1.0, 3.0
$t_{1/2,z}$ (h)		
Mean	19.04	17.29
CV%	44	51
CL/F (L/h)		
Mean	102.40	85.56
CV%	29	25
V_z/F (L)		
Mean	2672.1	2091.5
CV%	36	40
$XU_{0\text{-}96}$ (mg)		
Mean	427.27	488.99
CV%	31	26
$Fe\%_{0\text{-}96}$		
Mean	42.73	48.90
CV%	31	26
CLr (L/h)		
Mean	26.65	26.55
CV%	14	20

Source: Table 14.2.2.2.3 and 14.2.2.5.3

Table 64 **Geometric mean ratios and 90% CI in AUCτ and Cmax of SYR-322 in healthy subjects at steady state following multiple oral doses of 100 mg SYR-322 QD alone or in coadministration with multiple oral doses of 400 mg cimetidine QD or 1000 mg metformin BID.**

Table 10. Analysis of the Effects of Cimetidine and Metformin on the Steady-State Pharmacokinetics of SYR110322

Parameter	Treatment	N	Geometric LS means	Ratio of LS Means	90% CI
$AUC_{0\text{-}tau}$ (ng•h/mL)	SYR110322 100 mg QD	18	6838.18	1.065	1.032, 1.099
	Cimetidine 400 mg QD + SYR110322 100 mg QD	18	7283.54		
C_{max} (ng/mL)	SYR110322 100 mg QD	18	645.95	1.048	0.984, 1.116
	Cimetidine 400 mg QD + SYR110322 100 mg QD	18	677.08		
$AUC_{0\text{-}tau}$ (ng•h/mL)	SYR110322 100 mg QD	17	6893.43	1.000	0.972, 1.029
	Metformin 2000 mg BID + SYR110322 100 mg QD	17	6893.26		
C_{max} (ng/mL)	SYR110322 100 mg QD	17	769.90	0.895	0.820, 0.977
	Metformin 2000 mg BID + SYR110322 100 mg QD	17	688.88		

Source: Table 14.2.2.3.1.

Table 65 **Geometric mean ratios and 90% CI in AUCτ and Cmax of cimetidine in healthy subjects at steady state following multiple oral doses of 400 mg cimetidine QD alone or in coadministration with multiple oral doses of 100 mg SYR-322 QD.**

Table 12. Analysis of the Effects of SYR110322 on the Steady-State Pharmacokinetics of Cimetidine

Parameter	Treatment	N	Geometric LS means	Ratio of LS Means	90% CI
AUC_{0-tau} (µg•h/mL)	Cimetidine 400 mg QD	18	10.72	1.043	0.982, 1.107
	Cimetidine 400 mg QD + SYR110322 100 mg QD	18	11.17		
C_{max} (µg/mL)	Cimetidine 400 mg QD	18	2.07	0.993	0.907, 1.087
	Cimetidine 400 mg QD + SYR110322 100 mg QD	18	2.05		

Source: Table 14.2.2.3.2.

Table 66 **Geometric mean ratios and 90% CI in AUCτ and Cmax of metformin in healthy subjects at steady state following multiple oral doses of 1000 mg metformin BID alone or coadministration with multiple oral doses of 100 mg SYR-322 QD.**

Table 14. Analysis of the Effects of SYR110322 on the Steady-State Pharmacokinetics of Metformin

Parameter	Treatment	N	Geometric LS means	Ratio of LS Means	90% CI
AUC_{0-tau} (ng•h/mL)	Metformin 1000 mg BID	16	10112.82	1.189	1.095, 1.291
	Metformin 1000 mg BID + SYR110322 100 mg QD	16	12022.75		
C_{max} (ng/mL)	Metformin 1000 mg BID	16	1867.75	1.004	0.919, 1.097
	Metformin 1000 mg BID + SYR110322 100 mg QD	16	1875.65		

Source: Table 14.2.2.3.3.

Conclusions:

- Metformin or cimetidine has no effect on the extent and rate of absorption of SYR-322 at steady state.
- SYR-322 has no effect on the absorption of cimetidine at steady state.
- SYR-322 has no clinical significant effect on the rate and the extent of the absorption of metformin at steady state.
- Food has no effect on the extent of absorption of SYR-322 and may have minor effect on the rate of absorption of SYR-322.

Comments:

- Results from this study suggested that food had some effect on the rate of absorption of SYR-322 as the Cmax of SYR-322 had 14.4% reduction under the fed conditions as compared to the fasted conditions and the 90% CI of GMR ranged from 79.8% to 91.7%. However, results also suggested that the AUCt was

not affected by the high fat meal. Overall, the small change in Cmax and no change in AUCt suggest that food may not have clinically significant impact on the exposure to SYR-322.

- The sponsor used the standard high-fat meal specified by the FDA guidance, which is acceptable.
- The terminal elimination half-life of SYR-322 is approximately 22 hours; therefore the 96 hour washout period is approximately more than 4 half-lives, which is acceptable but not optimal.
- In the drug-drug interaction study, subjects received 6 days QD dosing of SYR-322 to reach steady state. The half life of metformin and cimetidine ranged 10-15 and 17-19 hours, respectively. Thereby the 6 days dosing of SYR-322 and the interaction drug is reasonable to reach steady state.
- Half-life of cimetidine was 15 when administered alone and 10 hour when coadministered with SYR-322. These half life values were significantly longer than reported values (2 to 4 hours) in literature. The sponsor mentioned that a more sensitive assay was used in the plasma sample analysis. The 10 fold improvement in the analytical method allowed for the quantitation of plasma samples at the terminal elimination phase, which would have been below detection according to the previously cited study. The mean of CF/F and CLr of the cimetidine did not change with the presence of SYR-322, suggesting that coadministration of SYR-322 has no effect on the clearance of cimetidine.
- Coadministration of SYR-322 with metformin resulted in 18.9% increase in AUCτ and the 90% CI of GMR for AUCτ was 109.5% to 129.1%. The results suggested an interaction between the two drugs; however the magnitude of change (less than 30%) would probably have no clinical effect, requiring dose adjustment of metformin in patients with normal renal function.

4.2.20 Study SYR-322-016: The effect of Multiple Doses of Fluconazole, Ketoconazole, or Gemfibrozil on the Single-Dose Pharmacokinetic Profile of SYR-322 in Healthy Subjects

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NDA; 22-271/Study 016 Study date January 9 to February 7 2006
The effect of Multiple Doses of Fluconazole, Ketoconazole, or Gemfibrozil on the Single-Dose Pharmacokinetic Profile of SYR-322 in Healthy Subjects

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Background: SYR-322 is excreted mainly be the kidneys, with 60% to 71% of the dose excreted as unchanged SYR-322 in urine and undergoes minimal metabolism in human. *In vivo* study results showed that the exposure to the demthylated metabolite SYR-322 M-I was less than 1% as compared to that of SYR-322 in plasma or urine. A drug-drug interaction was not expected of SYR-322 with the potent inhibitor of CYP450 enzymes.

However, the sponsor conducted this clinical study in healthy human subjects to test this hypothesis.

In vitro assays suggested that CYCP2D6 is primarily responsible for the formation of SYR-322 M-I. In addition, CYP3A4 is the primary isoform involved in the formation of minor hydroxylated and/or dehydrogenated metabolites of SYR-322.

In this drug-drug interaction, the sponsor evaluated the effect of fluconazole, ketoconazole and gemfibrozil on the pharmacokinetics of SYR-322 and its metabolite M-I in healthy male and female subjects. According to FDA guidance for drug interaction studies, fluconazole, ketoconazole and gemfibrozil is inhibitor to CYP2C9, CYP3A4, and CYP2C8/9, respectively. Subjects received antifungal drug fluconazole, ketoconazole, or lipid-lowering drug gemfibrozil, respectively, for 6 days in order to reach steady state; on the sixth day, a single oral dose of SYR-322 25 mg was given to these subjects. The PK of SYR-322 and its metabolite SYR-322 M-I with the presence of these inhibitors at the steady state was compared to the PK without inhibitors. The comparisons will determine if multiple doses of fluconazole, ketoconazole and gemfibrozil will have significant impact on the pharmacokinetics of SYR-322 and its metabolite M-I.

Objectives:

1. To determine the single-dose pharmacokinetics of SYR-322 (25 mg) in the presence of multiple doses of fluconazole (200 mg QD), ketoconazole (400 mg QD), or gemfibrozil (600 mg BID) in healthy subjects.

2. To compare the safety and tolerability of a single dose of SYR-322 25 mg when administered alone and SYR-322 in the presence of multiple doses of fluconazole, ketoconazole, or gemfibrozil in healthy subjects.

Study Design: This was a phase I, 14-day, open-label, randomized, open-label, single-center, pharmacokinetic study to evaluate the safety and tolerability of single doses of SYR-322 when administered alone and with multiple doses of fluconazole, ketoconazole, or gemfibrozil in healthy male and female subjects, age 18 to 45 years, inclusive. 48 subjects were divided into 3 groups and went through 2 treatments, which were listed as follow:

Treatment 1: Subjects received orally a single dose of SYR-322 25 mg (reference treatment).

Treatment 2: Subjects received coadministration of a single oral dose of SYR-322 25 mg on and fluconazole, ketoconazole, or gemfibrozil orally.

Group 1: Subjects received fluconazole 200 mg QD from day 6 to 11 orally.

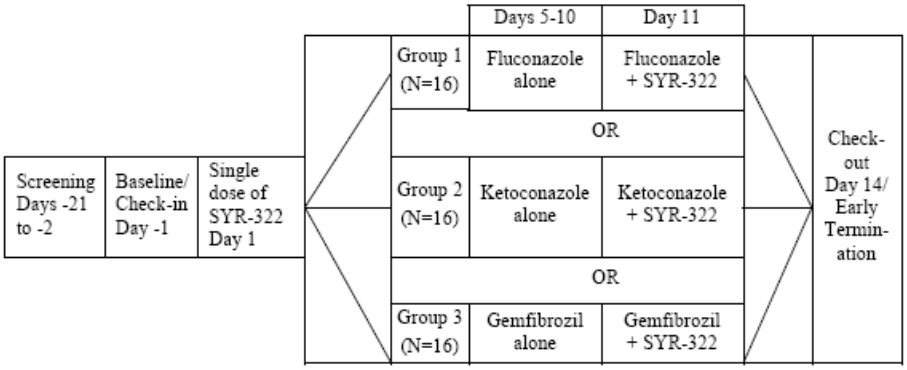
Group 2: Subjects received ketoconazole 400 mg QD from day 6 to 11 orally.

Group 3: Subjects received gemfibrozil 600 mg BID from day 6 to 11 orally.

Subjects will be housed in the clinical research unit for 14 consecutive nights. Subjects will be fasted over night (for at least 8 hours) prior to each morning dose on Day-1 through Day 11. Following study drug administration on Days 1 and 11, subjects continued to fast for additional 4 hours post dose. The study dose was administered orally with 240 mL of water. Subjects received a standardized diet containing approximately

35% fat during the time of their confinement in the study center, with no addition food or drink, except water, was allowed. An identical diet was given to all subjects on Day 1 and Day 11.

Table 67 Schematic drug-drug interaction study design.



PK sampling: Blood samples were collected on days 1 and 11 at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours post dose for the determination of SYR-322, SYR-322-M-I, and cyclosporine.

Urine samples were collected from the intervals of -10 to 0 hour on day 1 and at 0 to 72 hours post dose on Day 1 and 11 (in 24-hour increments,, 0-24, 24-48, and 48-72 hours) for the determination of SYR-322 and SYR-322 M-I.

PK analysis: PK analysis was conducted using noncompartmental methods with WinNonlin® version 4.0.1. Data manipulation, tabulation of descriptive statistics, and inferential statistics were performed using SAS Version 8.02

Statistical analysis: Descriptive statistics were used to summarize the PK parameters under both fast and fed conditions. To assess the effect of multiple doses of fluconazole, ketoconazole and gemfibrozil on the PK of SYR-322, ANOVA was performed on the log-transformed plasma PK parameters of AUCinf, AUCt and Cmax of SYR-322. If the two-sided 90% confidence interval of AUCinf and Cmax falls within 80% to 125%, then multiple doses of fluconazole, ketoconazole and gemfibrozil will have no significant impact on the PK of SYR-322.

Results: The 90% confidence interval (CI) of GMR (SYR-322 + Fluconazole, ketoconazole or Gemfibrozil/SYR-322) for plasma of SYR-322 and its metabolite M-I are evaluated, with the effect boundary set at the 80-125% for 90% CI of GMR according to the Draft Drug interaction Guidance.

1. Effect of fluconazole on PK of SYR-322 and its metabolite M-I

Mean plasma concentration of SYR-322 and metabolite M-I are in Figure 41 and Figure 42, respectively. The effects of multiple doses of fluconazole on the pharmacokinetics of SYR-322 and its metabolite M-I in plasma are listed below and also shown in Table 68.

- GMR of plasma AUC(0-inf) of SYR-322 decreased 0.87% and the 90% CI ranged from 96.45% to 101.89%.

- GMR of plasma Cmax of SYR-322 decreased by 19.6% and the 90% CI ranged from 70.10% to 92.28%.
- GMR of plasma AUC(0-inf) of metabolite M-I had an increase of 18.8% and 90% CI ranged from 101.03% to 139.57%.
- GMR of plasma Cmax of metabolite M-I had an increase of 16.2% and the 90% CI ranged from 105.93% to 127.48%.

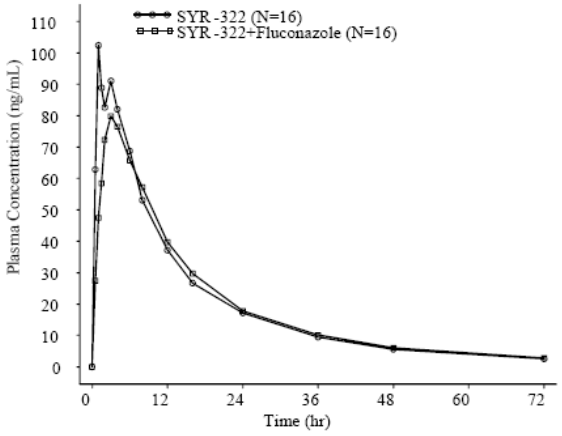


Figure 41 **Mean plasma concentration of SYR-322 in healthy subjects following a single oral dose of SYR-322 25 mg alone at Day 1 and coadministration with fluconazole 200 mg QD at Day 11 after pretreatment with fluconazole from Days 5 to 10.**

Figure 42 **Mean plasma concentration of SYR-322 metabolite M-I in healthy subjects following a single oral dose of SYR-322 25 mg alone at Day 1 and coadministration with fluconazole 200 mg QD at Day 11 after pretreatment with fluconazole from Days 5 to 10.**

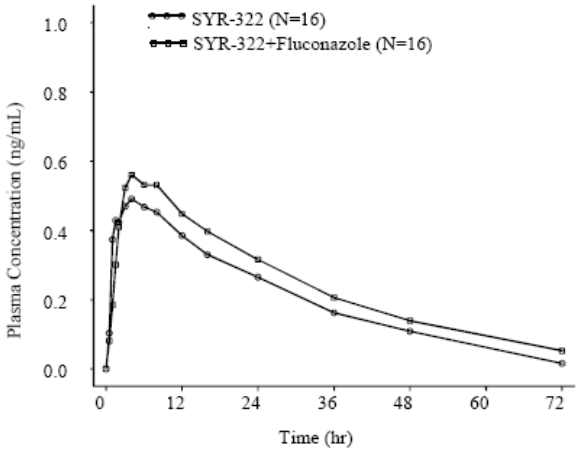


Table 68 **PK parameters of SYR-322 and metabolite M-I in healthy subjects following a single oral dose of SYR-322 25 mg alone on Day 1 and coadministration with fluconazole 200 mg QD at Day 11 after pretreatment with fluconazole from Days 5 to 10.**

Parameter, units	Geometric Mean (a)		Geometric Mean Ratio (T/R)*100 (%)	90% CI for Ratio
	SYR-322 25 mg + Fluconazole 200 mg Day 11 (T)	SYR-322 25 mg Alone Day 1 (R)		
SYR-322 (n=16)				
AUC(0-inf), ng·hr/mL	1469.16	1481.99	99.13	(96.45, 101.89)
AUC(0-tlqc), ng·hr/mL	1389.40	1414.84	98.20	(95.35, 101.14)
Cmax, ng/mL	89.26	110.98	80.43	(70.10, 92.28)
Tmax, hr (a) (b)	2.50	1.00	---	---
SYR-322 M-I (n=15)				
AUC(0-inf), ng·hr/mL (c)	27.50	23.16	118.75	(101.03, 139.57)
AUC(0-tlqc), ng·hr/mL	12.40	10.12	122.59	(104.72, 143.52)
Cmax, ng/mL	0.54	0.47	116.21	(105.93, 127.48)
Tmax, hr (a) (b)	4.00	4.00	---	---

Source: Table 15.2.1.3.
T=test treatment; R=reference treatment.
(a) Medians are reported for Tmax.
(b) P=0.033 for SYR-322 and P=0.635 for SYR-322 M-I, based on Wilcoxon signed rank test.
(c) n=4.

2. Effect of ketoconazole on PK of SYR-322 and its metabolite M-I

Mean plasma concentration of SYR-322 and metabolite M-I are shown in Figure 43 and Figure 44, respectively. The effects of multiple doses of ketoconazole on the PK of SYR-322 and metabolite M-I in plasma are shown in Table 69 and listed as follows:

- GMR of plasma AUC(0-inf) of SYR-322 had 15.4% increased and the 90% CI ranged form 110.99% to 119.97%.
- GMR of plasma Cmax of SYR-322 decreased by 22.04% and the 90% CI ranged from 109.55% to 135.94%.
- GMR of plasma AUC(0-inf) of metabolite M-I had an increase of 0.65% and the 90% CI were 88.30% to 114.74%.
- GMR of plasma Cmax of metabolite M-I had an increase of 36.2% and the 90% were from 123.42% to 150.24%.

Figure 43 **Mean plasma concentration of SYR-322 in healthy subjects following a single oral dose of SYR-322 25 mg alone on Day 1 and coadministration with ketoconazole 400 mg QD at Day 11 after pretreatment with ketoconazole from Days 5 to 10.**

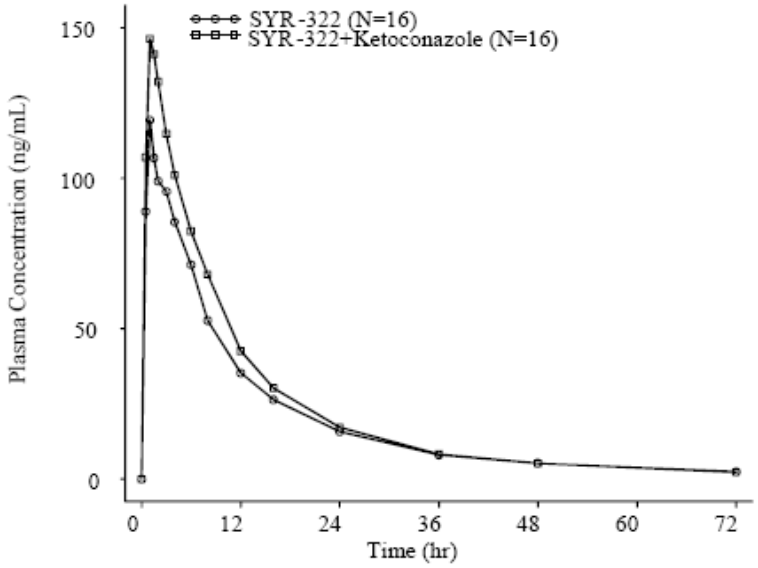


Figure 44 **Mean plasma concentration of SYR-322 metabolite M-I in healthy subjects following a single oral dose of SYR-322 25 mg alone on Day 1 and coadministration with ketoconazole 400 mg QD at Day 11 after pretreatment with ketoconazole from Days 5 to 10.**

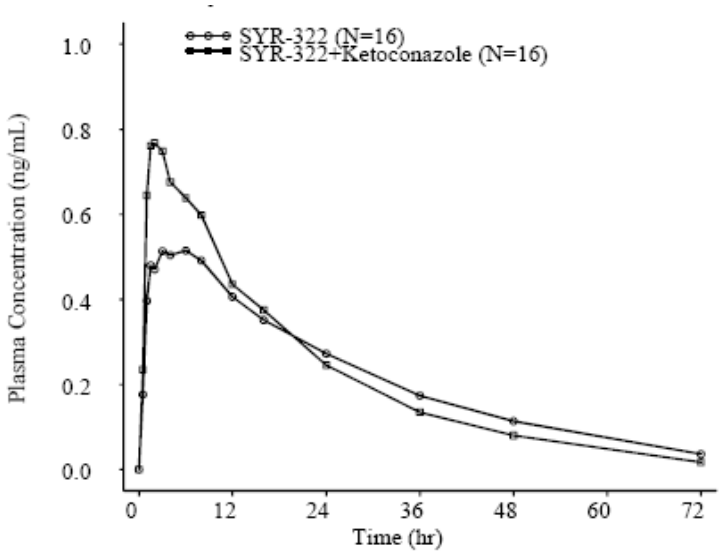


Table 69 **PK parameters of SYR-322 and metabolite M-I in healthy subjects following a single oral dose of SYR-322 25 mg alone on Day 1 and coadministration with ketoconazole 400 mg QD at Day 11 after pretreatment with ketoconazole from Days 5 to 10.**

Parameter, units	Geometric Mean (a)		Geometric Mean Ratio (T/R)*100 (%)	90% CI for Ratio
	SYR-322 25 mg + Ketoconazole 400 mg Day 11 (T)	SYR-322 25 mg Alone Day 1 (R)		
SYR-322 (n=16)				
AUC(0-inf), ng·hr/mL	1714.21	1485.55	115.39	(110.99, 119.97)
AUC(0-tlqc), ng·hr/mL	1651.05	1413.86	116.78	(112.35, 121.38)
Cmax, ng/mL	158.70	130.04	122.04	(109.55, 135.94)
Tmax, hr (a) (b)	1.00	1.25	---	---
SYR-322 M-I (n=15)				
AUC(0-inf), ng·hr/mL (c)	27.37	27.19	100.65	(88.30, 114.74)
AUC(0-tlqc), ng·hr/mL	11.94	11.15	106.99	(95.31, 120.11)
Cmax, ng/mL	0.74	0.54	136.17	(123.42, 150.24)
Tmax, hr (a) (b)	2.00	3.00	---	---

Source: Table 15.2.1.4.
T=test treatment; R=reference treatment.
(a) Medians are reported for Tmax.
(b) P=0.152 for SYR-322 and P=0.097 for SYR-322 M-I, based on Wilcoxon signed rank test.
(c) n=3.

3. Effect of gemfibrozil on PK of SYR-322 and its metabolite M-I

Mean plasma concentration of SYR-322 and metabolite M-I are shown in Figure 45 and Figure 46, respectively. The effects of multiple doses of gemfibrozil on the PK of SYR-322 and metabolite M-I in plasma are shown in Table 70 and listed as follow:

- GMR of plasma AUC(0-inf) of SYR-322 had an increased of 12.9% and the 90% CI were from 109.20% to 116.69%.
- GMR of plasma Cmax of SYR-322 had a decreased of 15.3% and the 90% CI were from 110.72% to 118.64%.
- GMR of plasma AUC(0-inf) of metabolite M-I had an increase of 91.1% and the 90% CI were from 164.78% to 221.71%.
- GMR of plasma Cmax of metabolite M-I had an increase of 72.6% and the 90% CI were from 157.10% to 189.73%.

Figure 45 **Mean plasma concentration of SYR-322 in healthy subjects following a single oral dose of SYR-322 25 mg alone on Day 1 and coadministration with gemfibrozil 600 mg BID at Day 11 after pretreatment with gemfibrozil from Days 5 to 10.**

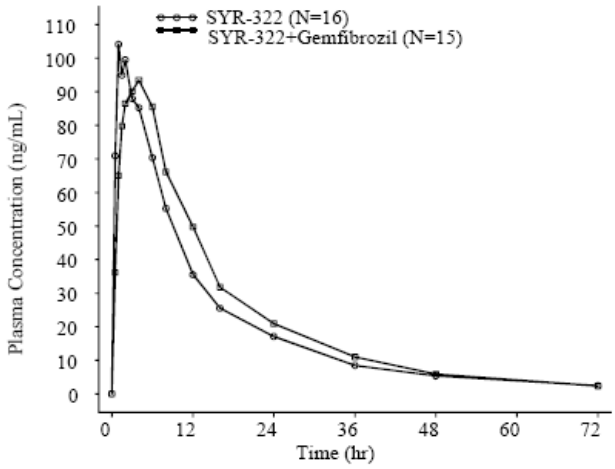


Figure 46 **Mean plasma concentration of SYR-322 metabolite M-I in healthy subjects following a single oral dose of SYR-322 25 mg alone on Day 1 and coadministration with gemfibrozil 600 mg BID at Day 11 after pretreatment with gemfibrozil from Days 5 to 10.**

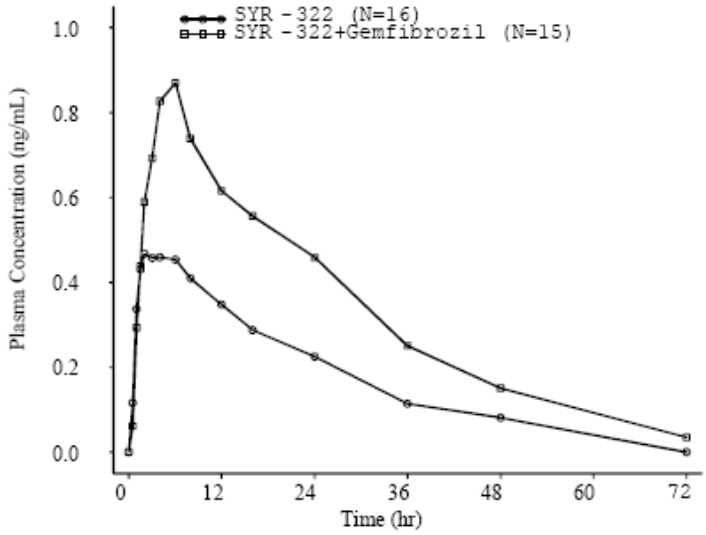


Table 70 **PK parameters of SYR-322 and metabolite M-I in healthy subjects following a single oral dose of SYR-322 25 mg alone on Day 1 and coadministration with gemfibrozil 600 mg BID at Day 11 after pretreatment with gemfibrozil from Days 5 to 10.**

Table 11.k Statistical Analysis of Plasma Pharmacokinetic Parameters for SYR-322 and its Metabolite M-I After Administration of SYR-322 With and Without Gemfibrozil

Parameter, units	Geometric Mean (a)		Geometric Mean Ratio (T/R)*100 (%)	90% CI for Ratio
	SYR-322 25 mg+ Gemfibrozil 600 mg BID Day 11 (T)	SYR-322 25 mg Alone Day 1 (R)		
SYR-322 (n=14)				
AUC(0-inf), ng·hr/mL	1665.52	1475.45	112.88	(109.20, 116.69)
AUC(0-tlqc), ng·hr/mL	1610.74	1405.41	114.61	(110.72, 118.64)
Cmax, ng/mL	105.66	124.70	84.74	(73.30, 97.96)
Tmax, hr (a) (b)	3.50	1.50	---	---
SYR-322 M-I (n=12)				
AUC(0-inf), ng·hr/mL (c)	42.07	22.01	191.14	(164.78, 221.71)
AUC(0-tlqc), ng·hr/mL	21.36	9.27	230.37	(189.34, 280.28)
Cmax, ng/mL	0.89	0.52	172.64	(157.10, 189.73)
Tmax, hr (a) (b)	6.00	3.00	---	---

Source: Table 15.2.1.5.
T=test treatment; R=reference treatment.
(a) Medians are reported for Tmax.
(b) P=0.047 for SYR-322 and P=0.129 for SYR-322 M-I, based on Wilcoxon signed rank test.
(c) n=3.

Reviewer's conclusions:

- The study results suggested that there is no significant difference in the extent of exposure of SYR-322 in subjects receiving coadministration of a single oral dose SYR-322 25 mg and 200 mg fluconazole or 400 mg ketoconazole or 600 mg gemfibrozil as compared to those receiving a single oral dose of SYR-322 25 mg alone.
- Multiple doses fluconazole, ketoconazole and gemfibrozil had no effect on the extent of absorption of SYR-322 as the point estimate in AUC(0-inf) ranged from 99.13% to 115.39% (100% reflects no change) and the 90% CI were all within 80% to 125% bound.
- Subjects receiving multiple doses of fluconazole had a reduction of 19.57% in the rate of absorption (Cmax) of SYR-322, and the 90% CI ranged from 70.10% to 92.28%. The Cmax is highly variable due to the small sample size. Combining no change in AUC0-inf and 19.57% reduction in Cmax, multiple doses of fluconazole may not have significant impact on the PK of SYR-322.
- Subjects receiving multiple doses of ketoconazole had an increase of 22.04% in Cmax of SYR-322 and the 90% confidence intervals ranged from 109.55% to 135.94%. The sample size is small and plasma concentration around Cmax is highly variable. Considering a 15% increase of AUC0-inf and 22.04% increase in

Cmax, it appeared that multiple doses of ketoconazole may not have significant impact on the PK of SYR-322.

Reviewer's comments:

- Though metabolite M-I has DPP-4 inhibitory activity similar to SYR-322, its plasma concentration is approximately 0.5% of the SYR-322. Thereby the changes in metabolite M-I exposure in plasma is unlikely to have clinical significance and the results are listed for information only.
  - Subjects receiving combination of SYR-322 and fluconazole as compared to those receiving SYR-322 alone had:
    - 18.75% increase in AUCinf of SYR-322 M-1 (90% CI was 101.03% to 139.57%).
    - 22.59% increase in AUCt of SYR-322 M-1 (90% CI was 104.72% to 143.52%).
    - 16.21% increase in Cmax of SYR-322 M-1 (90% CI was 105.93% to 127.48%).
  - Subjects receiving combination of SYR-322 and ketoconazole as compared to those receiving SYR-322 alone had:
    - 0.65% increase in AUCinf of SYR-322 M-1 (90% CI was 88.30% to 114.74%).
    - 6.99% increase in AUCt of SYR-322 M-1 (90% CI was 95.31% to 120.11%).
    - 36.17% increase in Cmax of SYR-322 M-1 (90% CI was 123.42% to 150.24%).
  - Subjects receiving combination of SYR-322 and gemfibrozil as compared to those receiving SYR-322 alone had:
    - 91.14% increase in AUCinf of SYR-322 M-1 (90% CI was 164.78% to 221.71%).
    - 130.37% increase in AUCt of SYR-322 M-1 (90% CI was 189.34% to 280.28%).
    - 72.64% increase in Cmax of SYR-322 M-1 (90% CI was 157.10% to 189.73%).

- Dose of fluconazole at 200 mg, ketoconazole at 400 mg and gemfibrozil at 600 mg were selected in this drug-drug interaction study. They are within the therapeutic dose ranges recommended by the manufacturer's prescribing guideline.
- The terminal elimination half life of fluconazole, ketoconazole and gemfibrozil were 30, 8 and 15 hours, respectively. Thereby the plasma concentration of these drugs would most likely reach steady state after once daily dosing for 6 days. The study design is acceptable.

- The half life of SYR-322 is approximately 21 hours. Thereby at the time of SYR-322 administration on day 11, most drugs should be eliminated already.

4.2.21 Study SYR-322-020: A Phase 1, Randomized, Open-Label, Single-Dose, Crossover Study to Determine the Effect of Cyclosporine (Neoral®) on the Pharmacokinetics of SYR-322 in Healthy Male Subjects

NDA; 22-271/Study 020	Study date: June 2006 – July 2007
A Phase 1, Randomized, Open-Label, Single-Dose, Crossover Study to Determine the Effect of Cyclosporine (Neoral®) on the Pharmacokinetics of SYR-322 in Healthy Male Subjects	

Background:

SYR-322 is excreted mainly be the kidneys, with 60% to 71% of the dose excreted as unchanged SYR-322 in urine. Renal clearance of SYR-322 exceeded the glomerular filtration rate, indicating that SYR-322 was also cleared by active renal tubular secretion. In SYR-322-015 study, it was found that administration of SYR-322 100 mg QD for 7 days resulted in a slight increase in plasma exposure and urinary excretion of fexofenadine, a P-glycoprotein (Pgp) substrate.

In this study, the sponsor evaluated the in vivo Pgp inhibitory effect by cyclosporine on the pharmacokinetics of SYR-322 and its metabolite M-I. Cyclosporine is a potent immunosuppressant that is used to prevent organ rejection after transplantation. Cyclosporine is also a Pgp inhibitor and may have impact on the renal clearance of SYR-322 through its Pgp inhibition.

Objectives:

1. To determine the effect of a single dose of cyclosporine (Neoral®) 600 mg on the pharmacokinetics of a single dose of SYR-322 25 mg.

2. To evaluate the safety and tolerability of a single dose of SYR-322 25 mg when administered alone and with cyclosporine 600 mg.

Study Design:

This was a phase I, randomized, open-label, single-dose, 2-sequence, 2-period, crossover, drug interaction study to evaluate the effect of a single dose of cyclosporine on the single-does pharmacokinetics of SYR-322 and its metabolite M-I in 24 (total) healthy subjects. A 13 days washout period separated the following 2 randomized treatment periods:

Treatment A: Subjects received orally a single dose of SYR-322 25 mg (reference treatment).

Treatment B: Subjects received orally a single dose of SYR-322 25 mg and a single dose of cyclosporine 600 mg (test treatment).

Serial plasma samples were collected post dose for the determination of plasma drug concentration of SYR-322 and PK analysis was conducted using noncompartmental analysis.

Subjects received a standardized diet containing approximately 30% fat during the time of their confinement in the study center. The diet included 3 meals and an optional snack. The study dose was administered orally with 240 mL of water in the morning after at least 8 hour fast. Subjects were required to continue fasting for 1 hour post dose.

Blood samples were collected at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 28, 32, 36, 48, and 72 hours post dose for the determination of SYR-322, SYR-322-M-I, and cyclosporine.

Urine samples were collected from the intervals of -12 to 0 hour, 0-24, 24-48, and 48-72 hours for the determination of SYR-322 and SYR-322 M-I.

Results:

Figure 47 **Average plasma concentration of SYR-322 following a single oral dose of SYR-322 25 mg alone or in coadministration with a single dose of 600 mg cyclosporine in healthy male subjects**

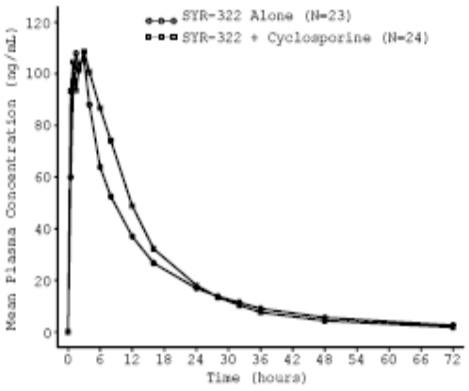


Figure 48 **Average plasma concentration of SYR-322 metabolite M-I following a single oral dose of SYR-322 25 mg alone or in coadministration with a single oral dose of 600 mg cyclosporine in healthy male subjects.**

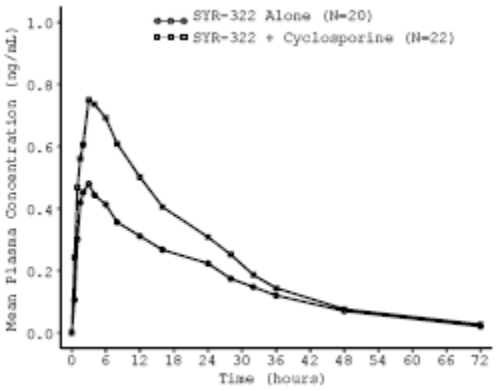


Table 71 provides the summary statistics and geometric mean ratios (GMRs) for the PK parameters of SYR-322 and its metabolite M-I in healthy male volunteers receiving single dose of SYR-322 25 mg alone and in coadministration of a single dose cyclosporine 600 mg. The 90% confidence interval (CI) of GMR (SYR-322 + Cyclosporine/SYR-322) for plasma or urine exposure of SYR-322 and its metabolite M-I are evaluated, with the effect boundary set at the 80-125% for 90% CI of GMR according to the Draft Drug interaction Guidance.

SYR-322

- Plasma AUC(0-48) and Cmax of SYR-322 had 13.2% and 5.4% increase in GMR.
- Ae(0-48) (urinary accumulation from 0-48 hours) of SYR-322 increased 8.1%; while CLr (renal clearance) decreased 4.5%.

SYR-322 M-I

- Plasma AUC(0-48) and Cmax of SYR-322 M-I had 47% and 54% increase in GMR, respectively.
- Ae(0-48) of SYR-322 M-I increased 19.8%; while CLr decreased 4.8%.

Table 71 **PK parameters of SYR-322 and metabolite M-I following a single oral dose of SYR-322 25 mg alone or in coadministration with a single dose of 600 mg cyclosporine in healthy male subjects.**

	LS Means of SYR-322 and Its Metabolite M-I		
Parameter (units)	SYR-322 25 mg + Cyclosporine 600 mg (T)	SYR-322 25 mg (R)	Ratio T/R·100 (90% CI) (a)
SYR-322 Plasma	n=24 (b)	n=23	
AUC(0-48) (ng·hr/mL)	1515.42	1338.76	113.20 (104.12, 123.06)
Cmax (ng/mL)	127.87	121.38	105.35 (95.13, 116.65)
Tmax (hr) (c,d)	1.00	1.50	—
SYR-322 Urine	n=24	n=23	
Ae(0-48) (mg)	14.90	13.79	108.11 (95.35, 122.59)
CLr(0-48) (L/hr)	9.83	10.30	95.46 (86.59, 105.23)
Fe(0-48) (%)	59.61	55.14	108.11 (95.35, 122.59)
SYR-322 M-I Plasma	n=22 (e)	n=20	
AUC(0-48) (ng·hr/mL)	12.23	8.31	147.24 (129.99, 166.79)
Cmax (ng/mL)	0.68	0.44	154.40 (137.57, 173.29)
Tmax (hr) (c,f)	3.00	2.00	—
SYR-322 M-I Urine	n=24 (g)	n=23 (h)	
Ae(0-48) (mg)	0.15	0.13	119.76 (91.88, 156.11)
CLr(0-48) (L/hr)	15.69	16.48	95.20 (86.11, 105.25)

T=test treatment=Treatment B, R=reference treatment=Treatment A, — =not applicable.
(a) Ratios and confidence intervals are presented as percentages.
(b) n=23 for Tmax.
(c) Tmax is presented as median (minimum, maximum).
(d) P=0.893 for Tmax.
(e) n=20 for Tmax.
(f) P=0.033 for Tmax
(g) n=22 for CLr(0-48).
(h) n=20 for CLr(0-48).

Conclusions:

- Cyclosporin does not have significant impact on the plasma pharmacokinetics of SYR-322.
- Cyclosporin seems to have no effect on urinary clearance of SYR-322.
- Cyclosporin increased the exposure to metabolite of SYR-322 M-I (AUC and Cmax increase approximately 50%), however it is unlikely to have any clinical impact as exposure to SYR-322 M-I is only at 0.5% to 1% as compared to that of SYR-322.

Reviewer's comments:

- The study results suggested that there is no significant difference in the plasma or urine SYR-322 exposure in subjects receiving coadministration of a single oral dose SYR-322 25 mg and 600 mg cyclosporine as compared to those receiving a single oral dose of SYR-322 25 mg alone.
- The results suggested that cyclosporine increase the plasma AUC(0-48) and Cmax metabolite M-I (a N-demethylated metabolite of SYR-322) by 47% and 54%, respectively. Though metabolite M-I has DPP-4 inhibitory activity similar to SYR-322, its plasma concentration was approximately 0.5% of the SYR-322.

Thereby the increase of metabolite M-I exposure in plasma is unlikely to have clinical significance.

- 25 mg is the highest SYR-322 dose being evaluated in the phase 3 study and in the NDA application. Cyclosporine 600 mg is approximate maximum therapeutic dose. Thereby it is appropriate to select the 25 mg SYR-322 and 600 mg cyclosporine for this drug-drug study.
- The terminal elimination half-lives for SYR-322 and cyclosporine are 16-18 hour and 8.4 hours, respectively. Thereby it is adequate to use the 13 days washout between the two treatment periods. The plasma and urine sampling schemes are adequate for the study.

4.2.22 Study SYR-322-026: An Open-label, Randomized, Crossover Study to Determine the Effect of Food on the Pharmacokinetics of SYR-322 in Healthy Male and Female Subjects

NDA22271, SYR-322/026 Study date January 11 to January 30 2007
An Open-label, Randomized, Crossover Study to Determine the Effect of Food on the Pharmacokinetics of SYR-322 in Healthy Male and Female Subjects

Background: SYR-322 is a DPP4 (dipeptidyl peptidase 4) inhibitor developed by Takeda pharmaceutics. After food intake, glucagon-like peptide 1 (GLP-1) is secreted into blood stream from the gastrointestinal tract. GLP-1 plays important role in the metabolism of sugar, and enhances secretion of insulin. Inhibition of DPP4 by SYR-322 will enhance the secretion of insulin and maintains blood concentration of GLP-1. In this study, the effect of food on the pharmacokinetics of SYR-322 is investigated.

Objectives: To assess the effect of food on the safety and pharmacokinetics of SYR-322 after a single oral dose administration of 25 mg SYR-322.

Methodology: This is a single-center, open-label, randomized 2-period, 2-way crossover study to evaluate the effect of food on the PK of SYR-322. Subjects were randomized to 1 of 2 treatment sequence and received a single oral dose of 25 mg SYR-322 under the fast (reference treatment) and fed (test treatment) conditions. In the second period, subjects received the alternate treatment. There was a 7-day washout between the two periods. All subjects received the study drug with 240 mL of water.

Table 9.c Treatments Administered

Sequence	Period 1	Period 2
AB	SYR-322 25 mg fasted	SYR-322 25 mg fed
BA	SYR-322 25 mg fed	SYR-322 25 mg fasted

A=reference treatment, B=test treatment.

In the fast condition, subjects were fasted overnight (more than 10 hours) prior to dosing and remained fasting for 4 hours after dose of SYR-322. Under the fed conditions, subjects fasted for 10 hours prior to consuming a high-fat and high-calorie meal and subsequent dosing 30 minutes later.

24 male and female subjects received treatment drug and all 24 subjects completed the study.

Food content for the breakfast: Subjects were provided a standard high-fat meal that was consumed within 30 minutes. Subjects received the SYR-322 dose immediately after completing the meal. The standard high-fat meal consists 2 eggs (fried in butter), 2 strips of beacon, slices of toast with butter, 4 oz of hash brown potatoes (fried with butter), and 8 oz (240 mL) of whole milk.

Study drug: SYR-322 25 mg oral tablet, Lot Z6419021.

Inclusion criteria: Healthy male and female of childbearing potential agreeing to use adequate contraception, age 19 to 55, inclusive, BMI within 18 to 32.

Exclusion criteria:

- The subjects who had previous exposure to SYR-322.
- The subjects who had a history of hypersensitive to SYR-322-related compounds.
- The subjects consumed alcohol-related product, Seville orange or orange juice, grapefruit or grapefruit juice, caffeine projects or vitamin supplements within 72 hours prior to Baseline/Check-in.
- The subjects used prescription medication, OTC medication, or herbal preparations within 14 days prior to dosing.
- The subjects used tobacco-containing products within 6 weeks prior to Baseline/Check-in.

PK sampling: Blood samples were collected at pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours post dose. Urine samples were collected at the interval of predose (-12 to 0 hour) and at 0 to 24 hours post dose.

Plasma sample analysis: Plasma samples were processed using protein precipitation and then analyzed using a validated LC/MS/MS method.

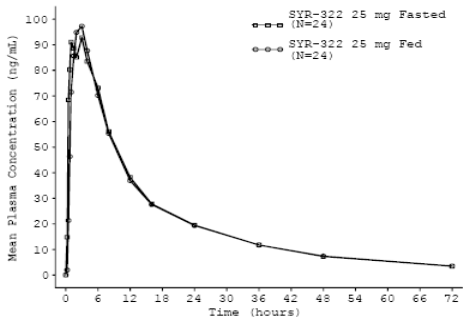
PK analysis: Noncompartmental analysis (NCA) was applied in the determination of the PK parameters of SYR-322, such as AUC, Cmax, Tmax, T/12, CL/F and λz. Cumulative urinary excretion from 0 to 24 hours was determined. Renal clearance and fraction of drug excreted in urine were calculated.

Statistical analysis: Descriptive statistics were used to summarize the PK parameters under both fast and fed conditions. To assess the food effect on single-dose PK of SYR-322, ANOVA was performed on the log-transformed plasma PK parameters of AUCinf, AUC0-72, AUCt and Cmax of SYR-322. If the two-sided 90% confidence interval of AUCinf and Cmax for the difference between fed and fast conditions falls within 80% to 125%, the presence of a food effect will be excluded.

Results: All 24 subjects completed this study. Geometric mean ratios (GMR) and 90% CI of AUC and Cmax of SYR-322 were summarized in Table 72. The results are summarized. The mean plasma concentration of the 24 subjects was illustrated in Figure 49. The renal clearance results were listed in Table 73.

- GMR of AUCinf of SYR-322 was reduced by 1.06% and the 90% CI ranged from 97.28% to 100.63% (Table 72).
- GMR of Cmax of SYR-322 increased by 3.41% and the 90% CI ranged from 92.38% to 115.75% (Table 72).
- The median Tmax was at 1.508 and 1.983 hours under the fast and fed conditions, respectively (Table 72).
- The renal clearance of SYR-322 was 10.597 and 10.414 L/hr under the fast and fed conditions, respectively (Table 73).

Figure 49 **Mean plasma concentration of SYR-322 after a single oral dose of 25 mg SYR-322 under fast or fed conditions.**



To summarize, in this pivotal food effect study, food did not have significant impact on the rate and extent of oral absorption of SYR-322, as both the 90% CI of GMR of AUCinf and Cmax fell within the range of 80% to 125%. Food had no effect on the cumulative urinary secretion of SYR-322 and renal clearance either.

Table 72 **Geometric means ratios and 90% CI of AUC and Cmax of SYR-322 in subjects receiving a single oral dose of 25 mg SYR-322 under fast and fed conditions.**

Parameter (unit)	N: Fed State (a) (Test - B)	N: Fasted State (a) (Reference - A)	Least Squares Means: Fed State (a) (Test - B)	Least Squares Means: Fasted State (a) (Reference - A)	Mean Ratio (100*Test/ Reference)	90% CI For Ratio	P-value for Treatment Difference
AUC(0-24) (ng*hr/mL)	24	24	1073.0837	1099.6100	97.59	(95.00 , 100.25)	0.134
AUC(0-tlqc) (ng*hr/mL)	24	24	1502.8182	1526.6951	98.44	(96.65 , 100.26)	0.154
AUC(0-inf) (ng*hr/mL)	24	24	1609.8343	1627.0067	98.94	(97.28 , 100.63)	0.294
Cmax (ng/mL)	24	24	114.014	110.256	103.41	(92.38 , 115.75)	0.615
Tmax (hr) (b)	24	24	1.983	1.508			0.934

NOTE: The statistical analysis was performed using an ANOVA model with terms for treatment, period, sequence, and subject(sequence), where subject(sequence) was a random effect while other factors were fixed effects for log transformed values of AUC(0-24), AUC(0-tlqc), AUC(0-inf), and Cmax. Least squares means, ratios, and confidence intervals (CIs) were reported in original scale. Analysis of Tmax was performed using Wilcoxon's signed rank test.
(a) Treatment A = SYR-322 25 mg under fasted conditions; Treatment B = SYR-322 25 mg under fed conditions.
(b) Median values were reported for Tmax.

Table 73 **PK parameters and summary statistics for SYR-322 after a single oral dose of 25 mg SYR-322 under fast or fed conditions.**

Table 15.2.1.2
Summary of Plasma Pharmacokinetic Parameters of SYR-322

Pharmacokinetic Set

Parameter (unit)	Treatment	%CV	Median	Minimum	Maximum
AUC(0-24)	SYR-322 25 mg Fasted	16.4802	1064.4946	765.0508	1560.1750
(ng*hr/mL)	SYR-322 25 mg Fed	14.0569	1081.6167	707.0958	1409.5562
AUC(0-tlqc)	SYR-322 25 mg Fasted	14.9957	1550.9453	1160.7678	2099.7728
(ng*hr/mL)	SYR-322 25 mg Fed	13.7783	1548.1613	1082.4293	2023.1449
AUC(0-inf)	SYR-322 25 mg Fasted	15.8948	1659.2797	1246.5568	2249.3806
(ng*hr/mL)	SYR-322 25 mg Fed	15.4085	1624.4048	1169.1235	2235.6543
Cmax	SYR-322 25 mg Fasted	32.181	108.500	67.000	194.000
(ng/mL)	SYR-322 25 mg Fed	25.093	114.500	75.700	201.000
Tmax	SYR-322 25 mg Fasted	58.072	1.508	0.517	4.017
(hr)	SYR-322 25 mg Fed	53.105	1.983	0.483	4.000
Lambda_z	SYR-322 25 mg Fasted	16.02527	0.03631	0.02294	0.04805
(1/hr)	SYR-322 25 mg Fed	17.78684	0.03603	0.02021	0.04459
T1/2	SYR-322 25 mg Fasted	17.842	19.090	14.426	30.213
(hr)	SYR-322 25 mg Fed	21.485	19.246	15.545	34.298
CL/F	SYR-322 25 mg Fasted	15.52809	15.06682	11.11417	20.05524
(L/hr)	SYR-322 25 mg Fed	14.93414	15.39049	11.18241	21.38354

Table 74 **Summary statistics of cumulative urinary excretion and renal clearance of SYR-322 after a single oral dose of 25 mg SYR-322 under fast and fed conditions.**

Table 15.2.1.5
Summary of Urine Pharmacokinetic Parameters of SYR-322

Pharmacokinetic Set

Parameter (unit)	Treatment	N	Mean	SE	SD	%CV	Median	Minimum	Maximum
Ae(0-24)	SYR-322 25 mg Fasted	24	11.598	0.5515	2.7018	23.295	11.952	3.922	15.708
(mg)	SYR-322 25 mg Fed	24	11.136	0.6189	3.0319	27.226	12.459	5.238	15.560
CLr(0-24)	SYR-322 25 mg Fasted	24	10.597	0.5208	2.5512	24.075	11.088	3.926	14.657
(L/hr)	SYR-322 25 mg Fed	24	10.414	0.5802	2.8423	27.294	10.860	4.512	14.211
Fe(0-24)	SYR-322 25 mg Fasted	24	46.393	2.2060	10.8073	23.295	47.809	15.688	62.832
(%)	SYR-322 25 mg Fed	24	44.545	2.4755	12.1276	27.226	49.835	20.950	62.240

Conclusion: In this pivotal food effect study, food has no significant impact on the rate and extent of oral absorption of SYR-322 in healthy volunteers receiving a single oral dose of 25 mg SYR-322.

Reviewer's Comments:

- A single oral dose of 25 mg SYR-322 was anticipated to be the maximum therapeutic dose for this drug. It has been proved to be safe and tolerable in multiple clinical studies in healthy subjects and patients with type 2 diabetic mellitus. The selection of 25 mg in this food effect study is acceptable.
- The sponsor applied the standard high-fat meal specified by the FDA guidance, which is acceptable.
- The exclusion and inclusion criteria were adequate.
- The terminal elimination half life of SYR-322 was approximately 19 to 20 hours under the fast and fed conditions. The 7-day washout period was appropriate. The plasma sample collection up to 72 hours was acceptable for the determination of terminal half life of SYR-322 as it covers 3 to 4 half-lives of the drug.

- The variation of Cmax was approximately 32% and 25% under the fast and fed conditions. Data from this study suggested that food has no effect on the rate of absorption of SYR-322.
- Cumulative urinary excretion of SYR-322 from 0 to 24 hours was 46%, which underestimation of fraction of dose excreted by urine (fe) due to insufficient urine collection time. Previous clinical studies showed that the urinary excretion approached completion approximately from 48 to 72 hours post dose.
- The sponsor validated a LC/MS/MS method for the determination of SYR-322 and its two metabolites in plasma samples. Plasma samples were processed with protein precipitation for clean up. The method was validated with regard to specificity, linearity, inter and intra day precision and accuracy, stability, dilution reproducibility and extraction recovery (from validation report).
    - The linear calibration range is from 1 to 1000 ng/mL for SYR-322
    - The daily precision of the assay for SYR-322 ranges from 2.0% to 9.0% and the accuracy is from -2.8% to 10.0%. (see table 4)
    - SYR-322 is stable after three repeated thaw and freeze, for at least 3 months storing in -20 °C freezers.
- During the plasma sample analysis for this food effect study, the calibration standards and QC samples were mostly within the specified range (Tables 5 and 6), demonstrating acceptable inter-day precision and accuracy (from bioanalytical study report).

Table 75 Precision and accuracy of the LC/MS/MS assay for the determination of plasma SYR-322 concentration.

Table 5 Precision and accuracy of SYR-322Z

Assay day		Concentration levels (ng/mL)			
	Nominal	1	2.5	50	800
1	Observed	1.00	2.53	55.3	805
		0.985	2.44	53.8	833
		1.01	2.53	53.0	763
		0.993	2.38	50.3	766
		1.05	2.50	48.5	837
	Mean	1.01	2.48	52.2	801
	SD	0.03	0.07	2.7	35
	CV(%)	3.0	2.8	5.2	4.4
	RE(%)	1.0	-0.8	4.4	0.1
2	Observed	1.13	2.42	48.0	769
		1.11	2.52	51.8	749
		1.05	2.51	48.7	814
		1.09	2.52	46.3	822
		1.14	2.44	48.3	792
	Mean	1.10	2.48	48.6	789
	SD	0.04	0.05	2.0	31
	CV(%)	3.6	2.0	4.1	3.9
	RE(%)	10.0	-0.8	-2.8	-1.4
3	Observed	1.10	2.56	50.7	796
		0.968	2.38	54.4	822
		1.00	2.46	51.7	768
		0.883	2.40	51.8	816
		1.07	2.43	52.9	815
	Mean	1.00	2.45	52.3	803
	SD	0.09	0.07	1.4	22
	CV(%)	9.0	2.9	2.7	2.7
	RE(%)	0.0	-2.0	4.6	0.4
Mean		1.04	2.47	51.0	798
SD		0.06	0.02	2.1	8
CV(%)		5.8	0.8	4.1	1.0
RE(%)		4.0	-1.2	2.0	-0.3

Table 76 **Summary of calibration standards during the plasma sample analysis for the SYR-322/026 study.**

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Run ID	CAL 1 (ng/mL)	CAL 2 (ng/mL)	CAL 3 (ng/mL)	CAL 4 (ng/mL)	CAL 5 (ng/mL)	CAL 6 (ng/mL)	CAL 7 (ng/mL)	CAL 8 (ng/mL)	CAL 9 (ng/mL)	CAL 10 (ng/mL)
1AIR-A-1	1.04	2.73	5.28	10.9	25.4	52.9	104	283	512	956
	0.945	2.33	4.59	9.53	24.0	49.8	94.5	252	453	921
2AIR-A-1	1.03	2.69	5.43	10.9	26.7	52.9	108	275	539	1010
	0.952	2.36	4.78	9.16	23.5	47.9	94.7	232	457	868
3AIR-A-1	1.05	2.57	5.17	10.2	25.0	51.2	103	268	527	980
	0.957	2.39	4.84	9.73	24.3	50.0	103	250	458	931
4AIR-A-1	1.01	2.55	5.16	10.1	25.8	50.1	104	257	494	942
	0.979	2.46	5.02	10.3	25.5	51.8	99.0	250	468	918
5AIR-A-1	1.05	2.47	5.03	9.97	25.6	50.3	101	258	501	939
	0.947	2.55	4.95	10.2	24.8	50.8	99.7	256	505	932
6AIR-A-1	0.978	2.59	5.44	10.7	26.1	52.2	100	249	499	937
	0.986	2.51	4.84	10.0	24.2	52.8	96.5	245	482	909
7AIR-A-1	0.984	2.55	4.94	10.3	25.3	51.6	101	250	500	969
	1.00	2.52	5.04	9.81	25.4	51.0	101	252	495	911
8AIR-A-1	e	e	5.07	10.4	25.0	51.0	96.4	245	484	955
	0.979	2.51	5.25	10.3	25.0	50.7	101	257	501	938
N	15	15	16	16	16	16	16	16	16	16
Theoretical Concentration	1.00	2.50	5.00	10.0	25.0	50.0	100	250	500	1000
Mean	0.993	2.52	5.05	10.2	25.1	51.1	101	255	492	938
S.D.	0.0367	0.109	0.232	0.474	0.809	1.33	3.71	12.2	24.5	32.2
%C.V.	3.69	4.34	4.60	4.66	3.22	2.60	3.69	4.77	4.97	3.43
% Difference from Theoretical	-0.744	0.694	1.06	1.62	0.432	2.14	0.539	1.98	-1.55	-6.17

Table 77 **Inter-assay precision and accuracy during the plasma sample analysis for the SYR-322/026 study.**

Table 5. Inter-assay Precision and Accuracy for SYR-322

Report 1275879

Run ID	QC 1 (ng/mL)	QC 2 (ng/mL)	QC 3 (ng/mL)	QC 4 (ng/mL)	QC 5 (ng/mL)
1AIR-A-1	2.64	20.4	51.5	293	779
	2.49	20.6	51.0	294	786
	2.64	20.6	53.4	300	764
	2.36	18.1	47.1	285	691
	2.44	18.5	47.7	284	706
	2.46	18.9	46.1	277	712
2AIR-A-1	d	20.8	52.9	316	827
	2.35	18.2	44.5	259	668
3AIR-A-1	2.56	22.9	53.2	328	781
	2.43	22.2	50.6	296	728
4AIR-A-1	2.53	22.2	54.9	310	757
	2.62	22.2	55.4	306	770
5AIR-A-1	2.61	20.3	49.6	304	792
	2.61	20.7	49.2	291	759
6AIR-A-1	2.58	20.7	50.6	305	770
	2.47	20.2	49.6	293	735
7AIR-A-1	2.67	20.8	51.7	307	766
	2.45	19.8	50.8	292	750
8AIR-A-1	2.59	20.7	50.9	290	753
	2.54	20.2	50.5	295	782
N	19	20	20	20	20
Theoretical Concentration	2.50	20.0	50.0	300	800
Mean	2.53	20.4	50.6	296	754
S.D.	0.0966	1.33	2.78	14.7	37.8
%C.V.	3.82	6.50	5.49	4.97	5.02
% Difference from Theoretical	1.14	2.24	1.12	-1.28	-5.77
Low Limit	2.13	17.0	42.5	255	680
High Limit	2.88	23.0	57.5	345	920

4.2.23 Study SYR-322-CPH006: Randomized, Open-label Cross-over Study to Assess the Effect of Food on the Safety, Tolerability and Pharmacokinetics of Single-dose SYR-322 in Healthy Male Subjects

NDA22271, SYR-322/CPH006 Study date September 7 to October 6 2006
Randomized, Open-label Cross-over Study to Assess the Effect of Food on the Safety, Tolerability and Pharmacokinetics of Single-dose SYR-322 in Healthy Male Subjects

This phase 1 study was conducted in Japan and the sponsor used SYR-322Z in the study report. SYR-322Z stands for the Z isomer of SYR-322, which is the same compound as SYR-322 in the other clinical study reports.

Background: SYR-322 is a DPP4 (dipeptidyl peptidase 4) inhibitor developed by Takeda pharmaceutics. After food intake, glucagon-like peptide 1 (GLP-1) is secreted into blood stream from the gastrointestinal tract. GLP-1 plays important role in the metabolism of sugar, and enhances secretion of insulin. Inhibition of DPP4 will enhance the secretion of insulin and maintains blood concentration of GLP-1.

Objectives: To assess the effect of food on the safety, tolerability and pharmacokinetics of SYR-322 after a single oral dose administration of 50 mg SYR-322.

Methodology: This study applied a 2-period, 2-way crossover design. All subjects received a single oral dose of 50 mg SYR-322 with 150 mL of water under the fast (overnight fast for at least 10 hours) or fed (30 minutes after starting of breakfast) conditions in period 1. In period 2, all subjects received 50 mg SYR-322 under alternative conditions (fasted/fed). In the fast condition, subjects were instructed to remain fasting for 4 hours after dose of SYR-322. There was a 7-day washout between the two periods. 10 Japanese male subjects received treatment drug and 9 completed the study.

Food content for breakfast: The breakfast **(**15.9 g protein, 23.2 g fat, 90.2 g carbohydrate: energy ratio: 10.5%, 33.8%, 55.7% respectively; total energy: 648 kcal) included bread, margarine, strawberry jam, chicken omelet with salad, sauce, canned white peaches and milk. Subjects ate breakfast over a period of about 15 minutes.

PK sampling: Blood samples were collected at pre-dose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48 and 72 hours post dose. Urine samples were collected at the interval of predose (-12 to 0 hour) and at 0 to 24, 24 to 48 and 48 to 72 hours post dose.

PK analysis: Noncompartmental analysis (NCA) was applied in the determination of the PK parameters of SYR-322 and its two metabolites. Cumulative urinary excretion ratio [% of dose (as unchanged compound)] was calculated based on the urinary concentration of SYR-322 and its metabolites.

Statistical analysis: Summary statistics were used to summarize the PK parameters under both fast and fed conditions. To assess the food effect on single-dose PK of SYR-322, ANOVA was performed on the log-transformed plasma PK parameters of AUCinf, AUC0-72, AUCt and Cmax of SYR-322. If the two-sided 90% confidence interval of AUCinf and Cmax for the difference between fed and fast conditions falls within 80% to 125%, the presence of a food effect will be excluded.

Results: Ten subjects received treatment drug in this study. Two subjects were completely excluded from the plasma PK analysis due to sample hemolysis and withdrawal of consent. The latter subject was also excluded in the urine PK analysis.

The PK parameters and the summary statistics of SYR-322 were listed in Table 78. Geometric mean ratios (GMR) and 90% CI of AUC and Cmax of SYR-322 were summarized in Table 79. The mean plasma concentration of the 8 subjects under the fast and fed conditions was illustrated in Figure 50. The effects of food on the PK of SYR-322 are summarized as following:

- GMR of AUCinf of SYR-322 was reduced by 4.9% and the 90% CI ranged from 90.4% to 100.0%.
- GMR of Cmax of SYR-322 was reduced by 14.1% and the 90% CI ranged from 71.1% to 103.7%.
- The median Tmax was at 1 and 3 hours under the fast and fed conditions, respectively (Table 1).
- The renal clearance of SYR-322 was 10.30 and 10.58 L/hr under the fast and fed conditions, respectively (Table 3).

To summarize, food did not have impact on the extent of absorption of SYR-322, however, food reduced the rate of absorption (Cmax) by 14.1% and delayed the Tmax from 1 hour under the fast condition to 3 hours. The 90% CI of GMR of Cmax fell out of 80% to 125% range. In addition, food has no effect on the cumulative urinary secretion of SYR-322 and renal clearance. These results combined suggested that the food has minor effect on the PK of SYR-322 and its clinically significance needs to be investigated.

Figure 50 Mean plasma concentration of SYR-322 after a single oral dose of 50 mg SYR-322 under fast or fed conditions.

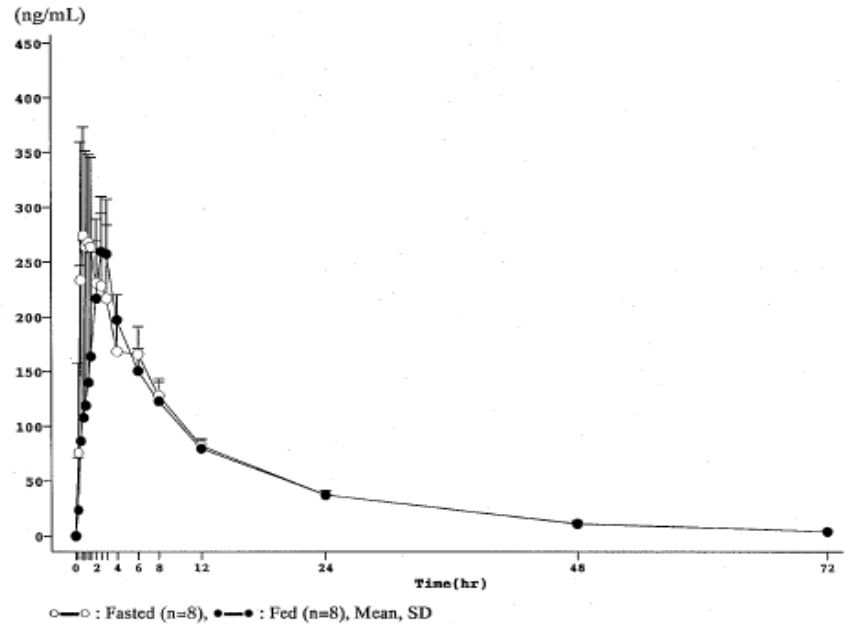


Figure 11.b Arithmetic mean plasma concentrations of SYR-322Z

Table 78 **PK parameters and summary statistics for SYR-322 after a single oral dose of 50 mg SYR-322 under fast or fed conditions.**

Table 11.c Summary statistics of pharmacokinetic parameters for SYR-322Z

3.1.7.1

Variable	Treatment	Summary Statistics								
		N	Mean	SD	SE	Min	Q1	Median	Q3	Max
AUC(0-72)	Fasted	8	3386.73	274.053	96.892	2965.4	3205.10	3368.10	3572.25	3837.5
(ng·hr/mL)	Fed	8	3216.78	307.695	108.787	2818.3	2976.30	3176.60	3472.85	3664.4
AUC(0-tlqc)	Fasted	8	3386.73	274.053	96.892	2965.4	3205.10	3368.10	3572.25	3837.5
(ng·hr/mL)	Fed	8	3216.78	307.695	108.787	2818.3	2976.30	3176.60	3472.85	3664.4
MRT(0-tlqc)	Fasted	8	14.184	0.8972	0.3172	12.52	13.640	14.365	14.870	15.20
(hr)	Fed	8	14.933	0.8013	0.2833	13.99	14.265	14.890	15.390	16.38
Cmax	Fasted	8	344.88	48.860	17.275	256.0	317.50	347.00	384.00	406.0
(ng/mL)	Fed	8	304.13	89.475	31.634	211.0	220.50	307.00	345.50	476.0
Tmax	Fasted	8	1.344	0.9057	0.3202	0.50	0.750	1.000	1.875	3.00
(hr)	Fed	8	2.469	0.8705	0.3078	0.75	2.000	3.000	3.000	3.00
AUC(0-inf)	Fasted	8	3481.91	261.369	92.408	3059.1	3310.60	3472.80	3669.85	3889.7
(ng·hr/mL)	Fed	8	3316.19	327.917	115.936	2901.3	3058.90	3288.60	3540.65	3851.9
λz	Fasted	8	0.0458	0.00555	0.00196	0.039	0.0425	0.0440	0.0485	0.057
(1/hr)	Fed	8	0.0464	0.00646	0.00228	0.037	0.0420	0.0465	0.0495	0.058
T1/2	Fasted	8	15.3156	1.77343	0.62700	12.070	14.2395	15.7000	16.3265	17.923
(hr)	Fed	8	15.2524	2.05443	0.72635	12.021	14.0475	15.0195	16.6475	18.569
CL/F	Fasted	8	14.43	1.082	0.383	12.9	13.60	14.40	15.10	16.3
(L/hr)	Fed	8	15.21	1.461	0.517	13.0	14.15	15.25	16.35	17.2
MRT	Fasted	8	16.408	1.4092	0.4982	13.56	15.720	16.760	17.465	17.81
(hr)	Fed	8	17.303	1.7238	0.6094	15.09	15.960	17.155	18.355	20.39

Table 79 **Geometric means ratios and 90% CI of AUC and Cmax of SYR-322 in subjects receiving a single oral dose of 50 mg SYR-322 under fast or fed conditions.**

Drug Name	PK Parameter	Geometric Mean Fast (N=8)	Geometric Mean Fed (N=8)	Ratio (%) (90% CI)
SYR-322	AUCt (ng*h/mL)	3377.021	3203.952	94.9% (90.7%-99.3%)
	$AUC_{0\text{-}72\ hr}$ (ng*h/mL)	3377.021	3203.952	94.9% (90.7%-99.3%)
	AUCinf (ng*h/mL)	3473.269	3302.163	95.1% (90.4%-100.0%)
	Cmax (ng/mL)	341.651	293.343	85.9% (71.1%-103.7%)

Figure 51 **Mean cumulative urinary excretion ratio of SYR-322 after a single oral dose of 50 mg SYR-322 under fast or fed conditions.**

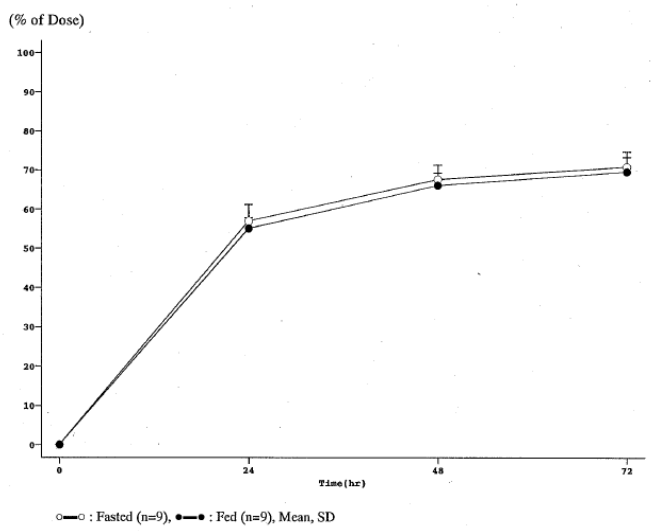


Figure 11.e **Arithmetic mean cumulative urinary excretion ratio of SYR-322Z**

Table 80 **Summary statistics for renal clearance of SYR-322 after a single oral dose of 50 mg SYR-322 under fast or fed conditions.**

Table 11.g Summary statistics for renal clearance of SYR-322Z

3.2.5.1

Variable	Treatment	Summary Statistics								
		N	Mean	SD	SE	Min	Q1	Median	Q3	Max
CLr (L/hr)	Fasted	8	10.30	1.023	0.362	8.8	9.70	10.15	10.90	12.1
	Fed	8	10.58	0.985	0.348	9.0	9.90	10.85	11.30	11.5

Reviewer's Comment:

- A single oral dose of 50 mg SYR-322 was used in the food effect study. This dose (50 mg) has been evaluated in the phase 1 study and proved to be safe and tolerable. The dose selection is reasonable.
- The food contents in the breakfast that subject took was quite different as compared to the food effect study (study 005 and study 026), in which a high-fat (approximately 50% of total caloric content of the meal) and high calorie (approximately 800 to 1000 calories) breakfast was selected according to the specification in the FDA's guidance (Guidance for industry: Food-effect bioavailability and Fed bioequivalence studies).

- The terminal elimination half life of SYR-322 was 15 hours under the fast and fed conditions. The results suggested that 7-day washout period was appropriate. The plasma sample collection up to 72 hours was reasonable for the determination of half life of SYR-322 as it covers approximately 5 half-lives of the drug.
- The variation of Cmax was approximately 15% and 30% under the fast and fed conditions. The 90% CI fell out of 80% to 125% range was probably not due to the high variation of data, rather the limited number of subjects in the study (N=8).
- Sponsor also determined the plasma concentration of the metabolites of SYR-322. SYR-322-M-I is N-demethylated metabolite of SYR-322. SYR-322 M-I is a potent and selective inhibitor to DPP4, however, its plasma concentration was only 1 of three hundredth of SYR-322, thereby it is unlikely to have any clinical significance. SYR-M-II is approximately one tenth of SYR-322, but it is not pharmacologically active.
- Cumulative urinary excretion of SYR-322 approached asymptotic state from 48 to 72 hours. Approximately 70% of dose was excreted from urine, which agreed with previous study results.

4.2.24 In vitro study of SYR-322

CYP450 Metabolism

Study SYR-322-00013: Determination of the Inhibitory potential of SYR322 on human CYP450 1A2, 2C9, 2C19, 2D6, and 3A4 using baculovirus-expressed protein.

The inhibition of SYR322 on CYP450 isozymes was investigated at the concentration range of 0.49 to 40 μM in 96-well plate using the known probe substrates.

Results: SYR322 did not inhibit CYP450 1A2, 2C9, 2C19, and 3A4, with the IC_{50} greater than 40 μM. SYR-322 showed some activity in the inhibition of 2D6 and may warrant in vivo confirmation study.

Study SYR-322-0015: Determination of the metabolic stability of SYR-322 in human, rat, monkey and dog cryo-preserved hepatocytes and human, rat, dog, and monkey microsomes.

Metabolic stability of SYR-322 at 1 μM was investigated in hepatocytes and microsomes from human, rat, monkey and dog. Results: SYR-322 was stable in human and monkey hepatocytes at all times, and ~50% and ~65% SYR-322 remained after 120 minutes incubation with dog and rat hepatocytes, respectively. Greater than 75% of SYR-322 remained after 30 minutes incubation in microsomes.

SYR-322-00021 study: Identification of the CYP450 isozymes involved in the metabolism of SYR110322-reaction phenotyping.

10 μM SYR-322 was incubated with recombinant human P450 enzymes (1A2, 2C8, 2C9, 2C19, 2D6, 3A4 and 2E1) either individually or as a Supermix. Incubation was conducted in a NAPDH regeneration system.

Results: N-demethylated metabolite M1 is the primary metabolite of SYR-322. 2D6 is the primary enzyme involved in the conversion of SYR-322 to M1. 3A4 is the primary enzyme involved in the formation of hydroxylated and dehydrogenated metabolites of SYR-322.

SYR-322-00022 study: Metabolism of SYR110332 in rat, dog, monkey and human cryopreserved hepatocytes (in vitro) and in rat, dog, and monkey plasma samples (in vivo)

In vitro metabolism of SYR-322 was evaluated in cryopreserved rat, dog, monkey and human hepatocytes at 10 mM after 3 hour incubation. In vivo metabolism of SRY-322 were conducted in Sprague Dawley rats, Beagle dogs and cynomolgus monkeys following oral administration of SYR-322 at the dose level of 100, 30 and 10 mg/kg.

Results: SYR-322 was metabolic stable, with less than 6% degradation in monkey and human hepatocytes preparation, and less than 20% degradation in rat and dog.

A total of 8 metabolites were tentatively identified in the in vitro and in vivo preparation. The N-demethylated metabolite M1 was a major metabolite of SYR-322 being found both in *in vitro*

preparation and *in vivo* studies in all species. The other 7 metabolites were formed in small quantities. M1 formation was higher in dogs than in rats and monkeys.

SYR-322-00029 study: In vitro evaluation of SYR110322 as an inhibitor of human cytochrome P450 enzymes.

The inhibitory potency of SYR-322 was determined in vitro by measuring the activity of each CYP enzyme in human liver microsomes in the presence and absence of SYR-322. The experiment also determined if SYR-322 was a mechanism-based inhibitor to CYP enzymes. The probe substrate concentration and incubation conditions were determined by the kinetic parameters (Km, Vmax). The concentration range for SYR-322 was from 0.1 to 100 µM.

Results: Under the experiment conditions, SYR-322 caused approximately 27% inhibition of 2D6, however the IC50 was greater 100 µM. SYR-322 did not cause direct inhibition to CYP1A2, 2C8, 2C9, 2C19 or 3A4/5. The estimated IC50 values for these enzymes were greater than 100 µM, the highest concentration examined.

SYR-322 appeared to cause a mechanism-based inhibition to 3A4/5, and the IC50 was 78 and > 100 µM using midazolam and testosterone as substrate, respectively. SYR-322 did not cause mechanism-based inhibition of CYP1A2, 2C8, 2C9, 2C19 or 2D6.

Table 2: Summary of experimental conditions for enzyme assays: Direct and metabolism-dependent inhibition of CYP enzymes by SYR110322

							SYR110322	
Enzyme	CYP Activity	Substrate concentration (µM)	Incubation volume (µL)	Protein[a] (µg/mL)	Incubation time (min)	Pre-incubation time (min)	Target concentrations (µM)	Solvent volume[b] (µL)
CYP1A2	Phenacetin *O*-deethylation	20	400	100	5	30	0, 0.1, 0.3, 1.0, 3.0, 10, 30, 100	8
CYP2C8	Paclitaxel 6α-hydroxylation	15	400	50	5	30	0, 0.1, 0.3, 1.0, 3.0, 10, 30, 100	8
CYP2C9	Diclofenac 4´-hydroxylation	4.0	400	100	5	30	0, 0.1, 0.3, 1.0, 3.0, 10, 30, 100	8
CYP2C19	*S*-Mephenytoin 4´-hydroxylation	35	400	100	5	30	0, 0.1, 0.3, 1.0, 3.0, 10, 30, 100	8
CYP2D6	Dextromethorphan *O*-demethylation	5.0	400	100	5	30	0, 0.1, 0.3, 1.0, 3.0, 10, 30, 100	8
CYP3A4/5	Midazolam 1´-hydroxylation	3.0	400	50	5	30	0, 0.1, 0.3, 1.0, 3.0, 10, 30, 100	8
CYP3A4/5	Testosterone 6β-hydroxylation	100	400	100	5	30	0, 0.1, 0.3, 1.0, 3.0, 10, 30, 100	8

[a] The human liver microsomal sample used for these experiments was a pool of nine individuals (samples 71, 72, 76, 79, 99, 101, 105, 140, and 142).
[b] 1.0 M potassium phosphate buffer (pH 6.5) was the vehicle used to dissolve the test article.

SYR-322-00115 study: In vitro examination of SYR110322S as an inducer of cytochrome P4450 expression in cultured human hepatocytes.

Human hepatocytes from three separate human livers were treated with DMSO control, SYR-322 at three concentrations (1, 10 or 100 µM) or three known P450 enzyme inducers (omeprazole at 100 µM, Phenobarbital at 750 µM or rifampin at 10 µM) once daily for three consecutive days. After treatment, cells were harvested and microsomes were prepared.

The prepared microsomes were incubated with the probe substrates for P450 enzymes to study the P450 enzyme activities. The details for the experiment were listed in the following table.

After microsomal incubation reaction, the formations of the metabolites were determined for the measurement of corresponding enzyme activities.

Results: SYR-322 caused litter or no change in CYP1A2, 2B6, 2C9 and 2C19 activity at the concentration up to 100 μM. SYR-322 caused significant induction of CYP3A4/5 activity, and the induction at 100 μM was 27.6% as effective as rifampin.

Enzyme	Substrate	Substrate Concentration (μM)	Quantity of Protein (mg/incubation)	Incubation Volume (mL)	Time (min)
CYP1A2	7-Ethoxyresorufin	10	0.1	1.0	60
CYP2B6	Bupropion	500	0.2	0.5	120
CYP2C9	Diclofenac	100	0.05	1.0	30
CYP2C19	*S*-Mephenytoin	400	0.04	0.2	240
CYP3A4/5	Testosterone	250	0.1	0.5	20

SYR-322-00123 study: Permeability of SYR-322 across Caco-2 cells

Permeability or SYR-322 (3 μM) from apical side to basal side (A to B), and basal side to apical side (B to A) after 2 hour incubation across Caco-2 cell monolayer was investigated. ^{3}H-verapamil (10 μM) and ^{14}C-mannitol (10 μM) were used as reference for high and low permeability compounds. ^{3}H-digoxin (3 μM) served as a typical substrate for P-gp.

Results: The permeability of [cyano-^{14}C]-SYR-322 resembled to that of ^{14}C-mannitol more than to ^{3}H-verapamil, suggesting that SYR-322 could be a compound with low permeability. The Papp ratios were 0.7 at 1 hour, and 1.7 at 2 hour, and both values were lower than that of ^{3}H-digoxin. The involvement of P-gp on the transport of SYR-322 is not conclusive and remains to be investigated.

SYR-322-00014 study: Determination of the potential for metabolic drug-drug interactions of SYR-322 and SYR110619 with rosiglitazone, glyburide and glipizide in human liver microsomes,

Metabolic stability of rosiglitazone, glyburide and glipizide in the presence of SYR-322 and SYR110619 as inhibitor was studied. Similarly, metabolic stability of SYR-322 and SYR110619 with the presence of rosiglitazone, glyburide and glipizide was investigated.

Results: No significant metabolic interactions occurred between SYR322 or SYR110619 and rosiglitazone, glyburide, or glipizide in human liver microsomes.

Protein binding study

SYR-322-00016 study: Determination of the rat, dog, and human plasma binding of SYR110322, and SYR110619 by equilibrium dialysis.

Equilibrium dialysis was utilized to determine the plasma protein binding. Dialysis was performed at 37 ºC for 16 hours. [^{3}H] acetaminophen (low binding control) and [^{14}C] warfarin (high binding control) were utilized as control.

Results: Human plasma protein binding of SYR-322 were 24% and 15% at 10 mM and 100 mM, respectively. Protein binding of SYR-322 was 40% and 24% at 10 mM in rat and dog; and 24% and 23% at 100 mM in rats and dogs, respectively.

SYR-322-030 study: Determination of the plasma protein binding of SYR110322 and SYR110619 in mouse plasma and SYR110324 (active metabolite) in mouse, rat, dog and human plasma fractions by equilibrium dialysis.

Equilibrium dialysis was conducted for 6 hours to SYR-322 and SYR-322 M1 (also known as SYR110324) in the concentration of 1, 10 and 100 µM.

Results: The human plasma protein binding for SYR-322 M1 ranged from 12.2% at 1 µM to 32.2% at 100 µM. Its plasma protein binding in mouse and rat ranged from 11.7% to 23.1%.

Plasma protein binding for SYR-322 were 29.62% and 24.10% at 10 and 100 µM in mouse, respectively.

SYR-322-00135 study: In vitro plasma protein binding of [^{14}C] SYR-322 in rats, dogs and humans.

In vitro plasma protein binding of [^{14}C] SYR-322 in rats, dogs and humans was determined by the ultrafiltration method. [^{14}C]SYR-322 was spiked into plasma of rats, dogs, and humans. The spiked samples were centrifuged at approximately 1,500×g for 15 minutes to obtain the filtrate. [^{14}C]SYR-322 concentration in spike sample and filtrate were measured for radioactivity by using liquid scintillation spectrometry.

Results: The protein binding of [^{14}C]SYR-322 in the plasma at the concentration range of 0.01 to 10 µg/mL were from 52.0% to 25.2%, 46.3% to 23.5%, and 38.4 to 28.2% in rats, dogs and humans, respectively. The results showed that the plasma protein binding of [^{14}C] SYR-322 was concentration dependent, and was moderate in all species.

PHARMACOMETRIC REVIEW

NDA:	22271
Drug name:	Alogliptin
Indication:	Type II Diabetes Mellitus
Proposed Regimen (Sponsor):	25 mg QD with 6.25 and 12.5 mg doses for patients with impaired renal function.
Applicant:	Takeda Global Research & Development Center, Inc.
OCP Reviewer	Sang Chung, Ph.D.
Pharmacometric Primary Reviewer:	Justin Earp, Ph.D.
Pharmacometric Secondary Reviewer:	Rajnikanth Madabushi, Ph.D.
Pharmacometric Team Leader:	Yaning Wang, Ph.D.
Type of Submission:	NDA
Submission Date:	12/27/2007
PDUFA Date:	10/27/2008

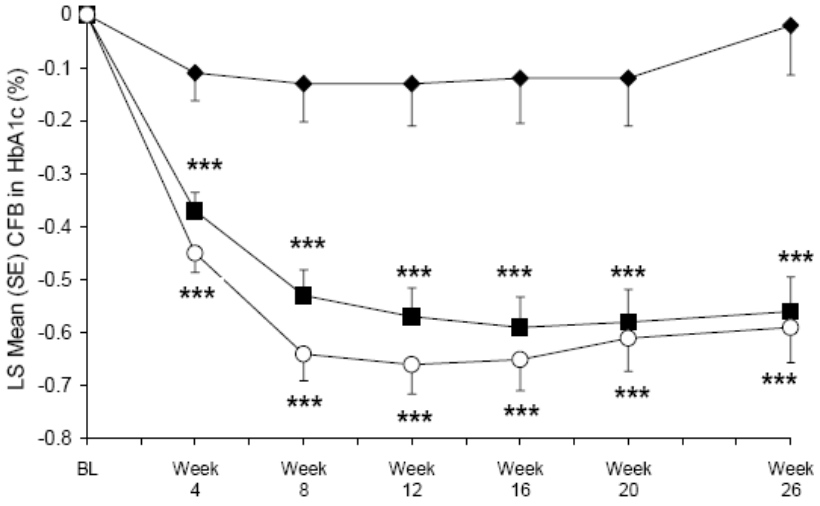
SUMMARY OF FINDINGS

Alogliptin (Nesina®) is a new DPP-IV inhibitor proposed for the treatment of type-II diabetes mellitus. This document addresses the following three questions regarding the safety and effectiveness of Nesina®.

1. Is there any benefit to 25 mg QD as a starting dose over 12.5 mg QD?

There is no clear benefit for starting with 25 over 12.5 mg alogliptin for reducing serum HbA1c. No concentration-effect relationship was evident for Alogliptin effects on reducing serum HBA1c concentrations. However, serum HbA1c concentrations were reduced and to similar extents with the 12.5 and 25 mg alogliptin compared to the placebo group (Figure 52, Figure 61, page 141).

Figure 52. Change in HbA1c in the Placebo Controlled Study 010. Solid diamonds indicate treatment with placebo. Solid squares indicate 12.5 mg alogliptin and open circles indicate treatment with 25 mg alogliptin.

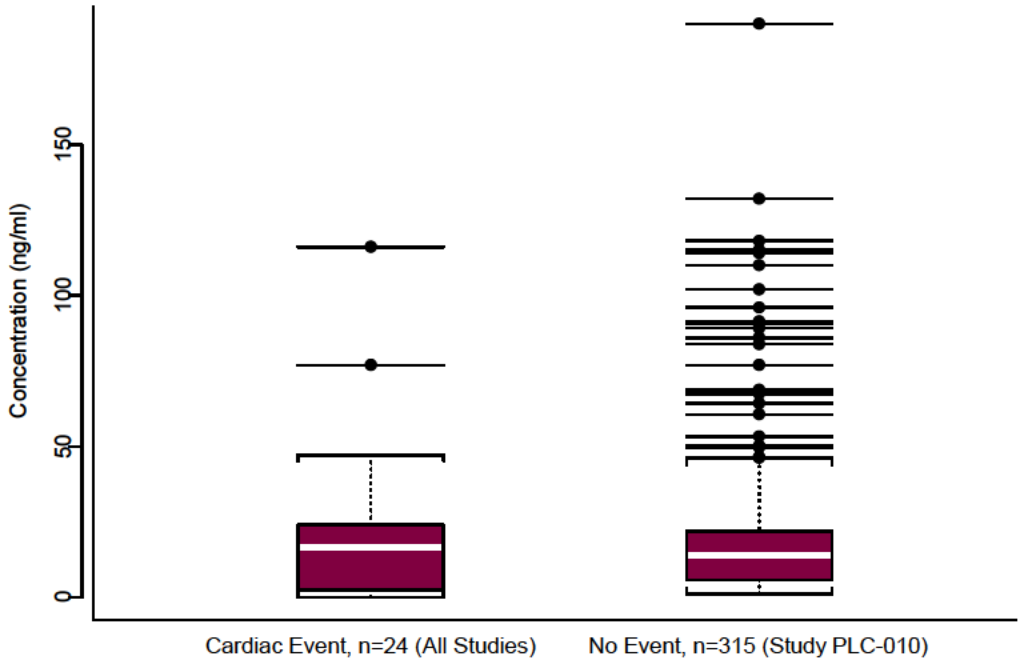


2. *Is there an exposure-safety relationship?*

No exposure-safety relationship was observed for either serious treatment emergent cardiac events or renal function with respect to alogliptin exposure.

The range of trough concentrations of alogliptin in individuals with serious cardiac events was similar to those experiencing no adverse events. This suggests cardiac events in these individuals are not exposure-related at the studied doses (Figure 53)

Figure 53. There is no Difference in Steady-State Trough Concentrations at 4 weeks for Patients with and without Adverse Cardiac Events



Time courses of creatinine clearance for each individual showed no evidence of deterioration of renal function throughout the 52-week study duration.

3. ***Is the sponsor's pharmacokinetic model sufficient to extrapolate to other clinical trial pharmacokinetic data?***

The sponsor's population pharmacokinetic model predicts the phase II pharmacokinetics for 25, 100, 400 mg of alogliptin in 45 patients after multiple dosing well, despite being developed from sparse data and a limited dose range (12.5 and 25 mg). Co-linearity of body weight with creatinine clearance effects on the clearance parameter was unnecessary and the linear effect of body weight on clearance was removed from the model in the reviewer's analysis. The revised model fit the data equally well and was used to indicate intra-patient variation on different occasions after multiple doses and to simulate Cmax concentrations for the cardiac safety analysis.

RECOMMENDATION

The Pharmacometrics group in Office of Clinical Pharmacology has reviewed the submitted pharmacometric information and has found the results acceptable.

If this submission is found acceptable by the review team it is recommended that both 12.5 and 25 mg alogliptin doses be approved.

Signatures:

Justin C. Earp, Ph.D.

Primary Pharmacometrics Reviewer

Office of Clinical Pharmacology

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INTRODUCTION

Takeda Global Research and Development (TGRD) has submitted alogliptin (Nesina®) for the treatment of type-II diabetes mellitus. Alogliptin is a selective and potent inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4) that rapidly degrades incretin hormones (glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]). By preventing the rapid degradation of these hormones, DPP-4 inhibitors enhance the body's ability to control elevated blood glucose by triggering pancreatic insulin secretion and suppressing pancreatic glucagon secretion. Potentiating incretin hormones via inhibition of DPP-4 is a mechanism of action that characterizes a distinct class of oral glucose-lowering agents.

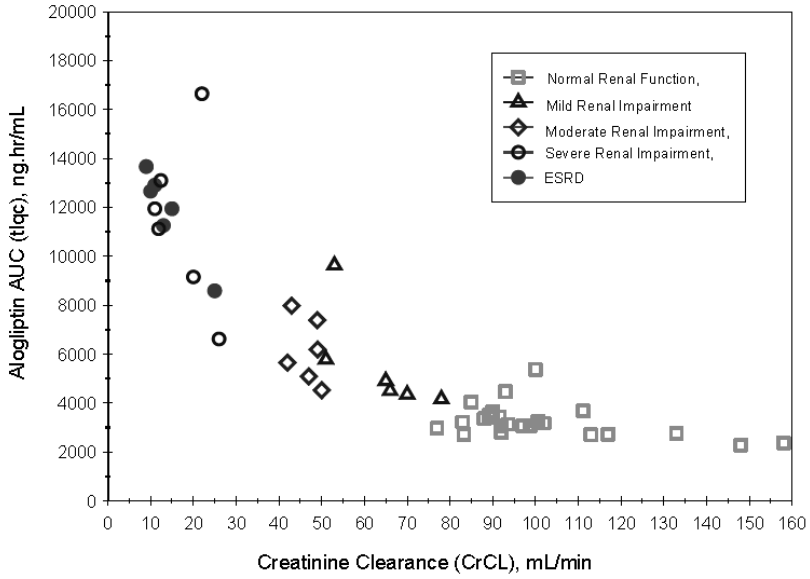
Alogliptin is 10,000 times more selective for DPP-4 than for other related enzymes (DASH, tryptase), including DPP8 and DPP9. Alogliptin has 2 minor metabolites, *N*-demethylated metabolite (<1% of the parent compound) and *N*-acetylated metabolite (4-6% of the parent compound). Alogliptin exists predominantly as the (*R*)-enantiomer and undergoes little or no chiral conversion to the (*S*)-enantiomer in vivo. (Source: Sponsor's Common Technical Introduction Document)

Takeda's clinical development program consisted of 5 registered trials to evaluate both their primary efficacy endpoint HbA1c and alogliptin pharmacokinetics. A total of 2239 subjects were enrolled across all 5 trials. This large database was used for both the sponsors and reviewer's analysis. Appendix A summarizes the sponsor's efficacy and population pharmacokinetic analysis and results.

5 REVIEWER'S ANALYSIS: QUESTION BASED REVIEW

Alogliptin is predominantly cleared by renal excretion (76%). Takeda showed creatinine clearance is related to alogliptin AUC_{0-24} (Figure 54). Takeda proposed three dose strengths of alogliptin, 25, 12.5, and 6.25 mg for patients with varying degrees of renal function. However when comparing the time course of HbA1c response (Figure 61) to alogliptin between 12.5 and 25 mg doses and exposure-response relationship. The 25 mg dose does not appear to be more effective than the 12.5 mg dose. This review looks at different aspects of the exposure-response relationship between alogliptin and HbA1c concentrations and the population pharmaokinetics of alogliptin to evaluate if 25 mg alogliptin once-daily is the best starting dose.

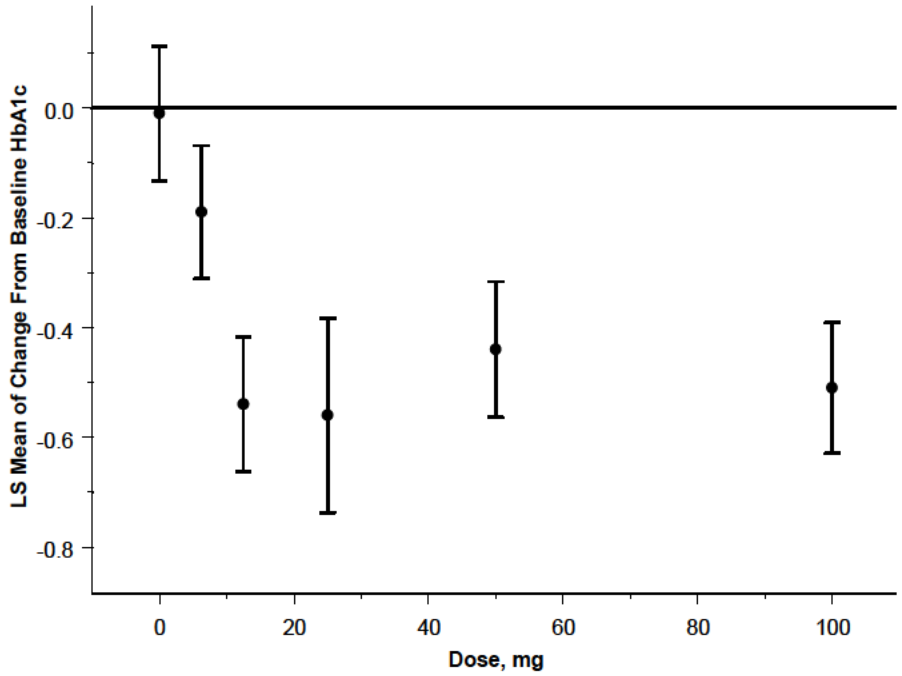
Figure 54. Aloglptin AUC Decreases with Creatinine Clearance



5.1 Is there any benefit to 25 mg QD as a starting dose over 12.5 mg QD?

Dose-response data was analyzed from study 003, a phase II dose-ranging study where doses of 6.25, 12.5, 25, 50, and 100 mg alogliptin were administered once daily for 12 weeks. Figure 55 shows the mean effect for each dose group on serum HbA1c. This figure would suggest that at the 6.25 mg dose there is no response and at any dose higher than that, the response is at a maximum and that no dose-response relationship exists above doses of 12.5 mg.

Figure 55. Dose-Response for Alogliptin Effect on Serum HbA1c Change from Baseline at 12 weeks. Error Bars Depict ±1 Standard Error Measure. The Solid Black Line is the Reference Line for No Change From Baseline.



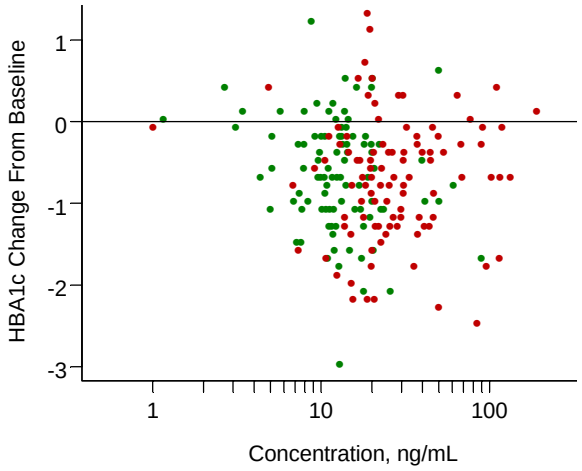
If concentrations within each dose group vary greatly between individuals it is possible that this may explain the variation in effect of alogliptin within each dose group. The dose given to an individual may not represent their overall exposure to the drug. Identifying a concentration-effect relationship for aloglitpin is important to discern whether drug effect was dependent upon drug exposure. In Figure 52 it is apparent that data for alogliptin effect on HbA1c at 12 weeks was already at steady-state since its levels were similar to that at all other time points up to 26 weeks. It seemed reasonable that exposure-response at 12 weeks would be similar to that found in the five phase-three clinical trials studied at 26 weeks. These later studies provided a much larger dataset (1252 patients) to assess whether a concentration-HbA1c change relationship exists.

Data from five phase III trials were used to evaluate the exposure-response relationships of Alogliptin on changes in HBA1c concentrations in patients. Each trial was designed to test the safety and efficacy of Alogliptin over 26 weeks in 5 different patient populations. Patient populations were defined by concurrent treatment given prior to and throughout the study. Each trial had three study arms. Individuals were given either hi- (25 mg) or low-dose (12.5 mg) alogliptin and placebo or placebo alone (Study PLC-010), hi- or low-dose alogliptin and metformin or metformin alone (Study MET-008), hi- or low-dose alogliptin and sulfonylurea or sulfonylurea alone (Study SULF-007), hi- or low-dose alogliptin and insulin or insulin alone (Study INS-011), and hi- or low-dose alogliptin and pioglitazone or pioglitazone alone (Study TZD-009).

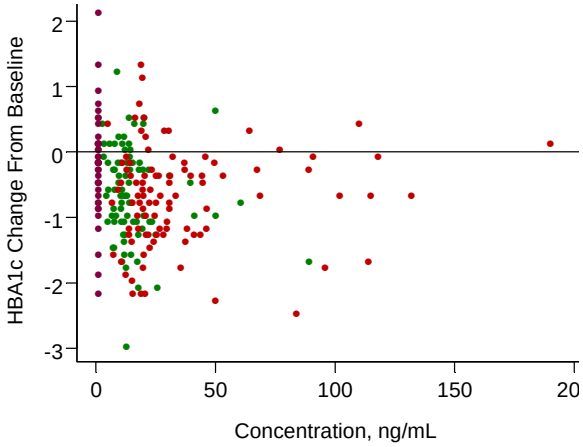
To test whether change in HBA1c was exposure-driven, steady-state trough concentrations of alogliptin after 4 weeks of treatment were used to indicate overall exposure to the drug. Aloglitpin trough concentrations are expected to reach steady-state after five to six days of dosing. Thus, trough concentrations at 4 weeks are expected to be at steady-state and provide a consistent measure of the individual's overall exposure to the drug (see questions 3, 4 for more details on alogliptin pharmacokinetics). These concentrations were plotted for each individual against their change from baseline in HbA1c after 26 weeks of therapy (Figure 56). Figure 56 shows no clear relationship between alogliptin concentrations and reduction of HBA1c from baseline. However, the alogliptin treated patients generally exhibit reduced HBA1c concentrations from baseline. As the treated groups are significantly reduced from placebo (Figure 56**,** Figure 62**,** Figure 63), it is possible that treatment effects have reached a maximum by the 12.5 mg alogliptin dose.

Figure 56. HBA1c Reduction from Baseline is not Dependent on Alogliptin Concentrations in Placebo Controlled Study 010. Green, Red and Purple Dots Indicate Low (12.5 mg), High (25 mg) and placebo Dose Groups of Alogliptin.

a) Log-Conentration Scale Without Placebo Data.



b) Linear Concentration Scale Including Placebo Data.



There appears to be no added benefit by giving 25 mg over 12.5 mg. The above concentration-HBA1c plots (Figure 56) show no relationship between alogliptin concentration and response or even dose and response. This is further supported by Figure 52 and Figure 61 which show the time course of change from baseline of HBA1c after 12.5 and 25 mg alogliptin in all five phase III efficacy studies. Furthermore it appears that the maximum change in efficacy is reached in both dose arms by week 12.

5.2 Is There An Exposure-Safety Relationship?

5.2.1 Serious Treatment-Emergent Cardiac Events:

Cardiac events were noted in both treated and placebo groups of patients in all phase III studies. However, there were fewer placebo treated patients in each study, totaling 534 placebo patients compared to 1961 and the dropout rate was higher for patients receiving placebo. In an effort to determine if the cardiac events were drug related, given the different numbers between placebo and treated the question was asked – do patients with serious treatment-emergent cardiac events have elevated concentrations of Alogliptin?

Patients with serious treatment-emergent cardiac events were identified by both the sponsor (\\Cdsesub1\evsprod\NDA022271\0009\m1\us) and the medical reviewer (Appendix B). Their steady-state trough concentrations at 4 weeks were used as an estimate of overall alogliptin exposure. Figure 53 shows the distribution of steady-state concentrations in individuals with cardiac events compared with the distribution of steady-state concentrations for people without cardiac events. Albeit the two populations are very different in sizes there appears to be no difference in concentrations between the patients who experienced cardiac related events and those who didn't.

5.2.2 Renal Safety: Does alogliptin alter renal function?

Alogliptin is cleared predominantly by the kidney (~76%). As there is exposure to this organ and drug-safety is always necessary, the question of whether alogliptin affects kidney function is pertinent to address. Serum creatinine concentrations, body weight, age, and gender were used to calculate creatinine clearances for patients from Study PLC-010. Renal impairment ranged from moderate to normal with creatinine clearance as low as 35 mL/min. Visual inspection of the time courses (Figure 57, Figure 58) suggests there is no impact of drug on renal function. A linear model was fit to each individual's creatinine clearance time course by mixed effects modeling either with the slope fixed to zero or allowing it to change. The difference in the minimum value of the objective function was not great enough (>3.84) to indicate that the slope was different from zero. As the slopes in the treatment groups were not negative or different from the placebo group, drug was not assumed to have an effect on renal function.

Figure 57. Time Courses of Creatinine Clearance from All Patients in Study PLC-010.

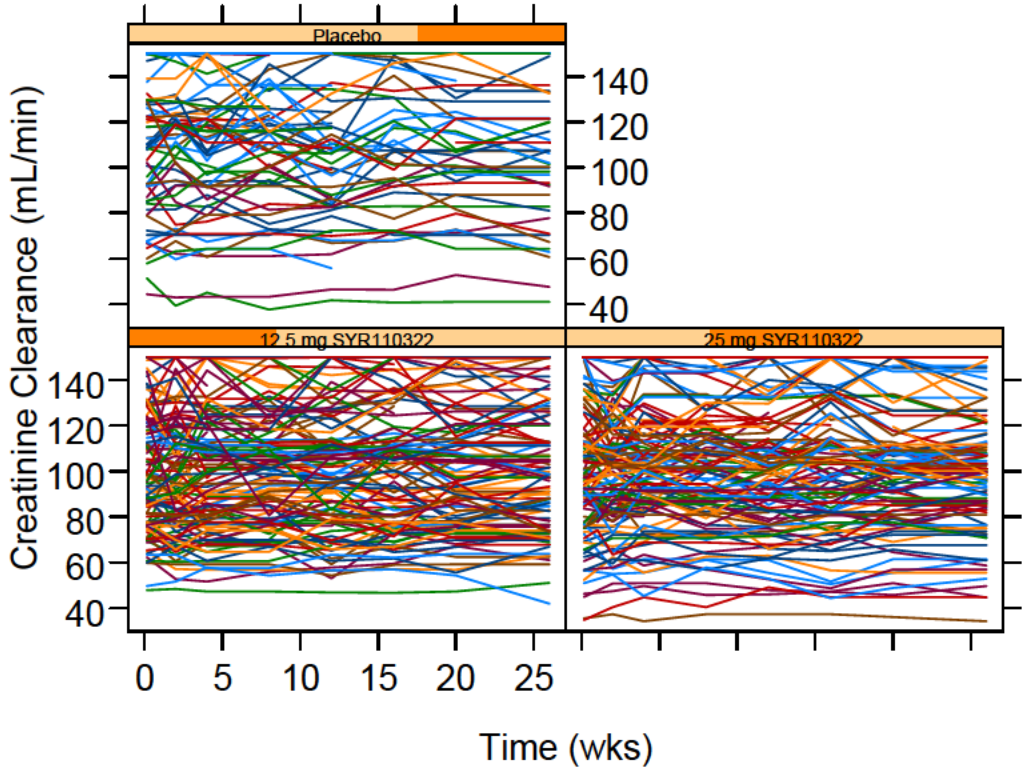
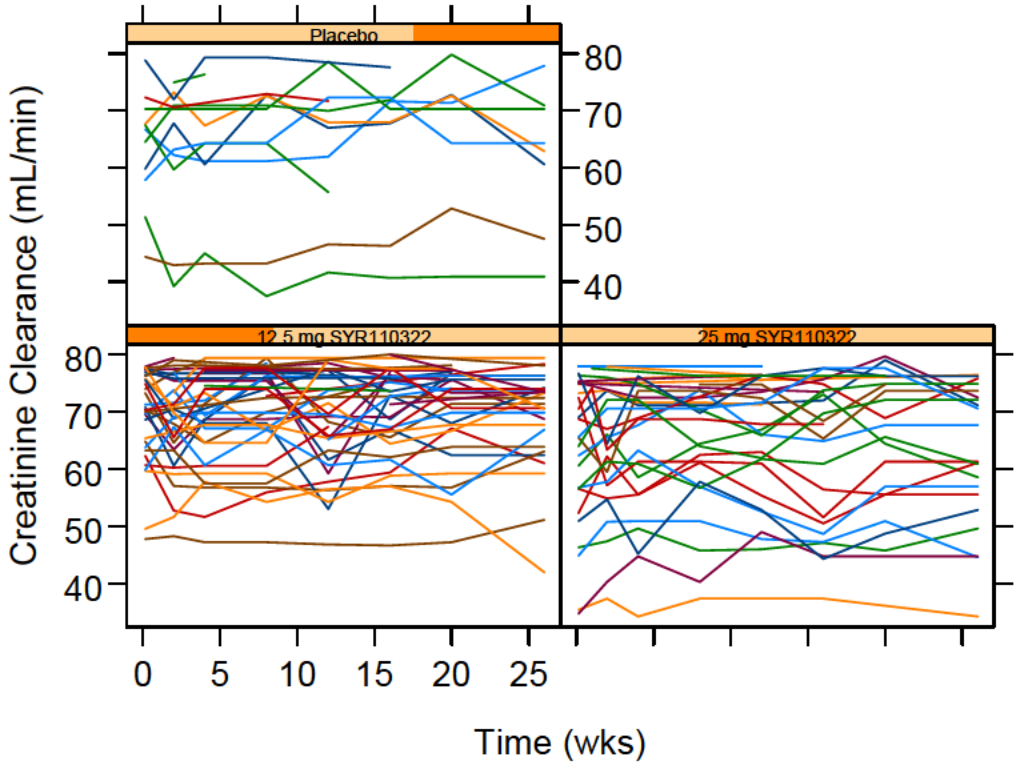


Figure 58. Time Courses of Creatinine Clearance in Study PLC-010 in Patients with Mild Renal Impairment.

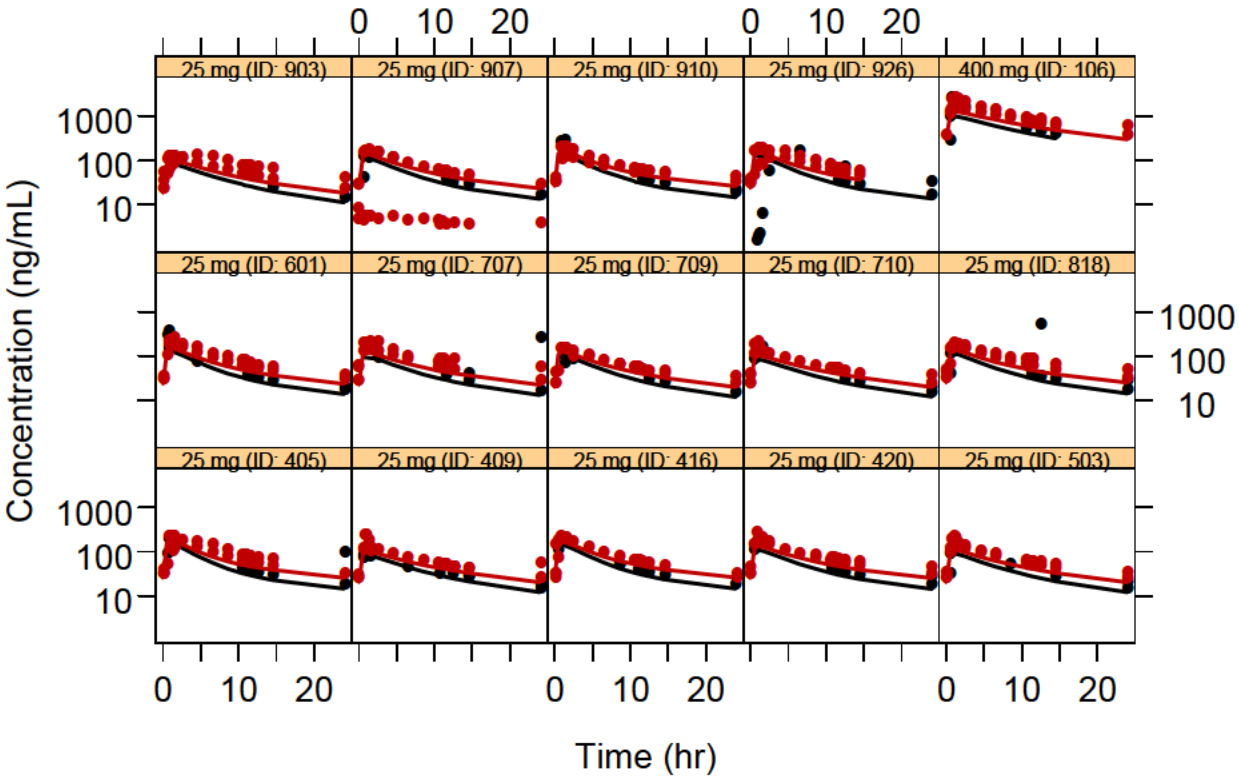


5.3 The population pharmacokinetic model was developed with sparse phase iii concentration data. Is The Sponsor's Model Sufficient To Extrapolate To Other Clinical Trial Pharmacokinetic Data And Inter-Occasion Variation?

5.3.1 Model Refinement:

The sponsor's final population pharmacokinetic model (developed using the MET-008 phase III trial) was used to predict the pharmacokinetics of individuals in the phase II multiple dose trial, study – 002. Figure 59 shows the model prediction (solid lines) for observed alogliptin concentrations (closed symbols) for day 1 (black) and day 14 (red) after initiating treatment with 25 mg alogliptin.

Figure 59. Sponsor's Population PK Model Prediction of 25-mg Multiple Dosing in Study 002.



In general the final model developed by the sponsor on only sparse data predicts the concentration time courses from the phase II data modestly well. Model limitations are 1) a general under prediction of the peak concentrations, 2) redundancy in creatinine clearance and body weight as covariates on clearance, 3) the limited use of available data, and 4) the model does not describe within subject variation between different occasions.

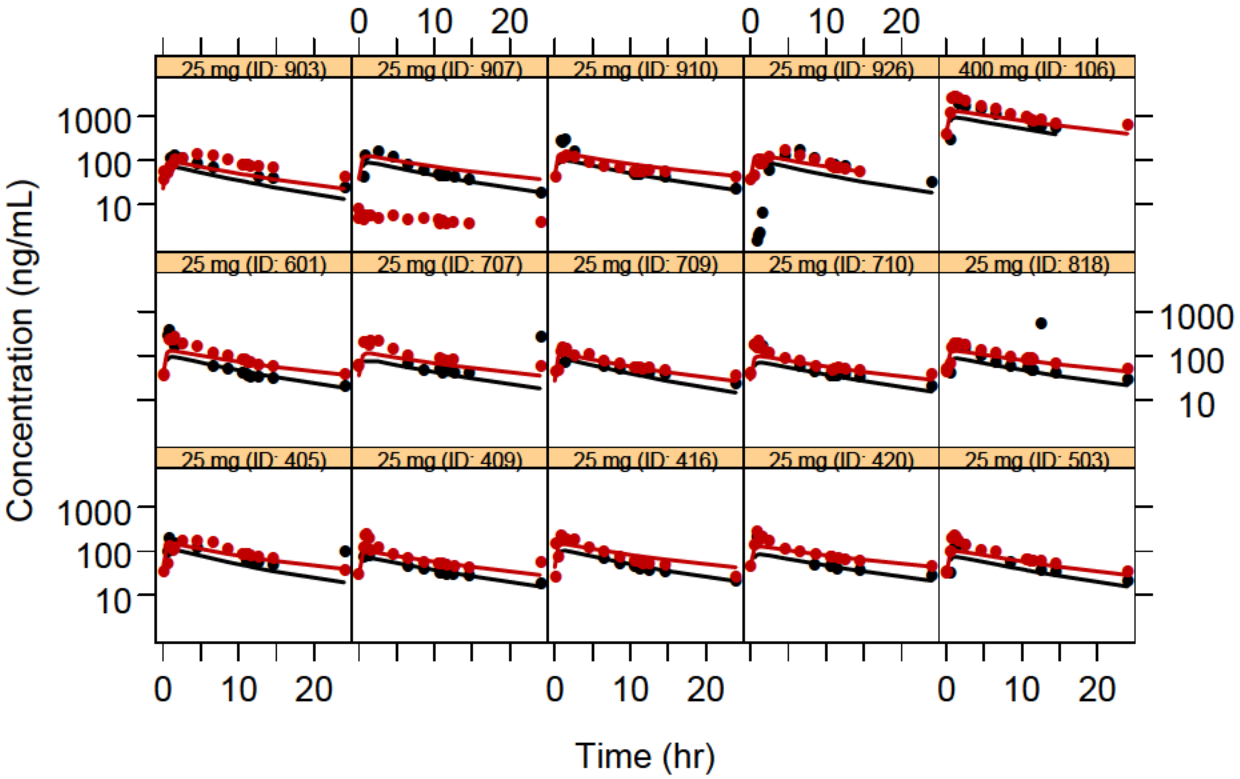
Under-prediction of the peak concentration was noted for about a third of the individuals in Figure 59 and Appendix C. This problem is common to pharmacokinetic models where oral absorption is present. Trough concentrations will likely be more reliable than simulated C_{max} values as an indication of an individual's predicted exposure.

The model was revised removing the covariate body-weight from clearance. Body weight only reduced the inter-individual variation by 0.84 %. Although the decrease in objective function was significant when weight was added as a covariate on clearance, the co-linearity between weight and creatinine clearance on the clearance of alogliptin was sufficient to use creatinine clearance instead of both. Additionally since the drug is cleared from the kidney, it makes sense that differences in creatinine clearance could explain inter-patient variation in clearance.

The sponsor provided data from five phase III studies. Only one of these studies were done where alogliptin was given without co-administration. However, study 008 (controlled with metformin co-administration) was used for the population pharmacokinetics. Furthermore, none of these five phase three studies had rich serial sampling of alogliptin concentrations. There were several phase studies including study 003 (dose-ranging) and study-002 (14-day multiple-dose PK in patients) that would have been beneficial to both the structural model development, assessment of covariates, and identifying inter-occasion variation within individuals.

The revised model (without body weight effects on clearance) was refit to data from both the sponsor's phase III dataset (study 008) and multiple dose study (study 002). Study 002 was a 14-day multiple-dose pharmacokinetic study in patients. Serial sampling was conducted on day 1 and 14 and provided a rich data set to assess the time course of concentrations in individuals and their intra-occasion variation. The updated model was used for simulation of C_{max} and trough concentrations (Figure 60).

Figure 60. Revised Population PK Model Prediction of 25-mg Multiple Dosing in Study 002.



As the drug is predominantly excreted unchanged (76% of oral dose), the sponsors were able to show a clean relationship between renal function and alogliptin clearance (Figure 54). Creatinine Clearance was a major covariate in the pharmacokinetic model and this established relationship combined with linear pharmacokinetics likely helped predict the concentrations across different studies for doses much higher than the population pharmacokinetic model was developed with.

5.3.2 What is the interoccasion variation in PK within individuals?

The exposure-HBA1c analysis (page 130) and exposure-cardiac event analysis (page 131) both assume that steady-state trough concentrations of alogliptin after 4 weeks of treatment are representative of the individual's overall exposure to the drug. Assessing the inter-day variation in the pharmacokinetics within the subject may give a better insight pertaining to the reliability of the steady-state concentrations 4 weeks post treatment-initiation for exploring their relationship with efficacy or safety responses.

The sponsor's population pharmacokinetics did not use serial sampled pharmacokinetic data from phase II trials. Data from the multiple dose trial – 002 in patients recently diagnosed with diabetes was incorporated into the POPPK database by this reviewer for

assessing the intra-subject variation on pharmacokinetic concentrations from different sampling days. A brief description of the data is provided below:

Study 002 was a double-blind, placebo-controlled, repeat-dose, multicenter study using 3 dose levels of SYR110322 in approximately 60 patients. Eligible patients were randomly assigned to 1 of 4 treatment groups (SYR110322 at 25, 100, or 400 mg, or placebo) in a 4:4:4 to 3 ratio. Patients took 1 dose of study drug daily for 14 days, followed by a 7-day follow-up period. Patients were housed in the clinic on Days -1 to 2 and Days 14 to 15, and visited the clinic for blood sampling on Days 6, 16, 17, and 21. Pharmacokinetic, pharmacodynamic, and safety data were collected at each study visit. (For details refer to sponsor's Study Report SYR-322-002 vol. 001 of 002)

The sponsor's final pharmacokinetic model was used to fit the inter-occasion η parameters with the phase II multiple-dose pharmacokinetic data. The parameter η is written in the model code such that it has normal distribution and standard deviation about a mean of zero. The parameter does not contribute to the population estimate of the model, but does account for variations between individuals and different occasions. A flag was inserted into the equations for clearance and volume to account for interoccasion variation in alogliptin concentrations. The equations for clearance and volume are:

$$\mathrm{CL} = \mathrm{TVCL} \cdot e^{(\eta_{\mathrm{CL}} + \mathrm{OCC}_1 \cdot \eta_1 + \mathrm{OCC}_2 \cdot \eta_2)}$$

$$\mathrm{V_C} = \mathrm{TVV_C} \cdot e^{(\eta_{\mathrm{V}} + \mathrm{OCC}_1 \cdot \eta_3 + \mathrm{OCC}_2 \cdot \eta_4)}$$

where TVCL is the expected population value of clearance, η_{CL} is the general inter-individual variation in clearance, η_V is the general inter-individual variation in the central volume of distribution, η_1 and η_2 are the within individual variation between occasions on clearance and are constrained to have the same final estimate, η_3 and η_4 are the within individual variation between occasions on the central volume of distribution and are also constrained to have the same final estimate, OCC_1 is a flag-variable assigned a value of 1 for study-day 1 and 0 to indicate study day 14, and OCC_2=1-OCC_1. The standard deviations for $\eta_{1/2}$ and $\eta_{3/4}$ after model fitting are 44.0% for clearance and 65.8% for the central volume of distribution. Inter-individual variation was estimated at 29.9%. This indicates that there is greater variation within patients from day-to-day than compared to the variation between patients. As the drug is predominantly cleared, variation in creatinine clearance within the individual over the time course of the study (Figure 57, Figure 58) could potentially explain the greater within-subject variation compared to between-subject variation.

PHARMACOMETRIC REVIEW CONCLUSIONS

1. No exposure-response was observed for alogliptin effects on serum HbA1c concentrations. It is likely that the 25 mg dose will offer no additional benefit than the 12.5 mg dose. If effects are not seen with 12.5 mg it is possible they wont be for the 25 mg dose.
2. Renal function has been shown to play a significant role in the clearance of alogliptin. Pharmacokinetic concentrations should be established before ruling out inefficacy of the 12.5 or 25 mg dose.
3. Treatment emergent cardiac event data for 12.5 and 25 mg doses does not show an increased exposure for patients with cardiac events. Further, the numbers of patients with events at the 12.5 and 25 mg doses do not differ in a dose-dependent manner. The data at the studied shows no relationship to exposure is inconclusive to indicate whether these events are drug related.
4. The sponsor's population pharmacokinetic model was reasonable. The inclusion of body weight both in creatinine clearance and as a direct covariate on clearance was unnecessary and yielded almost no reduction in inter-individual variation. However, the dataset used for the population model was lacking in that a much larger database with rich phase II dose ranging and multiple dose data was available in addition to four other pharmacokinetic studies. The sponsors did not make the best use of available data.
5. In light of the sponsor's fitting, the revised and re-fitted model provided an estimate of intra-individual variation in clearance (CV=44.0%) and volume (CV=65.8%).
6. Alogliptin does not affect renal function over the course of the study.

6 APPENDIX A: SPONSOR'S ANALYSIS

Efficacy Analysis

The sponsor did not directly report an exposure-response anlaysis. Instead data was provided that was supportive of 12.5 and 25 mg doses demonstrating an effect on the reduction of HbA1c (Figure 52, Figure 61). The pivotal trial designs that were conducted to test alogliptin efficacy at 12.5 and 25 mg doses are summarized in Table 81. Details, tables and figures provided below can be found in the sponsor's summary of efficacy.

Table 81. Sponsor's Clinical Trials for Efficacy of Alogliptin (SYR-322).

Table 1.a Overview of Alogliptin Efficacy Studies

Study (Phase)	Population	N(a)	Study Design	Doses (mg)	Duration of Active Treatment
Pivotal Phase 3 Studies					
010 (3)	Adults (18-80 years) with T2DM; naïve to treatment; experiencing inadequate glycemic control; failed treatment with diet and exercise for at least 3 months prior to Screening	329	Multicenter, randomized, double-blind, placebo-controlled, 3-treatment arms, alogliptin vs placebo	12.5, 25	26 weeks
007 (3)	Adults (18-80 years) with T2DM; experiencing inadequate glycemic control; currently receiving a sulfonylurea alone	500	Multicenter, randomized, double-blind, placebo-controlled, 3-treatment arms, alogliptin with glyburide vs placebo with glyburide	12.5, 25	26 weeks
008 (3)	Adults (18-80 years) with T2DM; experiencing inadequate glycemic control; currently receiving metformin	527	Multicenter, randomized, double-blind, placebo-controlled, 3-treatment arms, alogliptin with metformin vs placebo with metformin	12.5, 25	26 weeks
009 (3)	Adults (18-80 years) with T2DM; experiencing inadequate glycemic control; currently receiving a thiazolidinedione either alone or in combination with metformin or a sulfonylurea	493	Multicenter, randomized, double-blind, placebo-controlled, 3-treatment arms, alogliptin with pioglitazone (with or without metformin or a sulfonylurea) vs placebo with pioglitazone (with or without metformin or a sulfonylurea)	12.5, 25	26 weeks
011 (3)	Adults (18-80 years) with T2DM; experiencing inadequate glycemic control; currently receiving insulin either alone or in combination with metformin	390	Multicenter, randomized, double-blind, placebo-controlled, 3-treatment arms, alogliptin with insulin (with or without metformin) vs placebo with insulin (with or without metformin)	12.5, 25	26 weeks
Supportive Studies					
CPH-001 (1)	Healthy adult (20-35 years) men	60	Single-center, randomized, double-blind, placebo-controlled, single dose, parallel group	6.25, 12.5, 25, 50, 100, 200	Single dose
001 (1)	Healthy adult (18-55 years) men	36	Single-center, randomized, double-blind, placebo-controlled, single dose, dose ascending	25, 50, 100, 200, 400	Single dose
002 (1)	Adults (18-75 years) with T2DM	55	Multicenter, randomized, double-blind, placebo-controlled, repeat-dose	25, 100, 400	2 weeks
003 (2)	Adults (18-75 years) with T2DM	265	Multicenter, randomized, double-blind, placebo controlled, dose-ranging study	6.25, 12.5, 25, 50, 100	12 weeks
012 (3) (b)	Adults (18-80 years) with T2DM	1749(c)	Multicenter, open-label extension of controlled phase 3 studies	12.5, 25	Up to 2 years

(a) Number of subjects randomized to treatment.
(b) Data from Study 012 are from the interim report of this ongoing study.
(c) Number of enrolled subjects who either completed 1 of 7 phase 3 controlled studies, or required hyperglycemic rescue in 1 of 7 phase 3 controlled studies.

Statistical Analysis

Information is provided for the pivotal phase 3 studies; statistical plan information for the supportive studies is provided, when appropriate, in those sections.

Efficacy analyses were conducted using LOCF and the FAS, consisting of all randomized and treated subjects. For a particular variable, the FAS analysis consisted of all randomized and treated subjects with a Baseline value and at least 1 post-Baseline on-treatment value for the variable. The on-treatment period for efficacy variables extended from the date of first dose until 1 day (7 days for HbA1c) after the date of last dose of study drug. Observed data were also summarized to assess the impact of LOCF on the analyses. (Note: A 7-day window was used for all efficacy variables in Study 012. Only observed data were summarized in Study 012; LOCF was not used.) Efficacy values for by-visit analyses were selected using a windowing algorithm as specified in the statistical analysis plans for the individual studies.

The primary efficacy variable for all pivotal phase 3 studies was change from Baseline in HbA1c at Week 26. The primary efficacy analysis for each was an analysis of the change from Baseline to Week 26 in HbA1c using LOCF, the FAS, and an ANCOVA model as summarized in Table 2.

Table 82. Sponsor's Statistical Analysis

Table 2.a Primary ANCOVA Models for Pivotal Phase 3 Studies

Study Number	Statistical Model
007 008	ANCOVA model included: Treatment Baseline HbA1c (a) Geographic region Baseline dose of add-on treatment (b)
009 011	ANCOVA model included: Treatment Baseline HbA1c (a) Geographic region Baseline treatment regimen Baseline dose of add-on treatment (c)
010	ANCOVA model included: Treatment Baseline HbA1c (a) Geographic region Diabetes duration

(a) Included as continuous covariate.
(b) Glyburide dose for Study 007 and metformin dose for Study 008.
(c) Pioglitazone dose for Study 009 and insulin dose for Study 011.

All primary ANCOVA models included treatment group and geographic region as class effects, and Baseline HbA1c as a continuous covariate. Additional covariates were included for each study as summarized in Table 82. A descriptive summary was provided for the observed data at Week 26. Similar analyses were conducted at each scheduled visit to further characterize the analysis at Week 26. Additional descriptive summaries by subgroup factors, including age, race, and gender, were conducted to further characterize the results from the primary efficacy analysis.

For the primary analysis, a step-down procedure was used to control Type I error. For each study, the 25 mg QD dose was compared with placebo at the 2-sided 0.05 significance level using a contrast derived from the primary model. If this test was statistically significant, the 12.5 mg QD dose was evaluated in a similar fashion.

Continuous secondary efficacy variables were analyzed similarly to the primary efficacy variable. Categorical secondary variables were analyzed using nonparametric covariance-adjusted extended Mantel-Haenszel tests and logistic regression models.

All statistical tests were conducted at the 2-sided 0.05 significance level. Differences between alogliptin dosing groups were not tested statistically.

Secondary efficacy variables common across all 5 pivotal studies include the following:

Clinical Response Variables:

• Incidence of Week 26 HbA1c ≤6.5%, ≤7.0%, and ≤7.5%

• Incidence of Week 26 HbA1c decrease from Baseline ≥0.5%, ≥1.0%, ≥1.5%, and ≥ 2.0%

Glycemic Control Variables:

• Change from Baseline in HbA1c level at Weeks 4, 8, 12, 16, and 20

• Change from Baseline in FPG at Weeks 1, 2, 4, 8, 12, 16, 20, and 26

• Incidence of marked hyperglycemia (FPG ≥200 mg/dL)

• Incidence of rescue

Pancreatic Function Variables:

• Change from Baseline in fasting proinsulin at Weeks 4, 8, 12, 16, 20, and 26 (excluding

Study 011)

• Change from Baseline in insulin at Weeks 4, 8, 12, 16, 20, and 26 (excluding Study 011)

• Change from Baseline in proinsulin/insulin ratio at Weeks 4, 8, 12, 16, 20, and 26 (excluding

Study 011)

• Change from Baseline in C-peptide at Weeks 4, 8, 12, 16, 20, and 26

Body Weight

• Change from Baseline in body weight at Weeks 8, 12, 20, and 26

Exploratory Variables:

• Change from Baseline in total cholesterol, HDL, LDL, and triglycerides at Weeks 4, 8, 12,

16, 20, and 26

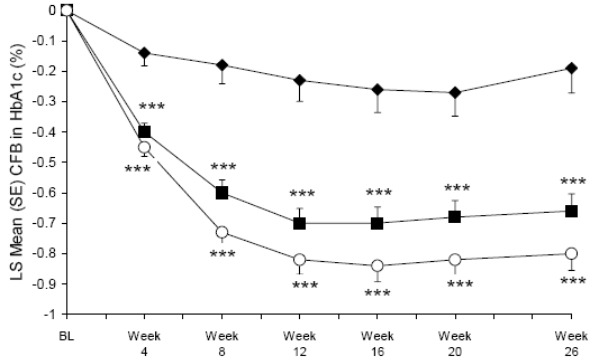
• Change from Baseline in HOMA-BCF at Week 26

The FAS (ie, all randomized subjects receiving at least 1 dose of study drug) was used to analyze efficacy.

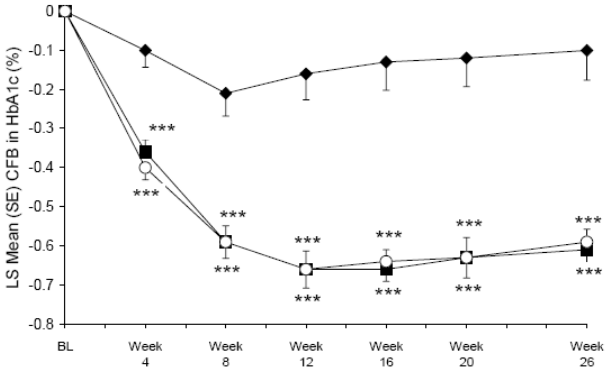
Efficacy variables for the open-label Study 012 were the change from Baseline in HbA1c by study visit, FPG, proinsulin, insulin, C-peptide, body weight, and the incidence of marked hyperglycemia. Descriptive statistics for change from Baseline in HbA1c, proinsulin, insulin, and C-peptide at Week 12, every 3 months, and at the interim endpoint were summarized. Descriptive statistics for change from Baseline in FPG and weight at Week 2, Week 4, Week 8, Week 12, every 3 months, and at the interim endpoint were summarized. Efficacy summaries were provided for both overall and by prior treatment in the pivotal phase 3 studies (Figure 52, Figure 61).

Figure 61. Change from Baseline in HbA1c (%) by study visit for Studies 007, 008, 009, 010, and 011. Solid diamonds indicate treatment with placebo. Solid squares indicate 12.5 mg alogliptin and open circles indicate treatment with 25 mg alogliptin.

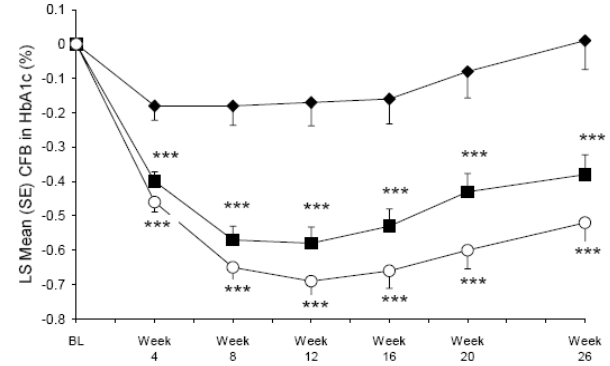
a) Pioglitazone Controlled Study 009.



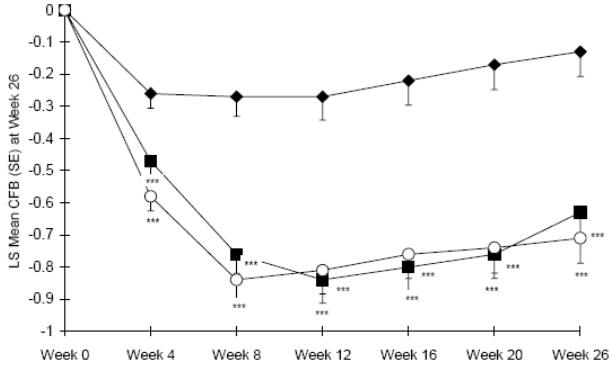
b) Metformin Controlled Study 008.



c) Sulfonylurea Controlled Study 007.



d) Insulin Controlled Study 011.



CFB = Change From Baseline, LS = Least Squares, *** = P < 0.001 compared with placebo.

Details regarding the above figures and analysis and further efficacy data for supportive studies can be found in the sponsor's summary of efficacy.

6.1 population pharmacokinetic analysis

6.1.1 Methods

3.1.1 *Summary of Study Used for Analysis*

Data for this analysis were obtained from Study 008. Study 008 was a phase 3, placebo-controlled, randomized, double-blind study designed to evaluate the PK, safety, and efficacy of 12.5 mg and 25 mg doses of alogliptin (SYR-322) in combination with metformin over 26 weeks of treatment.

3.1.2 *Study Population*

Study 008 included 527 randomized subjects with T2DM who were inadequately controlled with metformin alone. Subjects had been treated with metformin for at least 3 months before screening and had taken a stable dose of metformin ≥1500 mg or their maximum tolerated dose for at least 8 weeks before randomization. Subject HbA1c levels were between 7.0% and 10.0% at screening. Selected inclusion and exclusion criteria are listed in **Table 8.1** and **Table 8.2**. All subjects gave informed consent before entering the study.

3.1.3 *Dose Administration*

The study had a 4-week stabilization period during which subjects were standardized to a generic, immediate-release metformin formulation at a dose equivalent to their previous dose. Subjects received a daily metformin dose of 1500 mg or higher. If a subject had a documented intolerance to this dose, the subject remained at their maximum tolerated dose. The metformin dose remained stable throughout the study.

During the stabilization period, subjects also received dietary and exercise counseling plus training in home glucose monitoring. After the stabilization period, subjects were randomized to 26 weeks of treatment with one of the following three regimens in a 1:2:2 ratio:

- Placebo plus metformin.
- Alogliptin 12.5 mg/day plus metformin.
- Alogliptin 25 mg/day plus metformin.

Treatment assignment was stratified by both HbA1c levels at Week -1 (HbA1c <8.0% versus ≥8.0%) and by geographic region. The randomization mechanism used a stratified permuted block schedule. All doses of study drug (alogliptin, metformin, and placebo) were taken orally with 240 mL of water prior to the first meal of the day. The times of dosing for the visits where PK samples were obtained were recorded.

Given the PK characteristics of alogliptin, plasma concentrations were expected to be at steady state in all subjects by the time PK samples were collected at the Week 4 and Week 8 visits. Therefore, the actual dosing dates and times recorded on the CRFs were used to create a dose record for the day PK samples were collected, and steady state was assumed on the dose record using the NONMEM steady-state variable (SS=1).

3.1.4 *PK Sampling Strategy*

Two blood samples (1 trough and 1 nontrough) were obtained from each subject to determine plasma alogliptin concentrations. The trough sample was collected at the Week 4 visit, approximately 24 hours (range, 22 to 28 hours) after taking the study drug and before taking the next dose. The nontrough sample was collected at the Week 8 visit. The protocol did not specify the time at which this non-trough sample was to be collected. The nontrough sample could be obtained on another day within the randomized treatment period, provided that the subject had received blinded treatment for at least 4 weeks. The times of last study drug intake and the PK blood sample drawn at the Week 4 and Week 8 visits were documented.

3.1.5 *PK Assay Methodology*

Blood samples (2 mL) for determination of plasma alogliptin concentrations were collected into chilled (2°C to 8°C) tubes containing potassium EDTA as the anticoagulant. After collection, the tubes were stored in cryoblocks. Within 20 minutes of collection, samples were centrifuged under refrigeration (2°C to 8°C) at 900*g* for 10 minutes. After processing, the plasma samples were split equally and transferred into duplicate chilled polypropylene tubes. Plasma was stored frozen at -20°C or colder until analyzed for alogliptin concentrations using a validated high performance liquid chromatography method with tandem mass spectrometric detection. The assay had a lower limit of quantitation (LLOQ) of 1 ng/mL [**19**].

3.1.6 *Covariates*

The potential of selected covariates to explain variability in the PK parameters for alogliptin was explored. To avoid potential multicollinearity or confounding of effects in covariate submodels, the correlation between covariates was examined. Pair-wise scatterplots of all continuous covariates and boxplots of continuous covariates versus categorical covariates were generated. If a covariate was found to be highly correlated with another covariate, eg, weight and BSA, one or the other covariate was selected for evaluation based on the likelihood of a physiologic relationship with a parameter or the degree of correlation with a parameter based on univariate analyses.

6.1.2 Results

4.1 **Data**

4.1.1 *Data Description*

A total of 1226 plasma alogliptin concentrations from 526 subjects were received from Takeda Global Research & Development, Inc. (TGRD)for Study 008. Deleted from the dataset were 238 concentrations from 103 subjects who received placebo in the study. A total of 134 plasma concentrations (from 103 subjects) were also removed from the dataset due to missing concentration values, missing sample date or time, or missing previous dose date or time. Minimal imputation for missing covariate values was required for this analysis. Twelve subjects were missing the day and month of birth (imputed 01 July) and one subject had a missing baseline body weight value. Data deletions and exclusions are summarized in **Table 8.4**.

Ten concentration values that were BLQ were excluded from the analysis. These records represented 1.2% of the data and were not treatment-group dependent. Four subjects each had 1 concentration record excluded due to very long (84 and 339 hours) or negative time since last dose (TSLD) values that were not consistent with the study protocol.

During exploratory data analysis, 52 concentrations (23 subjects) were identified as outliers and were excluded from the analysis. These outliers were from individuals who had concentrations that were either 5-fold greater at a later time point than at an earlier time point within the same subject (for concentrations greater than TSLD=3 hours) or that had an absolute weighted residual (WRES) greater than 5 based on preliminary NONMEM runs. All of these concentrations were included in the dataset, but were excluded from the population PK analysis.

After all data deletions and exclusions were made, 788 alogliptin concentrations from 375 subjects were available for analysis. The plasma concentrations of alogliptin ranged from 1.07 to 347 ng/mL.

4.1.2 *Description of Demographic Characteristics and Covariates*

The subjects in Study 008 were evenly distributed by sex. Most subjects were white. For the population as a whole, the median age was 56 years (range, 23 to 80 years). Weight ranged from 45.5 to 141.6 kg, with a mean (SD) of 88 (19.1) kg.

Study 008 had an inclusion criteria of serum creatinine concentration of <1.5 mg/dL for men and <1.4 mg/dL for women. Based on the FDA guidance for clinical pharmacology studies in renally impaired patients, more than half of the subjects enrolled had mild renal impairment (CrCL between 50-80 mL/min) at Baseline, while about a third had normal renal function (CrCL >80 mL/min). Less than 10% of subjects had moderate (CrCL between 30-50 mL/min) or severe renal impairment (CrCL <30 mL/min) at baseline. For details of the demographic characterisitics refer sponsor' poppk report -------, (**Table 8.5**), on page ##.

4.2 **Population PK Model Development**

4.2.1 *Exploratory Data Analysis (EDA)*

Plasma samples for the determination of alogliptin concentrations were collected using a sparse sampling strategy. **Figure 9.2** demonstrates that most samples from Study 008 were collected either within 3 hours or more than 20 hours after dose administration. Each individual subject contributed between 1 and 4 plasma samples during the study. Most subjects contributed only 2 samples, (**Figure 9.3**) each of which was collected on a different study visit.

As shown in **Table 8.5**, Study 008 enrolled a diverse subject population characterized by wide distributions in Baseline CrCL, body size, and age. As expected, a significant correlation between body weight and BSA was identified using pairwise scatterplots of continuous covariates (**Figure 9.4**). In order to avoid potential multicollinearity or confounding effects on covariate submodels, body weight was used as the body-size variable throughout the analysis. This selection was based on the common use of weight-based dosing strategies among physicians practicing in this therapeutic area. Thirty-one

subjects received a cytochrome P450 2D6 substrate, 23 subjects received a cytochrome P450 2D6 inhibitor, and 22 subjects received a renal cation transporter substrate during the time period when sampling occurred. A detailed listing of specific medications from each class of concomitant medication is provided in **Appendix 10.5**.

Semi-logarithmic scatterplots of alogliptin concentration versus TSLD, stratified by dose and renal function category, were the primary figures used to evaluate the PK data (**Figure 9.5** and **Figure 9.6**). The sparse nature of the data made the identification of single exponential or biexponential decay difficult; however, the available data, as well as previous modeling exercises [**17**], supported the evaluation of multicompartment models. Scatterplots of alogliptin concentration versus TSLD stratified by renal function category (**Figure 9.6**) show that concentrations of alogliptin are generally higher as renal function declines. This finding was anticipated and is consistent with the mechanism of excretion of alogliptin (60% to 70% excreted unchanged in the urine).

Examination of plots of alogliptin concentrations versus TSLD with the points joined for each individual (**Figure 9.7**) helped to identify several trends in the data. In some subjects, plasma alogliptin concentrations were smaller at earlier time points than at later time points. These observations are most likely the result of an inaccurate dose or sample collection time or a very high degree of intraoccasion variability in PK. The observations noted above were not immediately removed from the analysis, but were later removed following initial attempts to model the data in NONMEM. These preliminary runs in NONMEM also identified some additional observations with absolute WRES values greater than 5; observations from these subjects were also excluded from the analysis before further model development was attempted.

A scatterplot of alogliptin concentration versus TSLD for subjects who were excluded from the analysis is provided in **Figure 9.8**. Data excluded during EDA represent 6.2% of the overall total number of observations and 5.8% of the subjects who had available data for PK analysis (398 subjects, 840 observations). Thus, the population PK model for alogliptin was developed using 788 observations from 375 subjects.

4.2.2 *Base Structural Model*

Previous studies [**17**,**33**] indicate that alogliptin undergoes biphasic elimination; therefore, a 2-compartment model with first-order absorption and first-order elimination was initially evaluated as the base structural model, using the FOCE method with interaction. IIV was estimated using an exponential error model, and RV was estimated using a constant coefficient of variation (CCV) error model.

Initial implementation of this model did not result in successful minimization of the objective function and produced large estimates of Vp that were not realistic (1.8E8). Given the small amount of plasma concentration data available from Study 008 to describe the distribution phase of alogliptin, this finding was not unexpected. In a previous population PK analysis that used full-profile data from subjects with T2DM [**17**], Vp was estimated with good precision and the demographic characteristics between Study 008 and Study 002 were similar. Based on these assessments from the previous analysis, the typical value of Vp was fixed to 191 L for the current modeling effort.

A 2-compartment open model with first-order input, first-order elimination, and Vp fixed to 191 L was applied to the alogliptin plasma concentration data in order to estimate the following parameters: ka, CL/F, Vc/F, and Q. IIV was estimated on ka, CL/F, and Vc/F. The estimated population mean values are shown in **Table 8.6**. The PK parameters were estimated with acceptable precision, and the magnitude of IIV was moderate for ka, CL/F, and Vc/F. RV was also relatively small for these sparse data at 32.71 %CV.

Goodness-of-fit plots (**Figure 9.9** through **Figure 9.14**) indicate a reasonable and relatively unbiased base model fit. **Figure 9.9** shows a small underprediction in peak and trough alogliptin plasma concentrations in some subjects, and **Figure 9.11** demonstrates an equal distribution of WRES above and below zero, with only a few larger WRES at lower predicted concentrations. Other models with more IIV terms or alternative residual error structure (additive plus proportional, log-error) were also explored; however, these modifications did not result in an improvement in the goodness of fit or resulted in numerical estimation difficulties, and were therefore not retained.

The parameter estimates and the assessment of goodness-of-fit plots described above indicate that the 2-compartment model is an acceptable base model. Although a 1-compartment model may also describe the data from Study 008, previous studies and population PK analyses have demonstrated that alogliptin undergoes a biphasic elimination and therefore the 1-compartment model was not evaluated [**17**,**33**]. The 2-compartment open model with first-order input, first-order elimination, and a Vp fixed to 191 L was selected as the base structural model.

4.2.3 *Forward Selection of Subject Covariates*

A covariate analysis was performed in order to explore the sources of variability in alogliptin PK. Forward selection of stationary covariates was completed first, followed by forward selection of time-varying covariates. Delta parameter versus covariate plots for CL/F and Vc/F were used to identify relationships between covariates and parameters (CL/F and Vc/F). Delta parameter versus covariate plots for the base structural model are provided in **Figure 9.15** and **Figure 9.16**. Due to small sample size in many of the groups for the categorical covariate "race," only 2 groups could be evaluated (white and other than white).

Results of the forward selection process are provided in **Table 8.7**. In addition, the change in MVOF and functional forms used (see **Appendix 10.4**) for each step of forward selection are provided in **Appendix 10.6**.The effect of CrCL as a power function on alogliptin CL/F produced the most significant effect and was the first covariate added to the model. The addition of CrCL to the model produced a 3.5 percentage point reduction in IIV on CL/F (from 28.09 %CV to 24.56 %CV) and a statistically significant drop in the MVOF (P=2.22E-16).

The second round of forward selection identified the effect of weight as a power function on Vc/F as the most important contributor to alogliptin PK. The addition of weight to the model resulted in a 20.2 percentage point reduction in IIV on Vc/F (from 29.17 %CV to 8.94 %CV) and a statistically significant drop in the MVOF (P=2.32E-13).

In the third round of forward selection, the most significant effect was that of weight as a linear function on alogliptin CL/F. The addition of weight on CL/F resulted in a 0.84

percentage point reduction in IIV on CL/F (from 25.94 %CV to 25.10 %CV) and a statistically significant drop in the MVOF (P=0.000021).

The fourth round of forward selection evaluated the effect of age on CL/F as a power function. Although the effect of age on CL/F resulted in a statistically significant reduction in the MVOF (P=0.000177), the additional parameter was estimated with poor precision [standard error of the parameter estimate divided by the parameter estimate·100% (%SEM) >150]. In addition, the implementation of age on CL/F in the model led to many correlations between parameters and model instability. As a result, age was not added to the model, and forward selection of stationary covariates was considered complete.

Following completion of forward selection for stationary covariates, the assessment of time-varying covariates was completed. All time-varying covariates were tested as additive shifts on both CL/F and Vc/F. The addition of time-varying covariates did not result in any statistically significant reductions in MVOF (P >0.1) and therefore, none were included in the model.

4.2.4 *Evaluation of the Full Multivariable Model and Statistical Error Models*

The IIV and RV models in the full multivariable model were further evaluated following forward selection of covariates. A significant correlation was noted between IIV on CL/F and IIV on Vc/F (P<0.0001), as well as between IIV on ka and IIV on Vc/F (P<0.0001) (**Figure 9.17**). This finding led to the investigation of off-diagonal omega block terms. The estimation of covariance between the IIV terms produced numerical problems for the estimation of IIV on ka and also indicated a significant correlation between IIV terms that could be estimated (IIV on CL/F and IIV on Vc/F, r=1). In order to avoid parameter boundary errors in NONMEM VI (initiated when a between-subject covariance yields a correlation close to 0, 1, or -1), IIV on Vc/F was estimated using the random effect term for the IIV on CL/F, multiplied by an estimated scalar constant, θ. The random effects model can be described using **Equation 6** and **Equation 7**:

$$CL/F_i = TVCL/F \cdot \exp(\eta_{i,CL}) \quad \textbf{(6)}$$

$$Vc/F_i = TVVc/F \cdot \exp(\eta_{i,CL}) \quad \textbf{(7)}$$

Where:

CL/F_i = the predicted value of clearance for the *ith* individual;

TVCL/F = the typical predicted value of clearance;

η_i = the IIV on CL/F for the *ith* individual;

Vc/F_i = the predicted value of central volume of distribution for the *ith* individual;

TVVc/F = the typical predicted value of central volume of distribution; and

θ = the ratio of the standard deviation of interindividual variability in volume and clearance (ω_v/ω_{cl}).

The variance for Vc/F can now be described by **Equation 8**:

$$\text{variance (Vc/F)} = \theta_2 \cdot \text{variance (CL/F)} \quad \textbf{(8)}$$

Assuming the IIV on CL/F and IIV on Vc/F were perfectly correlated (using the same random effect term) enabled NONMEM to converge without errors and permitted the estimation of IIV on ka.

Following evaluation of off-diagonal elements of omega, the addition of more IIV terms was evaluated (ie, IIV on Vp, Q, and both Vp and Q). Addition of more IIV terms to the model was not supported by the available data and caused numerical problems; therefore, no further IIV terms could be estimated in the model.

No further modifications to the residual error structure were evaluated based on the equal distribution below and above 0 on the goodness-of-fit plot of individual WRES versus individual predicted alogliptin concentrations.

4.2.5 *Backward Elimination of Subject Covariates*

Univariate backward elimination proceeded after evaluation of the IIV and RV error models. Each covariate was removed from each parameter equation separately, and the change in MVOF was used to evaluate the statistical significance of the contribution of the parameter removed. No covariates were removed according to the criteria described in **Section 3.3.8** (P = <0.000011 for all covariates). Because no covariates were removed during backward elimination, the reduced multivariable model is identical to the 2-compartment open model with first-order input, first-order elimination, and Vp fixed to 191 L following modifications to the IIV random effects model.

4.2.6 *Model Refinement*

Model refinement consisted of evaluating the effects of fixed parameters in the model, and investigating the influence of any remaining high weighted residuals. Fixed parameters (Vp) were evaluated by estimating the parameter in the model and with a sensitivity analysis. When Vp was not fixed, the model would not converge successfully or suffered from numerical difficulties, despite numerous permutations of the initial estimates.

Following unsuccessful attempts to estimate Vp, a sensitivity analysis was conducted to determine if the fixed value for Vp (191 L), which was identified from a previous study in subjects with T2DM, produced the smallest MVOF. Initially, values between -50% and +100% of 191 L were evaluated. This approach was modified as large values of Vp continued to produce small decreases in MVOF. The MVOF continued to decrease at +10000% (~19000 L) of the reference value (**Figure 9.18**). **Table 8.8** demonstrates that large changes in Vp had a minimal effect on the estimation of the other model parameters and suggests that the model is insensitive to changes in Vp. This idea is supported by **Figure 9.19**, which shows that large alterations in Vp primarily affect the shape of the alogliptin concentration-time profile outside the range of data available in this study (ie, TSLD>30 hr). Thus, although **Figure 9.18** suggests that the Vp may be greater than 191

L in this study, the data do not support the accurate estimation of this parameter. Therefore, a Vp of 191 L was retained in this analysis.

Finally, the influence of absolute WRES values >5 was evaluated. Removing all absolute WRES >5 had minimal impact on the main alogliptin PK parameters (ka, CL/F, Vc/F, and Q). The absorption constant increased by ~13%, CL/F and Vc/F increased by less than 1%, and Q decreased by less than 3%. Based on these findings, the 11 observations with absolute WRES >5 were determined to have no significant impact on the population PK model for alogliptin and were retained in the analysis.

4.2.7 *Final Population PK Model*

The final population PK model for alogliptin was a 2-compartment model with first-order absorption and first-order elimination. The peripheral volume of distribution was fixed to 191 L because inadequate data were available to describe the distribution phase and the Vp of 191 L from Study 002 in subjects with T2DM was reasonably well estimated. In addition, Studies 002 and 008 had similar subject demographics. IIV was estimated on ka and CL/F using an exponential error model and was obtained for Vc/F by allowing Vc/F and CL/F to share an eta and then estimating the ratio of the standard deviation of Vc/F to the standard deviation of CL/F using a fixed effect parameter. RV was described using a CCV error model. Significant covariate relationships included the effect of CrCL as a power function on alogliptin CL/F, weight as a power function on alogliptin Vc/F, and weight as a linear function on alogliptin CL/F. Equations for calculating the typical value of CL/F and Vc/F for the final model are provided in **Equation 9** and **Equation 10**, respectively. The final parameter estimates and standard errors estimated from the final model in Study 008 are provided in **Table 8.9**. All parameters were estimated with good precision except for ka and the term estimating the ratio of the standard deviations for Vc/F and CL/F, which were estimated with moderate precision, and IIV on ka which was estimated with poor precision. RV was moderate at 32.25 %CV.

$$TVCL/F_i(L/hr)=17.8\cdot\left(\frac{CrCL}{72.95}\right)^{0.375}+0.086\cdot(WTKG-85.15)$$

(9)

$$TVVc/F_i(L)=187\cdot\left(\frac{WTKG}{85.15}\right)^{1.5}$$

(10)

Where:

$TVCL/F_i$ = the typical value of the apparent oral clearance for the i_{th} subject;

$TVVc/F_i$ = the typical value of the apparent central volume of distribution for the i_{th} subject;

$CrCL_i$ = creatinine clearance in the i_{th} subject; and

$WTKG_i$ = weight (kg) for the i_{th} subject.

Figure 9.20 and **Figure 9.21** show the typical predicted values for CL/F across a range of CrCL and body weight, respectively.

Goodness-of-fit plots (**Figure 9.22** through **Figure 9.27**) generated from the final model indicate that the model was significantly enhanced by the inclusion of covariate effects. For example, plots of observed alogliptin plasma concentration versus predicted alogliptin plasma concentration (**Figure 9.22**) show that a relatively unbiased fit was achieved. Observed alogliptin plasma concentrations versus individual predicted alogliptin concentrations (**Figure 9.26**) demonstrate similar findings. Plots of WRES versus predicted alogliptin concentrations (**Figure 9.24**) show an equal distribution above and below 0, with only a few high WRES noted at lower alogliptin concentrations. In addition, **Figure 9.23** demonstrates that a CCV error model is appropriate and **Figure 9.25** suggests that there is no pattern in the weighted residuals over the dosing interval. Finally, the plot of individual WRES versus individual predicted alogliptin concentration (**Figure 9.27**) shows an acceptable distribution above and below 0, indicating that the error model for RV was sufficient. Individual overlay plots of typical value predicted alogliptin concentration, individual predicted alogliptin concentration, and observed alogliptin concentration also indicated overall good model fit (**Figure 9.28**).

Histograms of eta distributions (**Figure 9.29**) generated for the final model show that IIV for ka and CL/F are approximately normally distributed with a mean of approximately 0. Eta biplots (**Figure 9.30**) generated for the final model show that by allowing CL/F and Vc/F to share the same eta, there were no longer any significant correlations (P=0.6595) between IIV terms. In addition, delta parameter versus covariate plots for the final model indicate that there were no strong relationships remaining that could be evaluated (**Figure 9.31** and **Figure 9.32**).

Finally, the 52 observations classified as outliers that were removed from the analysis during EDA were placed back in the model to test their influence on the estimation of alogliptin parameters. The final population PK model including outliers produced minimal changes in PK parameter estimates, but did not permit the estimation of IIV on ka. CL/F and Vc/F changed by less than 3%; ka increased by approximately 12%; and Q increased by approximately 13%.

The control stream and report file for the final model are provided in **Appendix 10.7**.

4.2.8 *Model Qualification*

Model qualification was assessed using the visual predictive check method. One thousand steady-state datasets were simulated using subject dose and demographic characteristics from the observed dataset. The 5th, 50th (median), and 95th percentiles of plasma alogliptin concentration were calculated from each time point (every 5 minutes for 5 hours and every 10 minutes to 40 hours). The 5th, 50th, and 95th percentiles (**Appendix 10.8**) were plotted by dose and the corresponding observed concentrations from the analysis dataset were overlaid (**Figure 9.33** and **Figure 9.34**). The visual predictive check shows that most of the data fell within the 5th and 95th percentiles, indicating that the model developed for alogliptin adequately describes the data from Study 008.

4.2.9 *Summary of PK Parameters and Bayesian Predicted Individual Exposure Measures*

Summary statistics of individual predicted Bayesian PK parameters are provided in **Table 8.10** and a listing of individual predicted Bayesian PK parameters are provided in **Appendix 10.9**. The terminal elimination half-life for alogliptin, calculated using the

typical predicted values from the final model, was 20.9 hours. **Table 8.11** and **Table 8.12** show summary statistics for individual predicted exposure measures [AUC(0-24), Cmax, and C(24)] stratified by dose and renal function category as defined in the FDA Guidance for Pharmacokinetics in Patients with Impaired Renal Function [**34**].

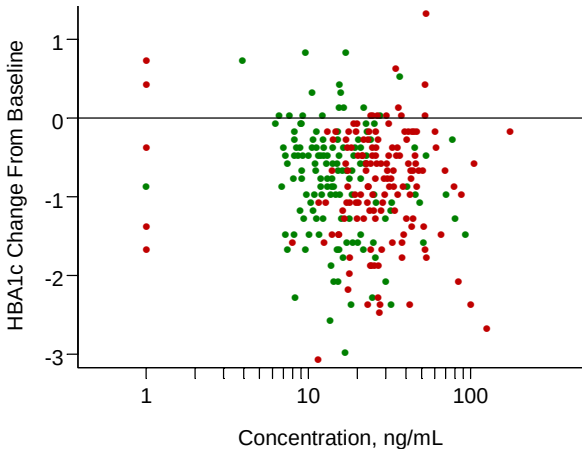
4.2.10 *Assessment of Clinical Relevance of Covariates*

Typical predicted steady-state CL/F, Vc/F, AUC(0-24), and C(24) values over a range of high and low values for CrCL and body weight are presented in **Table 8.13**. In addition, typical predicted alogliptin concentration-time profiles over a range of high and low values for CrCL and weight after receiving a 12.5 mg or 25 mg dose are also provided (**Figure 9.35** through **Figure 9.38**).

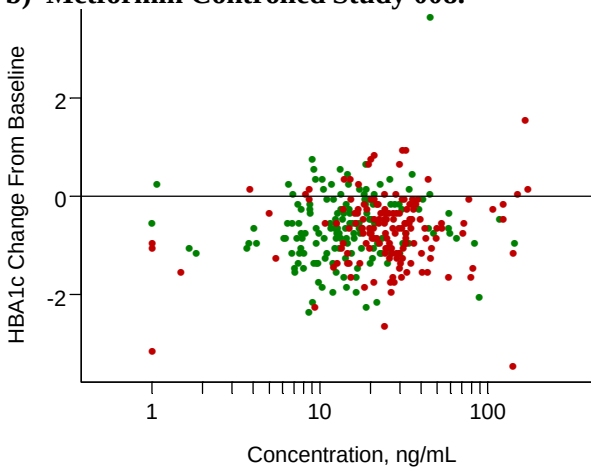
7 Appendix B: Alogliptin Concentration-Response plots for Phase III Studies

Figure 62. HBA1c Reduction from Baseline is not Dependent on Alogliptin Concentrations in Studies 007, 008, 009, 010, and 011. Green and Red Dots Indicate Low (12.5 mg) and High (25 mg) Dose Groups of Alogliptin.

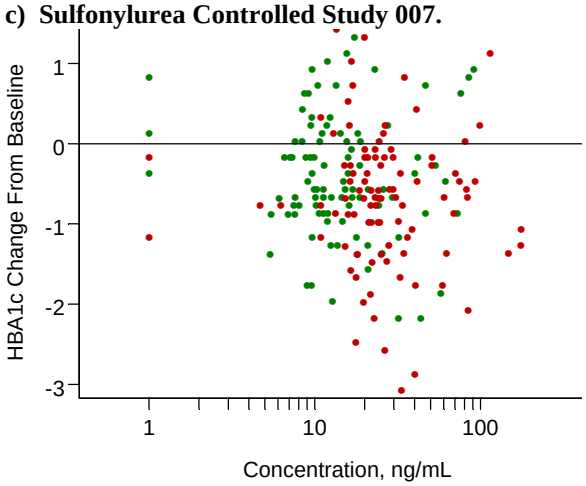
a) Pioglitazone Controlled Study 009.



b) Metformin Controlled Study 008.



c) Sulfonylurea Controlled Study 007.



d) Insulin Controlled Study 011.

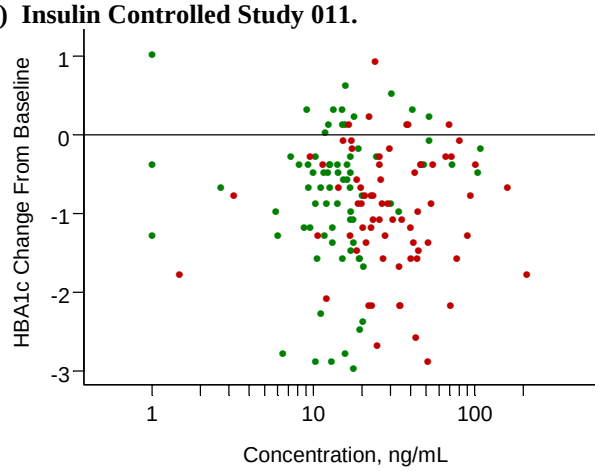
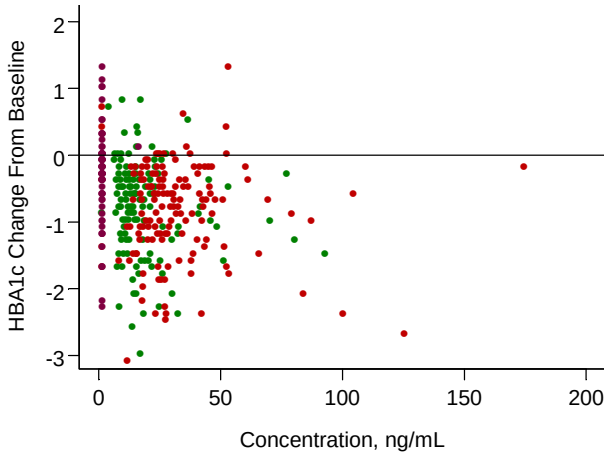
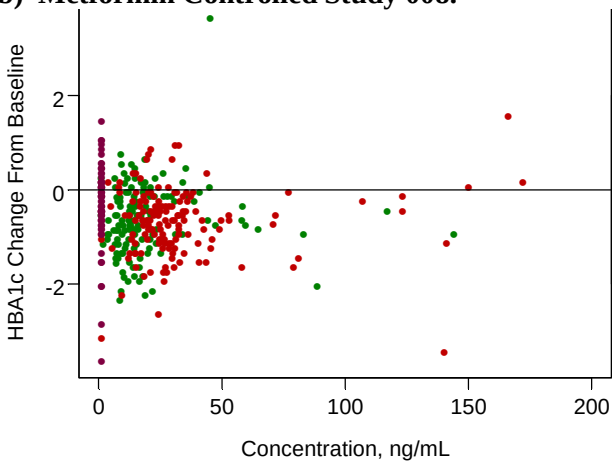


Figure 63. HBA1c Reduction from Baseline is not Dependent on Alogliptin Concentrations in Studies 007, 008, 009, 010, and 011. Green and Red Dots Indicate Low (12.5 mg) and High (25 mg) Dose Groups of Alogliptin. Purple Dots Indicate Placebo Group.

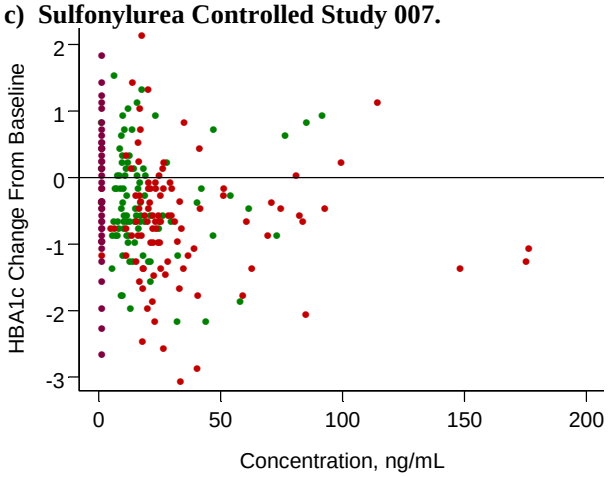
a) Pioglitazone Controlled Study 009.



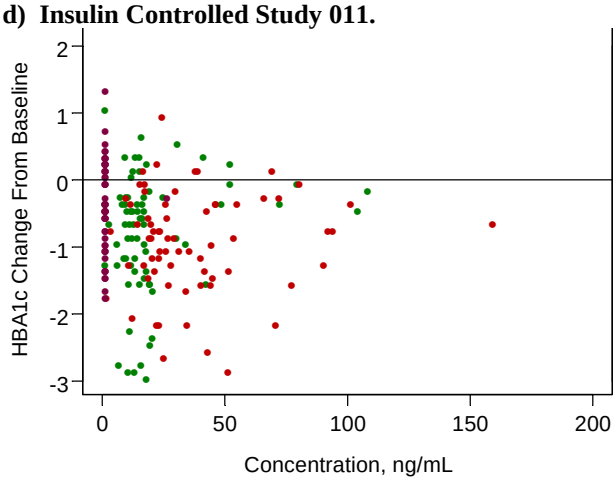
b) Metformin Controlled Study 008.



c) Sulfonylurea Controlled Study 007.



d) Insulin Controlled Study 011.



8 APPENDIX C: Table of Patients With Cardiac Events

Study	Treatment, mg	Subject ID	Cardiac Serious Treatment-Emergent Adverse Event	Alogliptin Trough Concentration	Predicted C_{max} Concentration
003	6.25	265-2017	Non-cardiac chest pain	1.22	24.495
003	25	105-2019	Angina pectoris	44.7	101.05
003	25	109-2008	Non-cardiac chest pain	.	108.45
003	***>25***	***249-2004***	***Angina pectoris***	***198***	***476.68***
007	12.5	256-7021	Cardiac failure congestive	21	54.449
007	12.5	315-7002	Arteriosclerosis coronary artery	9.6	46.474
007	12.5	422-7017	Myocardial infarction	74	60.793
007	12.5	424-7008	Electrocardiogram change	.	63.623
007	12.5	435-7002	Non-cardiac chest pain	10.5	42.801
007	25	239-7001	Angina pectoris	6.26	105.41
007	25	383-7021	Angina pectoris	23.3	120.98
008	Placebo	485-8008	Angina unstable	0	0
008	12.5	263-8006	Bradycardia	22	38.083
008	12.5	520-8010	Hypertensive heart disease	.	41.839
008	25	223-8006	Cardiac failure congestive	28.7	129.43
008	25	315-8012	Non-cardiac chest pain	76.9	106.29
008	25	447-8017	Non-cardiac chest pain	16.8	96.061
009	12.5	107-9005	Myocardial infarction	9.74	53.002
009	12.5	422-9009	Angina pectoris	<1	54.336
009	12.5	422-9009	Coronary artery disease	<1	54.336
009	12.5	463-9003	Sudden death	11.1	51.687
009	***25***	***107-9011***	***Cardiac failure congestive***	***116***	***99.311***
009	25	252-9006	Myocardial infarction	<1	90.802
009	25	301-9005	Angina pectoris	22.7	90.935
009	25	320-9003	Myocardial infarction	.	94.365
009	25	429-9002	Cardiac failure congestive	47.1	142.37
010	12.5	252-4005	Non-cardiac chest pain	18.9	64.636
010	12.5	440-4008	Palpitations	10	35.111
010	25	442-4005	Angina pectoris	16.5	94.273
011	Placebo	484-5001	Angina unstable	0	0
011	12.5	244-5024	Coronary artery disease	24.5	50.625
011	12.5	307-5003	Atrial fibrillation	35.4	60.801
011	12.5	329-5006	Atrial fibrillation	16.9	41.825
011	12.5	464-5005	Sudden death	<1	53.023
011	25	395-5008	Angina unstable	3.77	105.86

9 APPENDIX D: Pharmacokinetic Model Predictions

Figure 64. Revised Population PK Model Prediction of 100-mg Multiple Dosing in Study 002.

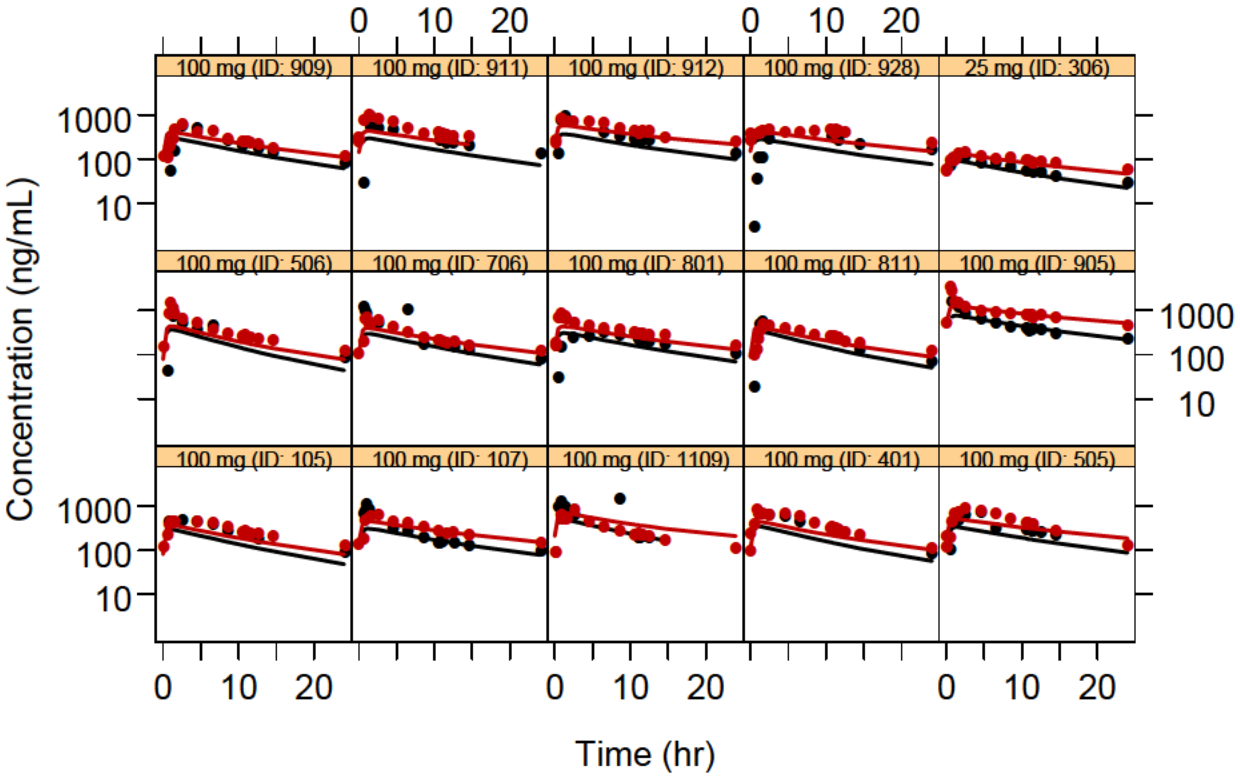
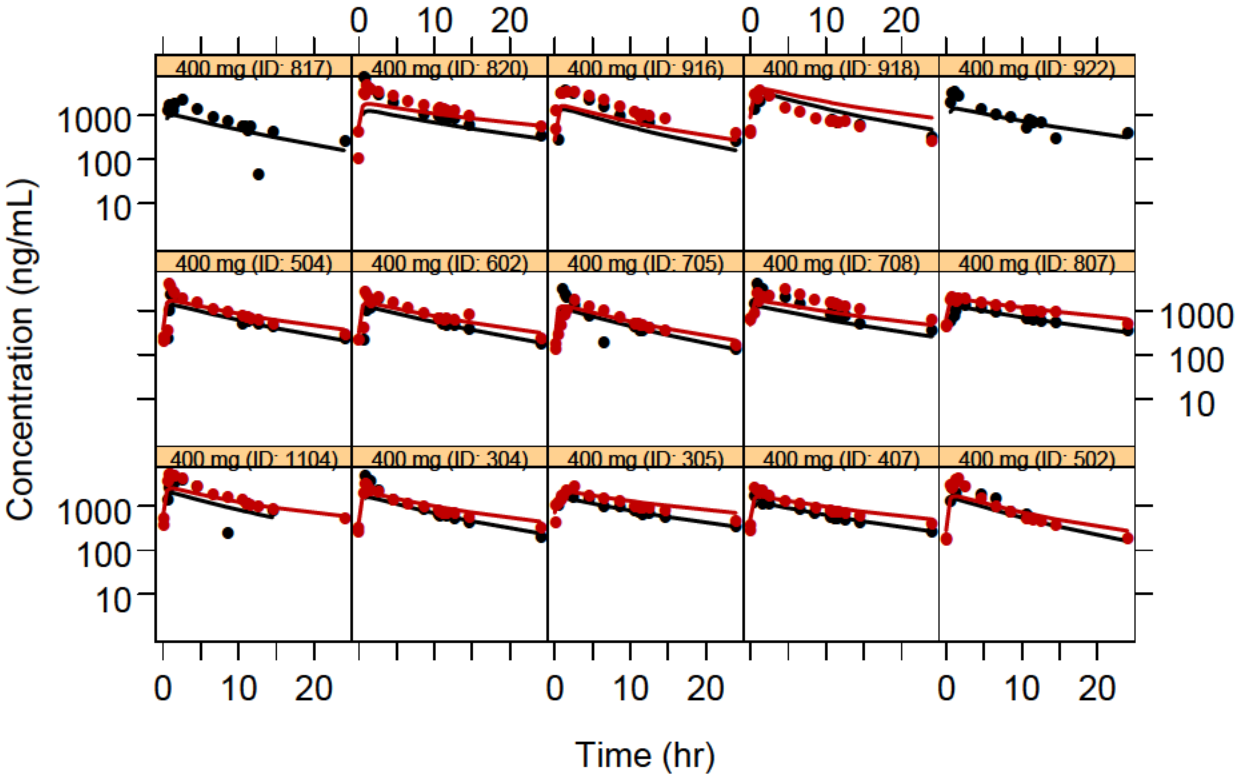


Figure 65. Revised Population PK Model Prediction of 400-mg Multiple Dosing in Study 002.



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