Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 022271/NDA 203414
Link to EDR	\\CDSESUB1\evsprod\NDA022271\0237 \\CDSESUB1\evsprod\NDA203414\0182
Submission Date	9/28/2022
Submission Type	Standard review
Brand Name	Nesina (alogliptin)/Kazano (alogliptin and metformin hydrochloride)
Generic Name	Alogliptin
Dosage Form and Strength	6.25 mg, 12.5 mg and 25 mg tablets
Route of Administration	Oral
Proposed Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant	Takeda Pharmaceuticals USA, Inc
Associated IND	IND 069707 / IND 101628
OCP Review Team	Dong Guo, Ph.D. Edwin Chiu Yuen Chow, Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY 3
1.1 Recommendations 4
1.2 Post-Marketing Requirements and Commitments 5
2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT 5
2.1 Pharmacology and Clinical Pharmacokinetics 5
2.2 Dosing and Therapeutic Individualization 5
2.2.1 General dosing 5
2.2.2 Therapeutic individualization 5
2.3 Outstanding Issues 5
2.4 Summary of Labeling Recommendations 5
3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW 5
3.1 Overview of the Product and Regulatory Background 5
3.2 General Pharmacology and Pharmacokinetic Characteristics 6
3.3 Clinical Pharmacology Review Questions 7
3.3.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims? 7
3.3.2 How is alogliptin measured across studies? 8
3.3.3 What is the PK and PD characteristics of the drug in dose finding study (Study 104)? 8
3.3.4 Whether the slightly decreased observed exposure of alogliptin in pediatric patients compared to adults is the reason for insignificant HbA1c reduction in pediatric patients? 12

1. EXECUTIVE SUMMARY

Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4) indicated to use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Takeda Pharmaceuticals USA, Inc has submitted the final study report for SYR-322-309 as required under Pediatric Research Equity Act (PREA), to fulfil Post-marketing Requirements (PMRs) 2007-2 and 2007-3 for NESINA (NDA 022271) and PMR 2009-1 for KAZANO (NDA 203414).

- PMR 2007-2: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin when added on to metformin in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10-14 years of age, and at least one-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.
- PMR 2007-3: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin in pediatric patients ages 10 through 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10-14 years of age, and at least on-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.
- PMR 2009-1: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin when added on to metformin in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10-14 years of age and at least one-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.

The study is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of alogliptin 25 mg once daily (QD) compared with placebo when administered as monotherapy, or when added onto a background of metformin alone, insulin alone, or a combination of metformin and insulin, in pediatric subjects aged 10 to 17 years (inclusive) with a confirmed diagnosis of T2DM who were experiencing inadequate glycemic control. The study failed the primary clinical endpoints of HbA1c. Thus, an indication for this population is not being requested. The supplement includes proposed language to update Section 8.4 *Pediatric Use* of the US prescribing information to describe the findings from the phase 3 pediatric study, SYR-322_309.

The clinical pharmacology review focuses on pharmacokinetics (PK) and pharmacodynamics (PD) data and analyses that were submitted, adult PK, PD, and clinical data in the original NDA submission, and rationales surrounding any uncertainty of a lack of clinical benefits of alogliptin in pediatric patients. The pediatric program of alogliptin consisted of one Phase 1 dose finding study (Study SYR-322_104, also refer as Study 104) and one Phase 3 study (Study SYR-322_309, also refer as Study 309). The dose finding study was conducted to compare the PK and PD of alogliptin in pediatric and adult T2DM patients (SYR-322_104, age 10-18, N = 24 and adults, N=22) to support the dose selection for Phase 3 study (Study 309) in pediatric patients (aged 10 to < 18 years old). In Study 104, the PK/PD results following a single alogliptin dose of 25 mg in pediatric (10 to < 18 years old) and adult subjects

suggested slightly lower PK and PD (DPP-4 inhibition % in plasmas) responses for younger children (10 - < 14 years old). However, steady state PK/PD simulations suggested that PK and PD were comparable for pediatric patients aged 10 to < 18 years old and adult patients, and was used for the basis to support the 25 mg dose in Study 309. As mentioned previously, in Study 309, there was no significant HbA1c reduction in pediatric patients as compared to placebo (See clinical review for details). A review of the clinical PK and PD data for adult patients in the original NDA was conducted, which found saturation of DPP-4 inhibition and HbA1c reduction at 12.5 mg dose and comparable efficacy for both 12.5 mg and 25 mg doses. As such, PK data of adult and pediatric patients were compared. The data suggested that PK exposures (C_{max} and AUC) in pediatric patients (at 25 mg) were higher than those in adult patients (at 12.5 mg). Based on clinical data across clinical trials (adult and pediatric patients), HbA1c change in pediatric patients in Study 309 at 25 mg was smaller than that observed in adult patients in other clinical trials. Therefore, the slightly lower PK exposure in pediatric patients observed in Study 104 is unlikely to explain the reason of insignificant reduction in HbA1c in Study 309.

Based on the results from the study in the current submission, the Applicant has fulfilled all requirements for PMR 2007-2, 2007-3, and 2009-1. The results from the study in this submission are updated to the currently approved package insert.

1.1 Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Study 309 did not demonstrate effectiveness in pediatric patients aged 10 to < 18 years old. The slightly lower PK exposure in pediatric patients observed in Study 104 is unlikely to explain the reason of insignificant reduction in HbA1c in Study 309.
General dosing instructions	Not applicable.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Not applicable.
Labeling	Not applicable.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable.
Other (specify)	Not applicable.

1.2 Post-Marketing Requirements and Commitments

No additional post-marketing requirements (PMRs) or post-marketing commitments (PMCs) is needed.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Refer to package insert of NESINA®.

2.2 Dosing and Therapeutic Individualization

The applicant did not propose an indication in pediatric patients.

2.2.1 General dosing

This section is not applicable for this NDA supplement.

2.2.2 Therapeutic individualization

This section is not applicable for this NDA supplement.

2.3 Outstanding Issues

This section is not applicable for this NDA supplement.

2.4 Summary of Labeling Recommendations

The Applicant did not propose any new change to the clinical pharmacology section 12.3. We recommend deleting the following language (b) (4)

(b) (4)

(b) (4)

The recommended modification is highlighted (addition, ~~deletion~~).

Section 12.3 Pharmacokinetics

Special Populations

(b) (4)

(b) (4)

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Both Nesina (alogliptin) and Kazano (alogliptin and metformin) were approved on January 25, 2013, and the following post-marketing requirements (PMRs) were issued at the time of NDA approval for Nesina and Kanano.

NDA 022271 (Nesina)

> PMR 2007-1: A clinical pharmacology study in pediatric patients with type 2 diabetes to evaluate the pharmacokinetics of alogliptin and to determine the dose(s) for the subsequent Phase 3 studies that will be conducted under the Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of alogliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive). At least 25% of randomized subjects will be 10-13 years of age.
>
> PMR 2007-2: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin when added on to metformin in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10-14 years of age, and at least one-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.
>
> PMR 2007-3: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin in pediatric patients ages 10 through 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10-14 years of age, and at least on-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.

NDA 203414 (Kazano)

> PMR 2009-1: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin when added on to metformin in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10-14 years of age and at least one-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.

The final study report for PMR 2007-1 was submitted on June 24, 2014, and the PMR fulfillment letter was issued on January 21, 2016 (clinical pharmacology review dated 6/25/2015 in DARRTS). After several discussions between the Applicants and the Agency (written response dated 12/12/2014 and 7/21/2015, and advice letter dated 3/3/2015 in DARRTS), the final protocol for SYR-322_309 to fulfill the other three PMRs (2007-2, 2007-3 and 2009-1) was acknowledged on July 31, 2015.

The Applicants submitted the study report for the phase 2 trial in pediatric patients with T2DM, SYR-322_309 in this review circle which was an efficacy supplement for regulatory action.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Refer to package insert of NESINA®.

3.3 Clinical Pharmacology Review Questions

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

There are two clinical trials conducted in the pediatric program of alogliptin. Table 1 summarizes the basic information and PK sampling for the two clinical studies conducted in pediatric T2DM patients.

Table 1: Clinical studies conducted in Pediatric T2DM patients.

Study	Design	Dose (mg)	Age group (N)	PK sampling
104	single dose, pk/pd/safety, dose finding study, pediatric and adult T2DM	12.5 mg	10 to < 14 yrs (5) 14 to < 18 yrs (7)	Predose, 1, 2, 4, 8, 12, 16, 24, 48, and 72 hours post dose
		25 mg	10 to < 14 yrs (4) 14 to < 18 yrs (7) Adults (22)	
309	multiple doses, efficacy and safety in pediatric T2DM	25 mg	10 to < 14 yrs (23) 14 to < 18 yrs (52)	One post dose at baseline (Day 1), weeks 12 and weeks 39, two samples at weeks 26, one sample at least 1 hour post dose and one ~ 24 to 36 hours post dose

SYR-322_104 (also refer as Study 104): A phase 1, randomized, open-label, single-dose, multicenter study that was designed to evaluate the PK, PD, and safety of alogliptin in pediatric subjects with T2DM and gender- and race-matched adult subjects with T2DM. The primary objective of this study is to compare the PK and PD of alogliptin in pediatric and adult T2DM patients to support the dose selection for Phase 3 study (Study 309) in pediatric patients (aged 10 to 17 years old, inclusive). Subjects in each pediatric group (Group 1, aged 10 to <14 years; and Group 2, aged 14 to <18 years) were randomized in a 1:1 ratio to 1 of 2 alogliptin dose levels (12.5 or 25 mg). All adult subjects (Group 3) received alogliptin 25 mg. Study drug was administered orally on Day 1 morning after an overnight fast of at least 8 hours (water was allowed during the fast). The PK exposures (C_{max} and AUC) of alogliptin and its pharmacodynamics endpoints (DPP-4 inhibition rate and baseline adjusted plasma GLP-1 concentration) in two groups of pediatric and one group of adult T2DM patients were analyzed. The result from this study is to guide the dose selection in pediatric patients with T2DM for the efficacy and safety evaluation clinical trial(s).

SYR-322_309 (also refer as Study 309): A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of alogliptin compared with placebo in pediatric subjects aged 10 to 17 years, inclusive, at the time of randomization, with a confirmed diagnosis of T2DM who were experiencing inadequate glycemic control. The primary objective of this study was to evaluate the efficacy of 25 mg alogliptin once daily (QD) compared with placebo when administered as monotherapy, or when added onto a background of metformin alone, insulin alone, or a combination of metformin and insulin, as measured by the glycosylated hemoglobin (HbA1c) change from baseline at Week 26 in pediatric subjects with T2DM. On Study Day 1, eligible subjects were randomly assigned in a 1:1 ratio to 1 of 2 treatment groups, 25 mg alogliptin QD or matching placebo. In addition to receiving double-blind study treatment, subjects were required to maintain their background antidiabetic therapy (if applicable) at the same dose throughout the first 26 weeks of the double-blind treatment period. Subjects who completed the 52-week double-blind treatment period completed an end-of-treatment visit and a follow-up visit 2 weeks after the end-of-treatment visit. Subjects who terminated double-blind study treatment prematurely also completed an end-of-treatment visit and a follow-up visit 2 weeks after the end-of-treatment visit. They were followed for the 52-week duration of the study and completed a projected Week-52 visit.

The descriptive statistics for pharmacokinetic parameters, estimated by noncompartmental analyses, were available for Study 104. In Study 309, sparse PK sampling were collected and used to refine the population PK model. The model was not fully reviewed as Study 309 did not establish effectiveness of alogliptin.

3.3.2 How is alogliptin measured across studies?

Plasma concentration of alogliptin was measured in the collected PK samples for Study 104 and 309. The bioanalytical method used for measuring the alogliptin concentration was the same as what is used in the original NDA submission. See clinical pharmacology review for details (clinical pharmacology review dated 8/28/2008 in DARRTS).

3.3.3 What is the PK and PD characteristics of the drug in dose finding study (Study 104)?

Pharmacokinetics characteristics:

The PK parameters obtained following a single dose from non-compartmental analyses of Study 104 were summarized in Table 2. The mean C_{max} and $AUC_{0\text{-}inf}$ values of alogliptin were 23% to 29% lower in pediatric subjects than in adult subjects after a single oral administration of alogliptin 25 mg. In each pediatric age group, the mean C_{max} and $AUC_{0\text{-}inf}$ values of alogliptin were approximately dose proportional for doses between the 12.5 mg and 25 mg. The mean $t_{1/2}$ values of alogliptin appeared to be generally similar in pediatric and adult subjects, as did the mean V_z/F values. The inter-subject variability for all plasma pharmacokinetic parameters of alogliptin was low (9% - 29%) except that for C_{max} in 12.5 mg administration group were 38% (n=5) and 55% (n=7) in age 10 to <14 yrs old group and age 14 to <18 yrs old group, respectively.

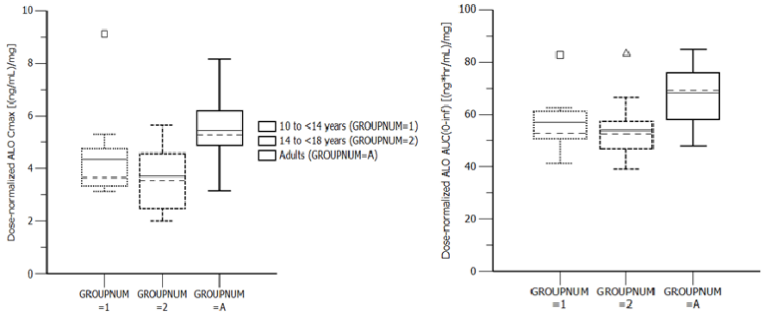
Table 2. Summary of Plasma Pharmacokinetic Parameter Estimates of Alogliptin Following a Single Oral Administration of Alogliptin 12.5 or 25 mg Tablets to Children, Adolescents, and Adults With T2DM

Treatment	Group	N	Statistic	Tmax (hr) (a,b)	Cmax (ng/mL)	AUC(0-inf) (ng·hr/mL)	CL/F (L/hr)	Vz/F (L)	T1/2 (hr)
ALO 12.5 mg	10 to <14 years	5	Mean	4.00	57.8	789	16.21	387.71	16.75
			%CV	2.00, 4.08	55	18	16	20	19
	14 to <18 years	7	Mean	3.00	44.2	689	19.18	426.03	15.38
			%CV	1.00, 23.97	38	27	23	26	12
ALO 25 mg	10 to <14 years	4	Mean	2.04	101.4	1222	20.65	543.36	18.09
			%CV	2.00, 2.08	23	10	12	22	10
	14 to <18 years	7	Mean	3.97	96.7	1318	19.11	468.69	17.15
			%CV	1.00, 4.08	29	9	10	19	21
	Adults	22	Mean	2.00	136.5	1704	15.06	420.79	19.33
			%CV	1.00, 4.07	25	16	17	25	17

Source: Table 15.2.2.1.
(a) Median is presented for Tmax instead of mean.
(b) Minimum, maximum is presented for Tmax instead of %CV.

Source: Table 11.d. Study report of SYR-322-104, Section 11.4, Page 57.

Figure 1. Box Plots of Dose-Normalized C_{max} and $AUC_{0\text{-}inf}$ values of Alogliptin Following a Single Oral Administration of Alogliptin 12.5 or 25 mg Tablets to Children, Adolescents, and Adults With T2DM



Note: The lower and upper boundaries of the box indicate the 25th and 75th percentiles, respectively; the solid and dashed lines within the box indicate the mean and median, respectively; the whiskers show the lowest data value within 1.5 IQR of the lower quartile, and the highest value within 1.5 IQR of the upper quartile, where IQR is the interquartile range (the difference between the third and first quartiles, the middle 50%).

Source: Figure 11.b. Study report of SYR-322-104, Section 11.4, Page 59.

Pharmacodynamics characteristics:

Descriptive statistics for pharmacodynamic parameters of DPP-4 inhibition and baseline-corrected GLP-1 after a single oral administration of alogliptin 12.5 or 25 mg tablets to pediatric (10 to < 14 years old and 14 to <18 years old) and adult patients with T2DM are presented in Table 3 (DPP-4 inhibition), Table 4 (GLP-1) and Figure 2 (a, DPP-4, b, GLP-1).

Administration of alogliptin resulted in DPP-4 inhibition and increased baseline-corrected GLP-1 concentrations in both pediatric and adult subjects with T2DM. There is no lag between time reaching alogliptin plasma concentration (PK T_{max} is 2 to 4 hours) and time to maximum DPP-4 inhibition (also 2 to 4 hours after dosing). However, based on anticipated PD effect, the time reaching maximum effect on

GLP-1 (~8 to 10 hours after alogliptin administration) is about 6 hours later than achieving the peak DPP-4 inhibition. Mean values for the E_{max}, $AUEC_{0-24}$ and E_{24} of DPP-4 inhibition and baseline-corrected GLP-1 concentration were lower in the pediatric groups than in the adult group; for example, the mean E_{max} values of DPP-4 inhibition in pediatric patients were up to 12% lower than that in adult patients, and the mean E_{max} values of baseline-corrected GLP-1 concentration in pediatric patients were 32% to 69% of the mean E_{max} value in adult patients. The mean $AUEC_{0-24}$ values for DPP-4 inhibition in Group 1 (10 to < 14 years) and Group 2 (14 to < 18 years) were approximately 8% and 16% lower, respectively, after the 12.5 mg dose of alogliptin than after the 25 mg dose of alogliptin. However, baseline-corrected GLP-1 concentrations appeared to be generally similar between Groups 1 and 2, independent of dose.

Table 3. Summary of Pharmacodynamic Parameter Estimates of DPP-4 Inhibition Following a Single Oral Administration of Alogliptin 12.5 or 25 mg Tablets to Pediatric (aged 10 to < 14 and 14 to < 18 years old) and Adult Patients With T2DM

Treatment	Group	N	Statistic	Time to Emax (hr) (a,b)	Emax (%)	AUEC(0-24) (%·hr)	E24 (%)
ALO 12.5 mg	10 to <14 years	5	Mean	4.05	83.7	1570	52.0
			%CV	2.00, 4.08	5	7	20
	14 to <18 years	7	Mean	4.00	81.6	1558	55.4
			%CV	2.00, 4.03	7	12	16
ALO 25 mg	10 to <14 years	4	Mean	2.08	89.3	1699	57.4
			%CV	2.00, 4.00	3	4	9
	14 to <18 years	7	Mean	4.00	90.4	1854	70.4
			%CV	3.97, 4.12	2	3	8
	Adults	22 (c)	Mean	2.00	92.7	1890	72.8
			%CV	2.00, 4.07	2	4	7

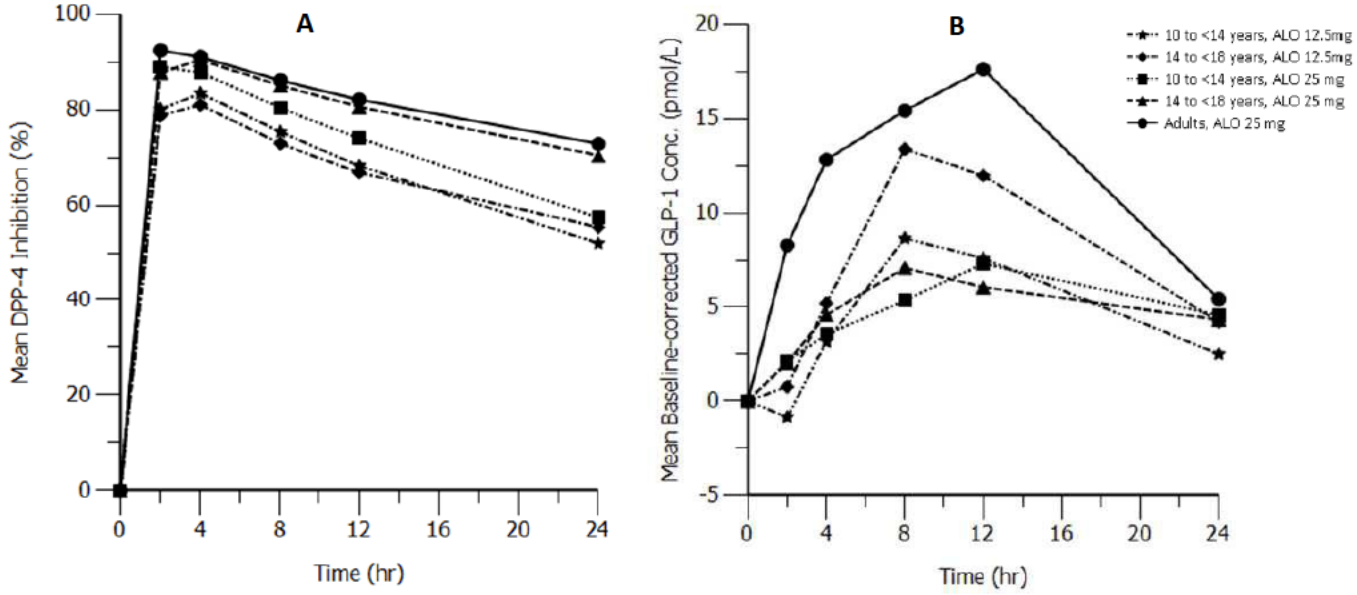
Source: Table 15.2.4.1.
(a) Median is presented for Time to Emax instead of mean.
(b) Minimum, maximum is presented for Time to Emax instead of %CV.
(c) N=21 for E24.
Source: Table 11.h. Study report of SYR-322-104, Section 11.4, Page 64.

Table 4. Summary of Pharmacodynamic Parameter Estimates of Baseline-Corrected GLP-1 Concentrations Following a Single Oral Administration of Alogliptin 12.5 or 25 mg Tablets to Pediatric (aged 10 to < 14 and 14 to < 18 years old) and Adult Patients With T2DM

Treatment	Group	N	Statistic	Time to Emax (hr) (a,b)	Emax (pmol/L)	AUEC(0-24) (pmol·hr/L)	E24 (pmol/L)
ALO 12.5 mg	10 to <14 years	5	Mean	8.17	11.7	118	2.5
			%CV	8.03, 12.00	40	79	213
	14 to <18 years	7	Mean	11.92	16.5	168	4.2
			%CV	8.00, 12.00	91	69	125
ALO 25 mg	10 to <14 years	4	Mean	11.99	7.5	120	4.6
			%CV	8.00, 12.00	52	51	80
	14 to <18 years	7	Mean	8.02	9.1	123	4.3
			%CV	4.00, 24.00	73	80	144
	Adults	21	Mean	12.00	23.8	279	5.4
			%CV	2.33, 24.02	51	37	115

Source: Table 15.2.4.2.
(a) Median is presented for Time to Emax instead of mean.
(b) Minimum, maximum is presented for Time to Emax instead of %CV.
Source: Table 11.i. Study report of SYR-322-104, Section 11.4, Page 64.

Figure 2. Mean DPP-4 Inhibition (Top Panel) and Baseline-Corrected GLP-1 Concentrations (Bottom Panel) vs Time Following a Single Oral Administration of Alogliptin 12.5 or 25 mg Tablets to pediatric (aged 10 to < 14 and 14 to < 18 years old) and Adult Patients With T2DM



Source: Figure 11.e. Study report of SYR-322-104, Section 11.4, Page 63.

The Applicant simulated steady state PK and PD (DPP-4 inhibition) data in the pediatric and adult patients with T2DM using a population PK/PD model built based on data from Study 104. The descriptive parameters of the simulated steady stat PK and PD were summarized in Table 5. The applicant also concluded that:

Based on the PK and PD data and PK/PD simulations, pediatric patients with T2DM require a 25 mg dose of alogliptin to achieve PK exposures and DPP-4 inhibition similar to those in adult patients with T2DM. Therefore, the 25 mg dose is proposed for evaluation in the pediatric phase 3 program (Study 309).

The FDA reviewer noted that the estimated steady state PK and PD parameters in pediatric groups (10 to < 14 years and 14 to <18 years old) was still ~8% to 23% lower than in adults treated with 25 mg alogliptin. However, based on available dosage strengths, no additional dose adjustment can be made to match PK and PD profiles closer to those in adult patients (detailed in section 3.3.4). Furthermore, as described later in the review, this difference is unlike to be the major contributor of the insignificant of HbA1c reduction in pediatric T2DM patients for Study 309.

Table 5. Estimated Mean Steady-State PK and PD Parameters

Group	Dose (mg)	C_{max} (ng/mL)	AUC(0-24) (ng·hr/mL)	C_{24} (ng/mL)	E_{max} (%)	AUEC(0-24) (%·hr)	E_{24} (%)
10 to <14 year	12.5	57.9	754.5	15.0	85.4	1812.7	64.5
	25	117.1	1479.7	28.0	91.3	2022.7	75.9
14 to < 18 year	12.5	51.0	651.0	12.7	84.7	1784.5	63.0
	25	99.5	1257.3	24.0	90.0	1976.0	73.4
Adult	25	152.0	1629.1	31.6	93.6	2082.4	80.0

Source: pharmacometrics memo for study SYR-322_104, page 11.

3.3.4 Whether the slightly decreased observed exposure of alogliptin in pediatric patients compared to adults is the reason for insignificant HbA1c reduction in pediatric patients?

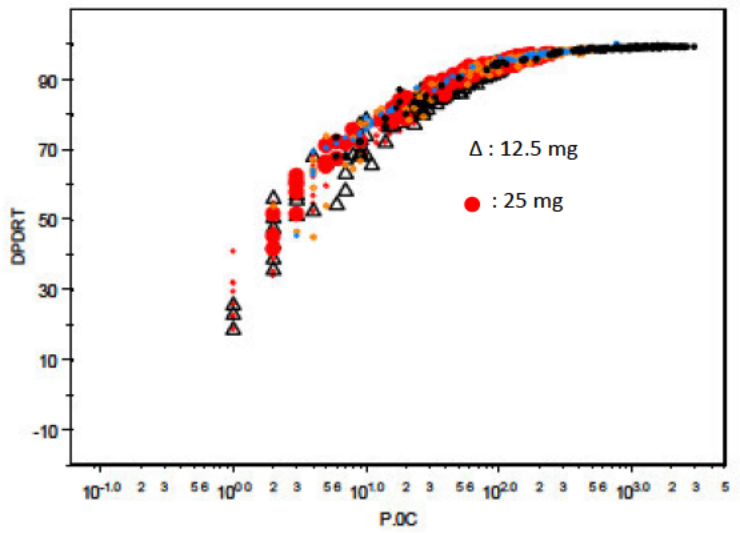
No, the available dose-response and exposure-response analyses for DPP-4 inhibition and clinical efficacy (HbA1c reduction) in adult patients with T2DM cannot explain the lack of efficacy in pediatric patients with T2DM at 25 mg dose. There are three key reasons.

- Based on exposure-response analyses for DPP-4 inhibition, maximal DPP-4 inhibition effect was observed in adult patients with T2DM for PK exposure range at 12.5 mg dose.
- Based on dose-response analyses for HbA1c reduction, maximal HbA1c reduction was observed in adult patients with T2DM at 12.5 mg dose.
- The observed PK exposures in pediatric patients at 25 mg dose was higher than those in adult patients at 12.5 mg.

Exposure-response relationship in T2DM adult patients

Using the adult plasma PK and DPP-4 inhibition data in the original NDA submission, the relationship between alogliptin plasma concentration and DPP-4 inhibition by treatment was shown in Figure 3. There was a clear positive relationship between increasing alogliptin plasma concentration and DPP-4 inhibition with maximal DPP-4 inhibition saturation occurring at concentration > 200 ng/mL. In addition, the relationships of alogliptin plasma concentration and DPP-4 inhibition for the PK exposure ranges of 12.5 mg and 25 mg doses were similar, suggesting maximal effect at the 12.5 mg dose.

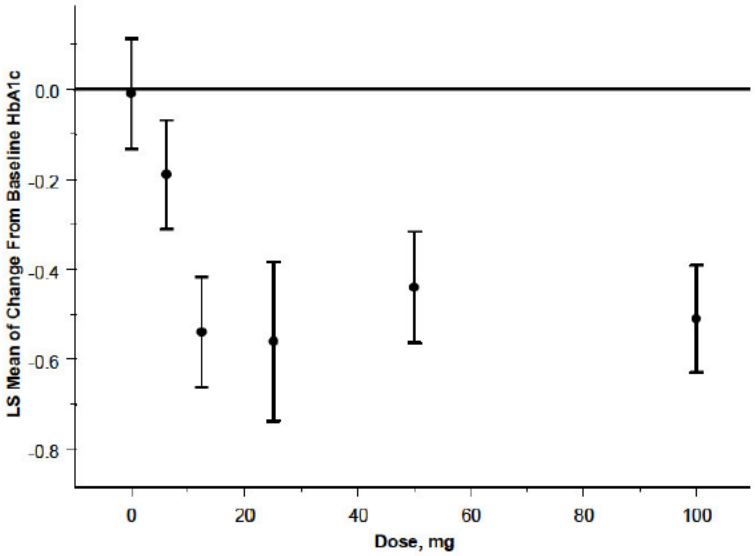
Figure 3. Relationship between alogliptin plasma concentration (P.0C) and DPP-4 inhibition by treatment: 6.25 mg (open red circle), 12.5 mg (open triangle), 25 mg (closed red), 200 mg (close black circle).



Source: Clinical Pharmacology review for NDA 022271 Figure 26, Page 86

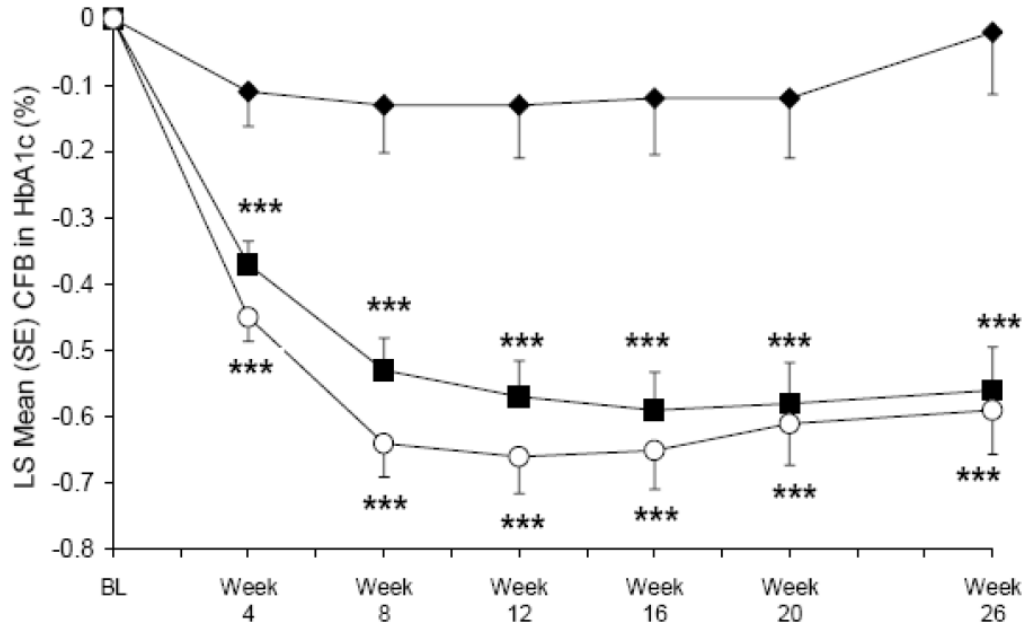
The dose-response relationship for HbA1c reduction in the original NDA submission was revisited. As mentioned in the clinical pharmacology review (dated 8/28/2008 in DARRTS), there is dose dependent HbA1c reduction in adult T2DM patients at 12-weeks between 6.25 mg and 12.5 mg, however, saturated at 12.5 mg (Figure 4). The HbA1c reduction after alogliptin treatment for 12 weeks, 26 weeks and 52 weeks are comparable (Figure 5). The net effects of HbA1c reduction at Week 26 for the 12.5 mg dose and the 25 mg dose were similar and not statistically different (Figure 6).

Figure 4. Dose-Response for Alogliptin Effect on Serum HbA1c Change from Change from Baseline at 12 weeks.



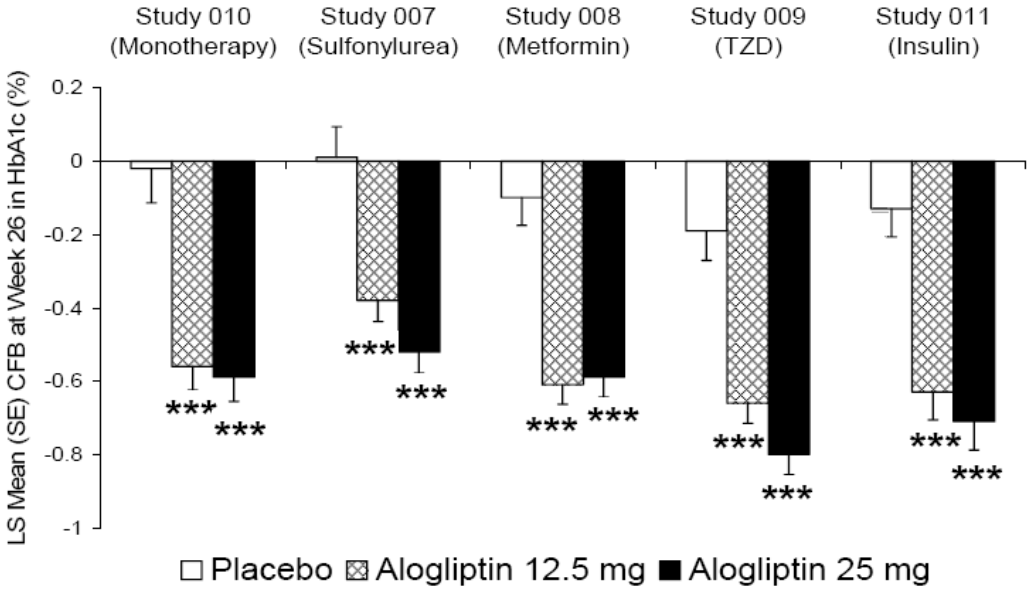
Source: Clinical Pharmacology review for NDA 022271 Figure 55, Page 176

Figure 5. Change in HbA1c in the Placebo Controlled Study 010.



Note: Solid diamonds indicate treatment with placebo. Solid squares indicate 12.5 mg alogliptin and open circles indicate treatment with 25 mg alogliptin.
Source: Clinical Pharmacology review for NDA 022271 Figure 52, Page 169

Figure 6. Change from baseline in HbA1c (%) at Week 26 for Phase 3 studies.



Source: Clinical Pharmacology review for NDA 022271 Figure 5, Page 57

Comparison of alogliptin exposure in pediatric T2DM patients administered alogliptin 25 mg and adult T2DM patients with alogliptin 12.5 mg and 25 mg administered.

A PK comparison between pediatric and adult patients across the clinical program of alogliptin was evaluated. As shown in Table 6, even though the C_{max} and $AUC_{0\text{-}inf}$ of alogliptin in pediatric patients were about 28% lower than those in adult patients taking the same dose (25 mg), the PK parameters were still higher than the adult patients taking 12.5 mg, which had shown to be effective in lowering HbA1c levels. Therefore, it is unlikely that the slightly lower PK exposures in pediatric patients with T2DM is the major reason for the insignificant HbA1c reduction in Study 309.

Table 6. Comparison of PK data in pediatric and adult patients with T2DM

Age Group	Dosage	N	Study/Population	C_{max} (ng/mL) *	AUC_{inf} (ng·hr/mL)
10 to <14 years	25 mg	4	SYR-322-104 T2DM patients	101.4 (23%)	1222 (10%)
14 to < 18 years	25 mg	7	SYR-322-104 T2DM patients	96.7 (29%)	1318 (9%)
Adult	12.5 mg	33	SYR-322-027 ** Healthy volunteers	60.3 (34%)	811 (19%)
Adult	25 mg	22	SYR-322-104 T2DM patients	136.5 (25%)	1704 (16%)
Adult	25 mg	36	SYR-322-027 Healthy volunteers	125.8 (29%)	1530.5 (15%)

* Mean (CV%)

** PK is comparable between T2DM patients and healthy volunteers (source: label for NDA 022271, section 12).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DONG GUO
05/23/2023 02:41:46 PM

EDWIN C CHOW
06/09/2023 02:40:24 PM