EMA/316473/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMEA/H/C/002182/II/0035

Invented name: Vipidia

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Takeda Pharma A/S submitted to the European Medicines Agency on 6 January 2023 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to update paediatric information following positive opinion of procedure P46/013 and confirmation of full compliance of PIP EMEA-000496-PIP01-08-M08 (PIP decision: P/0257/2020) based on reports from study studies SYR-322_104 and SYR-322_309.
The Package Leaflet is updated accordingly.
In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to introduce editorial changes.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0257/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0257/2020 was completed.

The PDCO issued an opinion on compliance for the PIP P/0257/2020.

2. Overall conclusion and impact on the benefit/risk balance

Final data from Study SYR 322_104 (Open-label, single dose of 12.5 or 25 mg, PK/PD study, with a matched adult control group), submitted within this procedure, indicated that in paediatric subjects with Type 2 Diabetes Mellitus (T2DM) aged 10 to 17 years, a 25 mg dose of alogliptin is required to achieve alogliptin exposures and DPP 4 inhibition similar to those previously observed in adults with T2DM. Important tables from the popPK analysis are shown at the end of this assessment report (see section 14.).

Study SYR 322_309 (Multicentre, randomised, double-blind, placebo-controlled study to evaluate safety and efficacy of alogliptin vs placebo in children from 10 to less than 18 years of age) failed to show efficacy for treatment with 25 mg alogliptin QD in 151 paediatric subjects aged 10 to 17 years with T2DM who were experiencing inadequate glycaemic control, which is consistent with data from studies in sitagliptin, another DPP 4 inhibitor. This study was previously assessed in Vipidia procedure EMEA/H/C/002182/P46/013. Important tables are reproduced at the end of this assessment report (see section 15.).

No new safety concerns were observed in either Study SYR 322_104 or Study SYR 322_309. Single doses of 12.5 and 25 mg alogliptin were well tolerated in paediatric and adult subjects with T2DM in Study SYR 322_104, and 25 mg alogliptin QD for 52 weeks in Study SYR 322_309 was generally safe and well tolerated.

The data derived from paediatric studies SYR 322_104 and SYR 322_309 are consistent with the paediatric data published by the scientific community for other DPP 4 inhibitors in relation to efficacy and safety in children (see section 10 of the assessment report for further details).

No indication in the paediatric population is proposed by the MAH, which is endorsed by the CHMP, however the product information is updated to reflect the results of these paediatric studies and the recommendation not to use Vipidia in the paediatric population because of lack of efficacy.

The benefit-risk balance of Vipidia, remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to update paediatric information following positive opinion of procedure P46/013 and confirmation of full compliance of PIP EMEA-000496-PIP01-08-M08 (PIP decision: P/0257/2020) based on reports from study studies SYR-322_104 and SYR-322_309.
The Package Leaflet is updated accordingly.
In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to introduce editorial changes.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0257/2020 and the results of these studies are reflected in the SmPC and, as appropriate, the Package Leaflet.

Annex: Rapporteur’s assessment comments on the type II variation

4. Abbreviations

AE	adverse event
AUC_{0-inf}	area under the plasma concentration-time curve from 0 to infinity
AUC_T	area under the plasma concentration-time curve over the dosing interval at steady-state
C_{max}	maximum observed concentration
DPP-4	dipeptidyl peptidase
E_{max}	maximum observed effect
EU	European Union
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
GMR	geometric mean ratio
GSDB	Global Safety Database
HbA1c	glycosylated haemoglobin
LS	least squares
PD	pharmacodynamic(s)
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
QD	once daily
SAE	serious adverse event
SmPC	Summary of Product Characteristics
$T_{1/2}$	terminal elimination half-life
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
US	United States

5. Introduction

Alogliptin (SYR-322) is an orally available, potent, and highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor developed to improve glycaemic control in type 2 diabetes mellitus (T2DM). Alogliptin was first approved for use in adults for the treatment of T2DM in Japan (April 2010), approved in the United States (US) (January 2013), European Union (EU) (September 2013), and subsequently in other countries. Approved strengths in Japan, the US, and Europe are 6.25, 12.5, and 25 mg, but doses may vary in other regions.

This AR is supportive of changes to the current Summary of Product Characteristics (SmPC) to reflect the results from Studies SYR-322_104 and SYR-322_309, the 2 alogliptin studies conducted in paediatric subjects aged 10 to 17 years with T2DM (Study SYR-322_104 also included adult subjects >18 years of age). Both studies were part of the Paediatric Investigation Plan (PIP) EMEA-000496-PIP01-08-M08. The Paediatric Committee granted a positive opinion on the full compliance check on the PIP (11 November 2022).

Study SYR-322_104, a comparative, randomized, open-label, multi-centre, single dose pharmacokinetic, pharmacodynamic and safety study of alogliptin (12.5 mg and 25 mg) between children, adolescents, and adults with T2DM (non-insulin dependent), evaluated the pharmacokinetics (PK), pharmacodynamics (PD), and safety of a single oral dose of 12.5 and 25 mg alogliptin in paediatric subjects and 25 mg alogliptin in gender- and race-matched adult subjects with T2DM. Results from Study SYR-322_104 were used to support the dose selection of 25 mg in Study SYR-322_309.

Study SYR-322_309, a multicentre, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of alogliptin compared with placebo in paediatric subjects with T2DM, was a 52-week study. This study enrolled and randomized subjects to double-blind treatment at 37 sites in 6 countries worldwide (22 sites in North America, 1 site in South America, 1 site in the EU, and 13 sites in countries considered similar to the EU with respect to subject demographics [Israel, Russian Federation, and Mexico]).

Both studies were conducted in accordance with International Conference on Harmonisation E6 and local regulatory requirements. Studies conducted outside of the EU met the ethical requirements of Directive 2001/20/EC.

6. Clinical Pharmacology aspects

In Study SYR-322_104, single oral administration of 25 mg alogliptin tablets gave mean maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from 0 to infinity ($AUC_{0\text{-}inf}$) values of alogliptin that were 23% to 29% lower in paediatric subjects with T2DM than in adult subjects with T2DM. Increases in the mean C_{max} and $AUC_{0\text{-}inf}$ values of alogliptin between the 12.5 and 25 mg doses were approximately dose proportional. The mean terminal elimination half-life ($T_{1/2}$) values following 12.5 mg alogliptin were 16.75 hours in children 10 to <14 years and 15.38 hours in adolescents 14 to <18 years. Following 25 mg alogliptin, mean $T_{1/2}$ values were 18.09 hours in children 10 to <14 years and 17.15 hours in adolescents 14 to <18 years. In adults, the mean $T_{1/2}$ value was 19.33 hours. Values for mean apparent clearance after oral administration of alogliptin were up to 37% higher in paediatric subjects with T2DM than in adult subjects with T2DM.

In Study SYR-322_104, single oral administration of 12.5 or 25 mg alogliptin tablets resulted in rapid DPP-4 inhibition that was similar in both paediatric and adult subjects. The mean maximum observed effect (E_{max}) values for DPP-4 inhibition were approximately 80% after the 12.5 mg dose of alogliptin and approximately 90% after the 25 mg dose of alogliptin in paediatric subjects and approximately

93% in adult subjects. Administration of alogliptin resulted in increased baseline corrected glucagon-like peptide-1 (GLP-1) concentrations in both paediatric and adult subjects; the mean E_{max} values for baseline-corrected GLP-1 in paediatric subjects administered 25 mg alogliptin were 68% (aged 10 to <14 years) and 62% (aged 14 to <18 years) lower compared with the mean E_{max} value in adult subjects.

A PK/PD model (Modeling and Simulation of PK/PD Data from SYR-322_104) was developed using adult and paediatric data from Study SYR-322_104 to characterize the time course of alogliptin concentrations and DPP-4 inhibition following single dose administration of alogliptin in paediatric subjects (aged 10 to <18 years) and adult subjects with T2DM. The individual PK and PD time course profiles were well described by the final model.

The PK and PD parameters following multiple doses of 25 mg alogliptin once daily (QD) were predicted from the model based on simulations. Following repeated dose administration of 25 mg alogliptin QD, the mean simulated DDP-4 inhibition levels at steady-state trough (24 hours postdose) were 75.9%, 73.4%, and 80% for paediatric subjects aged 10 to <14 years, 14 to <18 years, and adult subjects, respectively, supporting the dose selection of 25 mg QD for study SYR-322_309.

A population PK model for alogliptin in paediatric and adult subjects with T2DM was developed using combined data from Studies SYR-322_104 (intensive PK sampling) and SYR-322_309 (sparse PK sampling) and model-based simulations were performed to predict alogliptin exposure in paediatric subjects (Population PK Report). The mean steady state model-predicted values for area under the plasma concentration-time curve over the dosing interval at steady-state (AUC_{τ}) and C_{max} for paediatric subjects (aged 10 to 17 years, inclusive) with T2DM from Study SYR-322_309 were modestly lower (6% for AUC_{τ} and 23% for C_{max}) compared with those observed for adult subjects with T2DM from Study SYR-322_002. However, since no substantial differences were observed between paediatric and adult subjects in the population PK/PD analysis in PD parameter values such as E_{max} and the area under the plasma effect-time curve from time 0 to 24 hours postdose, these minor differences in exposure would not be expected to result in significant differences in DPP-4 inhibition.

Sparse data sampling was conducted in the phase III study and therefore estimation of Cmax and AUC in paediatric patients is largely based on the PK rich data from Study SYR-322-104. PK data in paediatric patients in study SYR-322-104 were adequate to estimate AUC and Cmax reliably. The differences in estimated Cmax and AUC between paediatric patients and adults were slightly higher in study 104 compared to the phase 3 study, although the overall key aspects are similar. It is proposed to slightly modify the text in section 5.2 (OC).

7. Clinical efficacy aspects

Alogliptin has been evaluated in a comprehensive adult global clinical development program comprising more than 50 clinical studies and involving more than 20,000 patients. In adults, treatment with 12.5 or 25 mg alogliptin QD for 26 weeks resulted in statistically significant least squares (LS) mean reductions in glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG) levels compared with placebo.

The primary objective of Study SYR-322_309 in paediatric subjects aged 10 to 17 years was to evaluate the efficacy of 25 mg alogliptin 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 HbA1c change from baseline at Week 26 in paediatric subjects with T2DM.

No statistically significant difference was observed between treatment with 25 mg alogliptin compared with placebo for the primary efficacy endpoint of HbA1c change from baseline to Week 26 among subjects in either the full analysis set or the per protocol set. Similar results were observed for the sensitivity analysis of handling dropouts or missing data using the washout imputation method. In addition, no statistically significant difference was observed between treatment with 25 mg alogliptin compared with placebo for the secondary endpoints of HbA1c change from baseline at Weeks 12, 18, 39, and 52 among subjects in either the full analysis set or the per protocol set. Mean (SD) compliance rates overall for the alogliptin and placebo treatment groups were similar at 78.84% (10.579) and 72.66% (14.281), ranging from 46.4% to 100.0% and 23.3% to 99.1%, respectively.

8. Clinical safety aspects

Alogliptin treatment was generally safe and well tolerated among all subjects who participated in Studies SYR-322_104 and SYR-322_309. No new safety signals were identified.

In Study SYR-322_104 among subjects aged 10 to <14 years, 3 of 5 subjects who received 12.5 mg alogliptin and 1 of 4 subjects who received 25 mg alogliptin had 1 or more treatment-emergent adverse events (TEAEs). Among subjects aged 14 to <18 years, 5 of 8 subjects who received 12.5 mg alogliptin and 2 of 7 subjects who received 25 mg alogliptin had 1 or more TEAEs. Among adults, 9 of 22 subjects had 1 or more TEAEs.

Among subjects aged 10 to <14 years, 2 of 5 subjects who received 12.5 mg alogliptin and none who received 25 mg alogliptin had 1 or more TEAEs that were considered by the investigator to be possibly, probably, or definitely related to study drug. Among subjects aged 14 to <18 years, 2 of 8 subjects who received 12.5 mg alogliptin and none who received 25 mg alogliptin had 1 or more TEAEs that were considered by the investigator to be possibly, probably, or definitely related to study drug. Among adults, 5 of 22 subjects had 1 or more TEAEs that were considered by the investigator to be possibly, probably, or definitely related to study drug.

No pregnancies or overdoses were reported.

No deaths, other serious adverse events (SAEs), adverse events (AEs) leading to study drug discontinuation, or other significant AEs occurred.

In Study SYR-322_309, most AEs were either mild or moderate and not related to study treatment or study procedure.

Overall, TEAEs considered related to study treatment were reported for 21 of 151 (13.9%) treated subjects. No notable difference was observed between treatment groups for TEAEs considered related to study treatment, as well as for TEAEs leading to study treatment dose interruption.

Thirty AEs of special interest were reported for 20 of 151 treated subjects (13.2%) in the safety analysis set and were similar with respect to treatment group. Of these, the most common were upper respiratory tract infection (7), gastroenteritis (4), and pharyngitis streptococcal (3).

No deaths occurred during the study and none of the 12 reported SAEs was considered related to study treatment.

One subject receiving alogliptin became pregnant and was discontinued from the study. Procedures for pregnancy reporting and follow-up were followed per protocol. Per communication with the study site, a healthy baby was born by caesarean delivery on 04 October 2021 and no issues were noted.

No overdoses were reported.

8.1. Postmarketing safety

A search of the Takeda Global Safety Database (GSDB) was conducted with parameters from 01 January 1900 through 25 July 2022 for postmarketing reports of potential exposure of paediatric patients to alogliptin. Search parameters included event seriousness, event outcome, case seriousness, case outcome, event system organ class and preferred term, country, sex, date of event receipt, and listedness. Reporting sources were spontaneous, spontaneous from literature, regulatory authority, and other.

Cumulatively, 13 unique cases comprising 27 events were reported. Of these 27 events, 2 were considered serious and the majority (25 events; 92.6%) were nonserious. No difference in reports was found with respect to gender; there were 12 reports each for females and males and 3 for which gender was not known.

The majority of the cases reported no AE associated with alogliptin administration in settings of accidental exposure or overdose. No causal association between alogliptin therapy and reported events could be established with available Takeda GSDB information. Individual case review identified 7 cases of reported accidental ingestion by a child, 2 cases of maternal exposure to alogliptin, 2 cases with therapy change due to partial response, 1 overdose case with no AE associated, and 1 case of off-label use in a patient aged 16 years.

9. Discussion and Conclusions

Alogliptin has been evaluated in a comprehensive adult global clinical development program comprising more than 50 clinical studies and involving more than 20,000 patients. In adults, treatment with 12.5 or 25 mg alogliptin QD for 26 weeks resulted in statistically significant LS mean reductions in HbA1c and FPG levels compared with placebo. However, in paediatric patients with T2DM, Study SYR-322_309 failed to show clinical efficacy of 25 mg alogliptin QD with the primary analysis as well as various secondary and exploratory analyses. Thus, the data do not support the intended paediatric indication(s) stated in the PIP.

In general, clinical studies in paediatric patients with T2DM are more challenging and have a higher rate of failure in establishing both efficacy and safety compared with adult studies. To understand why paediatric studies failed to show efficacy, Momper et al. reviewed over 40 paediatric studies and identified several common factors that contribute to failure of these studies. These factors include study design, placebo response, dosing, and possible differences between the paediatric and adult T2DM disease process (Momper et al. 2015).

In Study SYR-322_309, the design was similar to that for studies in adults, and there was no observed placebo response. While the mean PK exposure following a single dose of 25 mg alogliptin in paediatric subjects was 23% to 29% lower than in adult subjects in the SYR-322_104 study, the PD effect assessed via DPP-4 inhibition was similar between paediatric and adult subjects. In addition, 25 mg alogliptin QD is the maximal approved dose for alogliptin. However, sparse data sampling was conducted in the phase III study and therefore estimation of Cmax and AUC in paediatric patients is largely based on the PK rich data from Study SYR-322-104. PK data in paediatric patients in study SYR-322-104 were adequate to estimate AUC and Cmax reliably. The differences in estimated Cmax and AUC between paediatric patients and adults were slightly higher in study 104 compared to the phase 3 study, although the overall key aspects are similar. This should be reflected in the SmPC. Still, dosing is considered unlikely to be a decisive factor to the negative study results.

Although the pathophysiology of T2DM in paediatric patients appears to be similar to that in adults (Von and Hewett 2007), recent literature review suggested that disease progression in paediatric

patients may be more rapid than in adult patients (Barrett et al. 2020). Compared with the disease in adults, T2DM in paediatric patients has several unique features. Insulin resistance appears to be greater in children than in adults, even at the same relative amount of adipose tissue. The data indicate that there are potentially 2 subgroups of manifestations of T2DM in paediatric patients, with disease that progresses faster in one subgroup and is more easily controlled in another. Data from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study indicated that β-cell function may deteriorate more quickly in some paediatric patients with T2DM than in adults with T2DM. In addition, more rapid emergence of complications and comorbidities that include diabetic retinopathy, electrocardiographic changes indicating major cardiovascular risk, and increased occurrence of kidney hyperfiltration is observed in some paediatric patients with T2DM, therefore predicting a rapid decline in glomerular filtration rate (Barrett et al. 2020).

Thus, these differences between paediatric and adult patients with T2DM may have been a contributing factor to the negative results observed in Study SYR-322_309.

Results from Studies SYR-322_104 and SYR-322_309 are generally similar to those in the published data from paediatric studies in sitagliptin, another DPP-4 inhibitor. $AUC_{(0\text{-}inf)}$ of sitagliptin was also found to be 18% lower in paediatric subjects with T2DM following a single dose at 50, 100, and 200 mg compared with dose-adjusted results from a separate study of adults with T2DM following doses of 25 and 200 mg sitagliptin (Fraser et al. 2019). Due to non-dose proportionality of sitagliptin C_{max} and the concentration at 24 hours, these parameters were compared at 200 mg (the only dose common to both paediatric and adult subjects in the two studies being compared in the publication). The LS geometric mean ratio (GMR) for youths/adults and corresponding 90% CI for dose-adjusted (to 100 mg, the registered dose for adults) sitagliptin $AUC_{0\text{-}inf}$ was 0.82 (0.66, 1.01). The LS GMR (youth/adult; 90% CI) were 1.04 (0.75, 1.44) and 0.74 (0.48, 1.14) for sitagliptin C_{max} and concentration at 24 hours, respectively. These differences were deemed not clinically significant and resulted in similar values for DPP-4 half-maximal inhibitory concentration values for adult and paediatric subjects. At 24 hours after dosing, DPP-4 inhibition following a 200 mg dose of sitagliptin was 75.8 % (72.2% with placebo subtraction) in paediatric subjects compared with 80.1% in adult subjects.

It would appear that for both alogliptin and sitagliptin, while paediatric exposure is lower than that seen in adults, the expected DPP-4 inhibition was similar in both paediatric and adult patients at similar doses. Thus, it is suggested that the negative efficacy results of DPP-4 inhibitors in paediatric subjects are not due to the lack of exposure.

The lack of treatment effect for DPP-4 inhibitors in paediatric patients with T2DM has also been observed in phase 3 studies with sitagliptin. Results were as follows:

- Study MK 0431 083 investigated initial oral therapy in a 54-week, double-blind, randomized, controlled clinical trial evaluating the safety and efficacy of DPP-4 inhibition with 100 mg sitagliptin QD in paediatric subjects with T2DM. This study enrolled 190 participants aged 10 to 17 years with HbA1c levels of 6.5% to 10% (7.0%-10% if on insulin) and used a placebo control for the first 20 weeks, after which metformin replaced placebo. The primary efficacy endpoint was change from baseline in HbA1c at Week 20. Study results showed that DPP-4 inhibition with sitagliptin did not provide significant improvement in glycaemic control but was generally well tolerated with a safety profile similar to that reported in adults (Shankar et al. 2022).

- Data were pooled from Studies MK 0431A and MK 0431A XR, two 54-week, double-blind, randomized, placebo-controlled studies of 100 mg sitagliptin QD or placebo added onto treatment of paediatric subjects with T2DM aged 10 to 17 years experiencing inadequate

glycaemic control on metformin with or without insulin. The 220 randomized and treated participants had HbA1c levels of 6.5% to 10.0% (7.0%–10% if on insulin) at baseline, were overweight or obese at screening or diagnosis, and negative for pancreatic autoantibodies. The primary endpoint was change from baseline in HbA1c at Week 20. Results did not suggest that addition of sitagliptin to metformin provides durable improvement in glycaemic control in paediatric subjects with T2DM (Jalaludin et al. 2022).

The above results suggest that the response to alogliptin treatment is consistent with that of sitagliptin therapy in paediatric patients with T2DM.

Two studies with saxagliptin in paediatric subjects are posted on clinicaltrialsregister.eu: EudraCT No. 2010-020360-38 and 2010-024568-16; results were inconclusive (the sponsor discontinued enrolment). An additional paediatric study with saxagliptin is currently ongoing (EudraCT No. 2015-005042-66), as well as a study with the DPP-4 inhibitor linagliptin in paediatric subjects with T2DM (EudraCT No. 2016-000669-21).

It is noteworthy that the GLP-1 receptor agonists liraglutide and dulaglutide have demonstrated efficacy in the respective paediatric studies (Arslanian et al. 2022; Tamborlane et al. 2019). It has been well established that GLP-1 receptor agonists are more efficacious than DPP-4 inhibitors in adults with T2DM because the efficacy of DPP-4 inhibitors is contingent on the endogenous GLP-1 secretion which is reduced in patients with T2DM, while GLP-1 receptor agonists are more direct, potent, and durable to stimulate GLP-1 secretion (Gilbert and Pratley 2020). Such differences between the two classes of antidiabetics may also exist in paediatric patients with T2DM.

In summary, among the paediatric studies with DPP-4 inhibitors that are authorised for T2DM treatment in adult patients in the EU market, sitagliptin and alogliptin have had negative efficacy results, saxagliptin data from the completed studies are inconclusive, and studies with linagliptin and saxagliptin are currently ongoing.

9.1. Conclusions

- PK and PD data from Study SYR-322_104 indicate that in paediatric subjects with T2DM aged 10 to 17 years, a 25 mg dose of alogliptin is required to achieve alogliptin exposures and DPP-4 inhibition similar to those previously observed in adults with T2DM.
- Study SYR-322_309 failed to show efficacy for treatment with 25 mg alogliptin QD in 151 paediatric subjects aged 10 to 17 years with T2DM who were experiencing inadequate glycaemic control, which is consistent with data from studies in sitagliptin, another DPP-4 inhibitor.
- No new safety concerns were observed in either Study SYR-322_104 or Study SYR-322_309. Single doses of 12.5 and 25 mg alogliptin were well tolerated in paediatric and adult subjects with T2DM in Study SYR-322_104, and 25 mg alogliptin QD for 52 weeks in Study SYR-322_309 was generally safe and well tolerated.
- The data derived from Studies SYR-322_104 and SYR-322_309 are consistent with the data recently published by the scientific community for DPP-4 inhibitors.

Main PopPK data and main SYR-322_309 results are shown at the end of this document.

10. Changes to the Product Information

The following modifications are proposed (new text underlined, ~~deleted text strikethrough~~):

4.2 Posology and method of administration

Posology
(…)

Paediatric population
The safety and efficacy of ~~Vipidia~~ alogliptin in children and adolescents < 18 years old have not been established. ~~No data are available.~~ Currently available data are described in sections 4.8, 5.1 and 5.2, but no recommendation on a posology can be made. Alogliptin should not be used in the paediatric population because of lack of efficacy. Please refer to section 5.1.

4.8 Undesirable effects

Tabulated list of adverse reactions
(…)

Paediatric population
In a clinical trial with alogliptin in paediatric patients with type 2 diabetes mellitus aged 10 to17 years, the profile of adverse reactions was comparable to that observed in adults.

5.1 Pharmacodynamic properties

Clinical efficacy
(…)

Paediatric population

~~The European Medicines Agency has deferred the obligation to submit the results of studies with Vipidia in one or more subsets of the paediatric population in the treatment of type 2 diabetes mellitus (see section 4.2 for information on paediatric use).~~
A double-blind, randomized, placebo-controlled, multinational (6 countries, 37 sites), study was conducted in paediatric patients (10 to 17 years old) with type 2 diabetes mellitus with insufficient glycemic control, despite dietary treatment and/or exercise therapy, with or without metformin and/or insulin background therapy. A total of 151 patients (including 27 without background therapy, 124 with metformin and/or insulin therapy) were randomized 1:1 and received treatment with either alogliptin 25 mg (n=75) or placebo (n=76) once daily. No statistically significant difference was observed between treatment with 25 mg alogliptin compared with placebo for the primary efficacy endpoint of HbA1c change from Baseline to Week 26 among subjects for the Full Analysis Set (FAS) or Per Protocol Set (PPS), the sensitivity analysis of the FAS, or any subgroups including the patients without background antidiabetic therapy and patients on background therapy of metformin and/or insulin. Similar results were observed for the secondary endpoints of HbA1c change from Baseline at Weeks 12, 18, 39, and 52 among subjects in the FAS and the PPS.
The results of this study are presented in Table 5.

Table 5. HbA1c Change from Baseline at Week 26 in Pediatric Patients (10-17 years) with Type 2 Diabetes Mellitus Administered Alogliptin 25 mg or Placebo once daily		
Treatment Group	***HbA1c (%)****	***Difference in HbA1c (%) Alogliptin vs. Placebo****

alogliptin 25 mg	*0.091 ± 0.288* *(n= 54)*	*0.102* *[-0.627, 0.831]*
Placebo	*-0.011 ± 0.281* *(n= 56)*	
*Least squares mean ± S.E [ ] shows two-sided 95% confidence interval		

5.2 Pharmacokinetic properties

(...)

Paediatric population

~~The pharmacokinetics of alogliptin in children and adolescents < 18 years old has not been established. No data are available (see section 4.2).~~

The pharmacokinetics of alogliptin following oral doses of alogliptin benzoate were evaluated in children with type 2 diabetes mellitus aged 10 to 17 years. Based on the population pharmacokinetic analysis, the mean paediatric exposures were modestly lower (6% for AUCτ and 23% for Cmax) compared with adult exposures following multiple daily 25 mg doses (see section 4.2).

10.1. Revised proposal for 5.2 (see 12.1)

The pharmacokinetics of alogliptin following oral doses of alogliptin benzoate were evaluated in children with type 2 diabetes mellitus aged 10 to 17 years. Based on the population pharmacokinetic analysis, the mean paediatric exposures were modestly lower i.e. less than 25% difference with AUCτ and Cmax of adult exposures following multiple daily 25 mg doses (see section 4.2). The body weight range was from 54.5 to 195 kg in children and from 71.7 to 130 kg in adults.

10.2. Justification for the Proposed Modifications to Product Labelling

As discussed above, the data from Study SYR-322_309 demonstrate a lack of efficacy, thus the study does not support a paediatric indication. As per the Paediatric Regulation (EC) 1901/2006, as amended, and in line with the SmPC guideline, the Company proposes to include in Vipidia product information, the information from the results of the above mentioned alogliptin studies SYR-322_104 and SYR-322_309 performed in the paediatric population, accordingly. Additionally, the *PD properties*, *PK properties*, and *Undesirable effects* sections of the SmPC have been updated to include the available paediatric data from Studies SYR-322_104 and SYR-322_309. These updates to the product labelling provide new information regarding the safety and pharmacological properties of alogliptin in the paediatric population and, importantly, indicate that the use of alogliptin in paediatric subjects should be avoided due to the lack of efficacy.

10.3. Assessor's comment on the proposed product information

The proposed modifications of the product information adequately reflect the study results and are consistent with applicable regulations. However, sparse data sampling was conducted in the phase III study and therefore estimation of Cmax and AUC in paediatric patients is largely based on the PK rich data from Study SYR-322-104. PK data in paediatric patients in study SYR-322-104 were adequate to estimate AUC and Cmax reliably. The differences in estimated Cmax and AUC between paediatric patients and adults were slightly higher in study 104 compared to the phase 3 study, although the overall key aspects are similar. It is proposed to slightly modify the text in section 5.2 (OC).

Otherwise, these proposals are therefore acceptable.

11. List of Questions

11.1. Clinical pharmacology

Other concern

1. Sparse data sampling was conducted in the phase III study and therefore estimation of Cmax and AUC in paediatric patients is largely based on the PK rich data from Study SYR-322-104. The differences in estimated Cmax and AUC between paediatric patients and adults were slightly higher in study 104 compared to the phase 3 study, although the overall key aspects are similar. It is proposed to slightly modify the text in section 5.2 e.g. "…. the mean paediatric exposures were modestly lower i.e. less than 25% difference in AUCτ and in Cmax compared with adult exposures. " Further, the applicant is requested to include the body weight ranges in children and adults in the text.

MAH response

The EMA suggestions are acceptable. Please see the proposed SmPC text below:

5.2 Pharmacokinetic properties

..[..]..

Paediatric population

The pharmacokinetics of alogliptin following oral doses of alogliptin benzoate were evaluated in children with type 2 diabetes mellitus aged 10 to 17 years. Based on the population pharmacokinetic analysis, the mean paediatric exposures were modestly lower i.e. less than 25% difference with AUCτ and Cmax of adult exposures following multiple daily 25 mg doses (see section 4.2). The body weight range was from 54.5 to 195 kg in children and from 71.7 to 130 kg in adults.

Assessment of the MAH response

The MAH agreed to the CHMP suggestions. Issue resolved.

12. Literature References

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13. Annex: Most important data from popPK analysis

13.1. Demographics/baseline

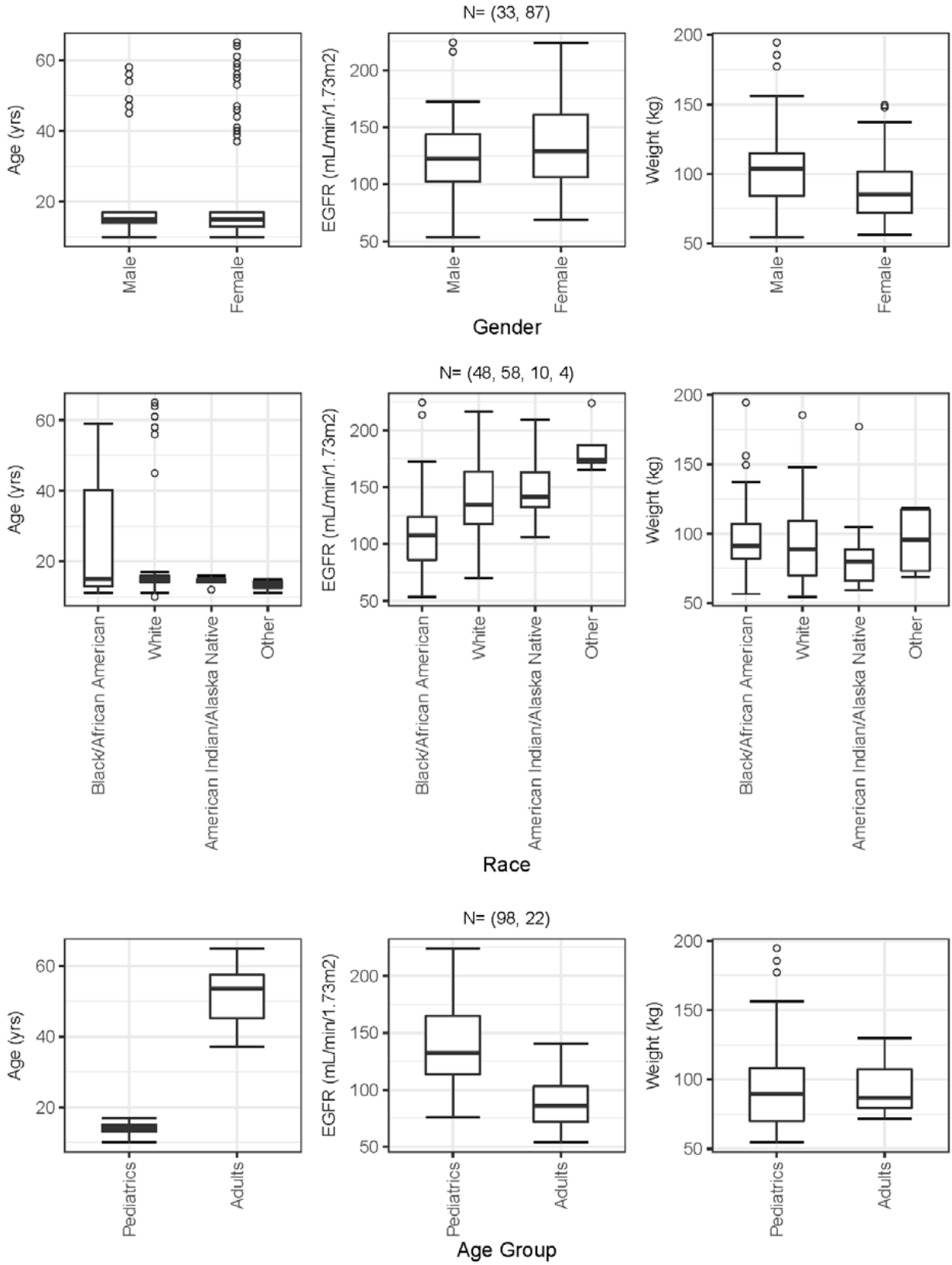
Population Pharmacokinetic Analysis of Alogliptin Benzoate (SYR-322) in Children, Adolescents, and Adults With Type 2 Diabetes Mellitus

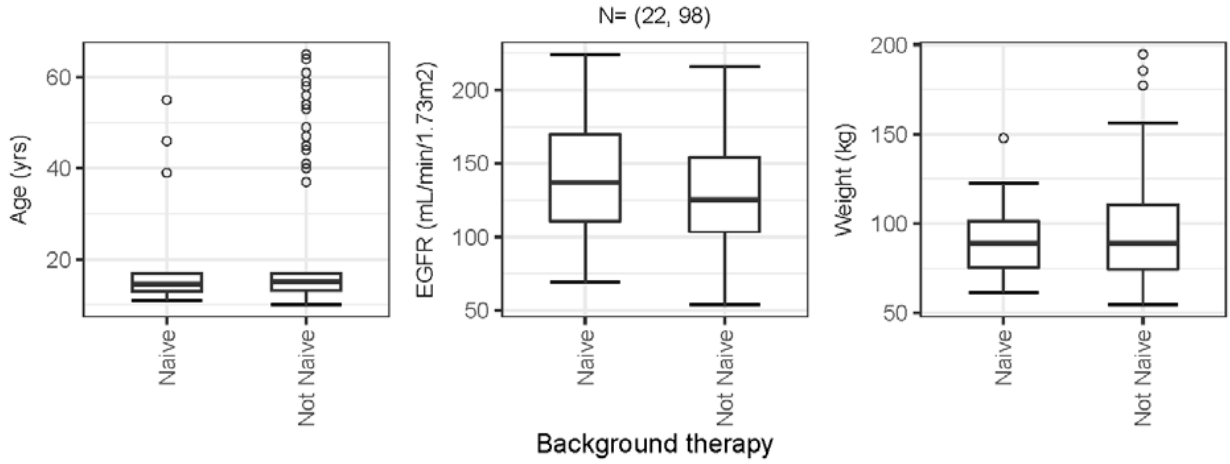
Table 5-2 Summary of Subject Demographics in PopPK Analysis

Covariate	Statistic	Study		Overall
		SYR-322_104	SYR-322_309	
	Number of Subjects (%)	46 (38)	74 (62)	120
Age (yrs)	Mean (SD)	31.9 (19.6)	14.2 (1.9)	21 (14.9)
	Median (Min-Max)	16.5 (11-65)	14 (10-17)	15 (10-65)
Weight (kg)	Mean (SD)	98.1 (21.4)	90.7 (29.2)	93.6 (26.6)
	Median (Min-Max)	94.1 (68.1-195)	85.1 (54.5-186)	89.1 (54.5-195)
eGFR ($mL/min/1.73m^2$)	Mean (SD)	103 (27.8)	146 (35.3)	129 (38.5)
	Median (Min-Max)	103 (53.6-167)	136 (79.0-224)	127 (53.6-224)
Gender, N (%)	Female	34 (74)	53 (72)	87 (72)
	Male	12 (26)	21 (28)	33 (28)
Race, N (%)	American Indian/Alaska Native	.	10 (14)	10 (8)
	Black/African American	32 (70)	16 (22)	48 (40)
	White	14 (30)	44 (59)	58 (48)
	Other	.	4 (5)	4 (3)
Age category, N (%)	Adults	22 (48)	.	22 (18)
	Pediatrics	24 (52)	74 (100)	98 (82)
Background therapy, N (%)[a]	Naive	9 (20)	13 (18)	22 (18)
	Not Naive	37 (80)	61 (82)	98 (82)

Source: SYR322_dataset_v2.csv

Figure 9-5 Box and Whisker Plots of Baseline Continuous Covariates versus Categorical Covariates, All Subjects, PK Population





13.2. Results

Table 5-3 Parameter Estimates of Final PopPK Model (Run 040a)

Parameter	Units	NONMEM Estimates			
		Estimate	%RSE[a]	95% CI	IIV CV%[b] (%RSE)
CL/F in pediatric	L/hr	17.2	6.16	15.1 to 19.3	53.3 (18.3)
CL/F in adults	L/hr	12.8	3.11	12.0 to 13.6	12.6 (39.2)
Vc/F	L	133	7.52	113 to 153	28.8 (27.5)
Q/F	L/hr	10.0	14.0	7.26 to 12.7	15.0 fixed
Vp/F	L	112	5.95	98.9 to 125	15.0 fixed
Ka in pediatrics	hr^{-1}	0.689	11.8	0.53 to 0.848	15.0 fixed[d]
Ka in adults	hr^{-1}	1.76	25.6	0.878 to 2.64	[d]
CL/F~weight	unitless	0.75 fixed	-	-	-
Vc/F~weight	unitless	1 fixed	-	-	-
Q/F~weight	unitless	0.75 fixed	-	-	-
Vp/F~weight	unitless	1 fixed	-	-	-
$\sigma^2_{prop\ SYR\text{-}322\_104}$	unitless	0.0547	8.59	0.0455 to 0.0639	23.4[c]
$\sigma^2_{prop\ SYR\text{-}322\_309}$	unitless	0.304	10.6	0.241 to 0.367	55.1[c]

[a] RSE=SE/Estimate.

[b] CV for IIV calculated as $CV_{TVP}=\sqrt{\omega_P^2}$ .100 if $\omega_p^2 \leq 0.15$, else $CV_{TVP}=\sqrt{\omega_P^2-1}$ .100

[c] Proportional residual error expressed as CV.

[d] Single IIV for pediatrics and adults combined.

Abbreviations: CL/F = apparent total clearance, Vc/F = apparent volume of central compartment, Vp/F = apparent volume of peripheral compartment, Q/F = inter compartment clearance between central and peripheral compartments, Ka=first-order absorption, IIV = inter-subject variability, CI=confidence interval, RSE=relative standard error, CV=coefficient of variation, σ^2_{prop} = proportional residual error

The reference population is a 70-kg subject.

Source: 040a.sum

Table 5-5 Summary of Steady-State SYR-322 PK Parameters in the Simulated Pediatrics Population

Statistic	$AUC_{0-\tau}$ (ng·hr/mL)		C_{max} (ng/mL)	
	12.5 mg QD	**25 mg QD**	**12.5 mg QD**	**25 mg QD**
Geometric mean (%CV)	574 (61.7)	1150 (61.7)	52.0 (38.7)	104 (38.7)
95% Confidence interval	554 - 595	1110 - 1190	50.8 - 53.2	102 - 106
5^{th} percentile	227	454	28.5	57.0
95^{th} percentile	1460	2910	96.8	194

Source: 040assim1.tab and 040assim2.tab

Table 5-6 Summary of Steady-State SYR-322 PK Parameters in the Simulated Adult Population

Statistic	$AUC_{0-\tau}$ (ng·hr/mL)		C_{max} (ng/mL)	
	12.5 mg QD	**25 mg QD**	**12.5 mg QD**	**25 mg QD**
Geometric mean (%CV)	779 (16.3)	1560 (16.3)	69.7 (21.2)	139 (21.2)
95% Confidence interval	771 - 787	1540 - 1570	68.8 - 70.6	138 - 141
5^{th} percentile	597	1190	49.7	99.5
95^{th} percentile	1020	2030	99.0	198

Source: 040assimad1.tab and 040assimad2.tab

14. Annex: Most important data from study SYR-309_322

14.1. Demographic and baseline characteristics (safety analysis set)

	Placebo (N = 76)	Alogliptin 25 mg QD (N = 75)	Total (N = 151)
Age (years)			
n	76	75	151
Mean (SD)	14.3 (2.21)	14.2 (1.92)	14.2 (2.06)
Median	14.0	14.0	14.0
Minimum, maximum	10, 17	10, 17	10, 17
Age categories per protocol; n (%) (years)			
10-13	28 (36.8)	23 (30.7)	51 (33.8)
14-17	48 (63.2)	52 (69.3)	100 (66.2)
Age categories per EUDRACT; n (%) (years)			
10-11	10 (13.2)	8 (10.7)	18 (11.9)
12-17	66 (86.8)	67 (89.3)	133 (88.1)
Age categories per PREA PMRs; n (%) (years)			
10-14	39 (51.3)	40 (53.3)	79 (52.3)
15-17	37 (48.7)	35 (46.7)	72 (47.7)
Gender n (%)			
Male	25 (32.9)	22 (29.3)	47 (31.1)
Female	51 (67.1)	53 (70.7)	104 (68.9)
Ethnicity; n (%)			
Hispanic or Latino	6 (7.9)	9 (12.0)	15 (9.9)
Not Hispanic or Latino	31 (40.8)	26 (34.7)	57 (37.7)
Missing	39 (51.3)	40 (53.3)	79 (52.3)
Race; n (%)			
American Indian or Alaska Native	14 (18.4)	11 (14.7)	25 (16.6)
Asian	1 (1.3)	0	1 (0.7)
Black or African American	16 (21.1)	16 (21.3)	32 (21.2)
White	44 (57.9)	44 (58.7)	88 (58.3)
Multiracial [a]	1 (1.3)	4 (5.3)	5 (3.3)
Height (cm)			
n	76	75	151
Mean (SD)	164.7 (9.54)	163.1 (8.79)	163.9 (9.18)
Minimum, maximum	144, 187	142, 184	142, 187
Weight (kg)			
n	76	75	151
Mean (SD)	92.23 (26.826)	90.72 (28.815)	91.48 (27.749)
Minimum, maximum	48.0, 165.9	54.0, 185.5	48.0, 185.5
BMI (kg/m^2)			
n	76	75	151
Mean (SD)	33.632 (7.8581)	33.669 (8.6592)	33.650 (8.2381)
Minimum, maximum	20.64, 56.34	18.83, 68.14	18.83, 68.14
BMI categories (kg/m^2); n (%)			
<25	7 (9.2)	6 (8.0)	13 (8.6)
25 - <30	22 (28.9)	25 (33.3)	47 (31.1)
≥30	47 (61.8)	44 (58.7)	91 (60.3)
BMI Z-score			
n	76	75	151
Mean (SD)	2.087 (0.5652)	2.050 (0.5978)	2.069 (0.5799)
Minimum, Maximum	0.49, 3.14	-0.27, 3.19	-0.27, 3.19
Tanner stage scores for breast development in girls; n (%) [b]			
1	1 (2.0)	0	1 (1.0)
2	1 (2.0)	2 (3.8)	3 (2.9)
3	10 (19.6)	7 (13.2)	17 (16.3)
4	11 (21.6)	20 (37.7)	31 (29.8)
5	27 (52.9)	24 (45.3)	51 (49.0)
Missing	1 (2.0)	0	1 (1.0)

Demographic and Baseline Characteristics (Safety Analysis Set)

	Placebo (N = 76)	Alogliptin 25 mg QD (N = 75)	Total (N = 151)
Tanner stage scores for genital development in boys; n (%) [b]			
1	0	0	0
2	2 (8.0)	3 (13.6)	5 (10.6)
3	2 (8.0)	4 (18.2)	6 (12.8)
4	7 (28.0)	6 (27.3)	13 (27.7)
5	14 (56.0)	9 (40.9)	23 (48.9)
Baseline HbA1c (%)			
n	76	75	151
Mean (SD)	8.11 (1.330)	8.16 (1.513)	8.13 (1.420)
Minimum, maximum	5.7, 11.3	6.3, 11.5	5.7, 11.5
Baseline blood glucose (mmol/dL)			
n	76	75	151
Mean (SD)	8.1 (3.11)	8.8 (3.49)	8.4 (3.31)
Minimum, maximum	3, 17	5, 18	3, 18
Subjects with NAFLD; n (%)	5 (6.6)	3 (4.0)	8 (5.3)
Prior antidiabetic therapy; n (%)			
Schedule A (Naïve to antidiabetic therapy)	14 (18.4)	13 (17.3)	27 (17.9)
Schedule B (Entered study on antidiabetic therapy)	62 (81.6)	62 (82.7)	124 (82.1)

14.2. Subject disposition

	Number of Subjects (%)				
	Placebo (N = 77)		Alogliptin 25 mg QD (N = 75)		Total (N = 152)
	With AD treatment N = 63	Without AD treatment N = 14	With AD treatment N = 62	Without AD treatment N = 13	
Subjects randomized [a]					
Treated	62	14	62	13	151 (99.3)
Not treated	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Completed study treatment	51 (81.0)	13 (92.9)	52 (83.9)	10 (76.9)	126 (82.9)
Hyperglycemic rescue while on study treatment	19 (30.2)	3 (21.4)	17 (27.4)	0 (0.0)	39 (25.7)
Discontinued study treatment	11 (17.5)	1 (7.1)	10 (16.1)	3 (23.1)	25 (16.4)
Primary reason for study treatment discontinuation [b]					
PTE/AE	2 (18.2)	0 (0.0)	2 (20.0)	0 (0.0)	4 (16.0)
Significant protocol deviation	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)
Lost to follow-up	3 (27.3)	0 (0.0)	2 (20.0)	2 (66.7)	7 (28.0)
Voluntary withdrawal	3 (27.3)	1 (100.00)	4 (40.0)	1 (33.3)	9 (36.0)
Pregnancy	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (4.0)
Principal investigator discretion	2 (18.2)	0 (0.0)	1 (10.0)	0 (0.0)	3 (12.0)
Hyperglycemic rescue while on study	20 (31.7)	3 (21.4)	17 (27.4)	0	40 (26.3)
Discontinued study	9 (14.3)	1 (7.1)	9 (14.5)	3 (23.1)	22 (14.5)
Primary reason for discontinuation from study visits [c]					
PTE/AE	1 (11.1)	0	0	0	1 (4.5)
Significant protocol deviation	1 (11.1)	0	0	0	1 (4.5)
Lost to follow-up	3 (33.3)	0	3 (33.3)	2 (66.7)	8 (36.4)
Voluntary withdrawal	2 (22.2)	1 (100)	4 (44.4)	1 (33.3)	8 (36.4)
Pregnancy	0	0	1 (11.1)	0	1 (4.5)
Principal investigator discretion	2 (22.2)	0	1 (11.1)	0	3 (13.6)

14.3. Efficacy results

Primary Endpoint - HbA1c Percent Change from Baseline at Week 26 (Full Analysis Set)

	Placebo (N = 76)	**Alogliptin 25 mg QD (N = 75)**
Baseline		
n	76	75
Mean (SD)	8.11 (1.330)	8.16 (1.513)
Median	7.70	7.70
Minimum, maximum	5.7, 11.3	6.3, 11.5
Week 26		
n	56	54
Mean (SD)	8.24 (2.428)	7.87 (2.099)
Median	7.55	7.35
Minimum, maximum	5.6, 20.0	5.3, 14.2
Change from baseline to Week 26		
n	56	54
Mean (SD)	0.03 (2.041)	-0.20 (1.601)
Median	-0.10	-0.10
Minimum, maximum	-4.6, 8.7	-4.2, 4.0
LS mean (SE)	-0.011 (0.2809)	0.091 (0.2879)
Alogliptin vs placebo		
LS mean difference (SE)		0.102 (0.3677)
95% CI for difference		(-0.627, 0.831)
P-value		0.782