30 March 2023
EMA/212741/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trajenta

International non-proprietary name: linagliptin

Procedure No. EMEA/H/C/002110/II/0049

Note

Variation 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, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 14 December 2022 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 information on paediatric population based on final results from study DINAMO 1218-0091; this is a Phase III double-blind, randomised, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind, active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus. The Package Leaflet is updated accordingly.

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/0446/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0446/2021 was completed.

The PDCO issued an opinion on compliance for the PIP P/0446/2021.

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

The company evaluated clinical data on the use of linagliptin in children and adolescents with type 2 diabetes mellitus (T2DM).

Pharmacokinetic (PK) analysis

In support of the variation, linagliptin PK was assessed in the paediatric population in the two studies (1218-0056 and 1218-0091 (DINAMO)). Linagliptin PK was assessed using descriptive analysis per study, and also by the use of a sufficiently validated population PK (popPK) model.

In summary, the PK analyses suggested no difference in the PK between children/adolescents and adults concerning body weight, sex, race, renal function and antidiabetic background therapy at baseline and support the comparability of the linagliptin PK between paediatric and adult T2DM patients.

Exposure-effect

The relationship between linagliptin exposure and HbA1c was investigated using a sufficiently validated pharmacokinetic/pharmacodynamic (PK/PD) model, which was modified from a previously developed model to which the new paediatric data were added.

A smaller effect of linagliptin treatment was observed in children compared to adults.

Phase 3 trial

Trial 1218.91 (DINAMO™) was a Phase III randomised, double-blind, placebo-controlled parallel-group trial with 3 treatment arms (placebo, 5 mg linagliptin, 10 mg empagliflozin) lasting 26 weeks in children from 10 to ≤17 years of age.

Patients on empagliflozin who did not achieve HbA_{1c} <7.0% at Week 12 (i.e., non responders) were re-randomised at Week 14 to either continue with 10 mg empagliflozin or increase to 25 mg empagliflozin. The trial also included a double-blind, active treatment safety extension period up to 52 weeks: patients on placebo were re-randomised at Week 26 to receive either linagliptin or empagliflozin (10 mg or 25 mg).

In total, 158 patients were randomised to double-blind linagliptin (53 patients), empagliflozin pooled (52 patients), or placebo (53 patients) once daily treatment.

In the 26-week Phase III trial 1218.91 in adolescents, treatment with 5 mg linagliptin was not associated with a relevant reduction in HbA1c.

The rates of any adverse events (AEs) in the placebo and linagliptin 5 mg groups were generally comparable, as were the rates of severe AEs, AEs leading to discontinuation, drug-related AEs, and serious adverse events (SAEs). With the exception of hypoglycaemia, the rates of adverse events of special interest (AESIs) and specific AEs up to the end of the placebo-controlled period were comparable in the placebo and linagliptin 5 mg groups. No unexpected safety concerns were identified for linagliptin in the paediatric programme.

Benefit-risk balance

No unexpected safety concerns were identified for linagliptin in the paediatric programme. However, treatment with 5 mg linagliptin was not associated with a relevant benefit. The benefit-risk balance of Trajenta in adolescents is negative.

The benefit-risk balance of Trajenta in adults 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, II, IIIA and IIIB

Update of sections 4.2, 4.8, 5.1, and 5.2 of the SmPC in order to update information on paediatric population based on final results from study DINAMO 1218-0091; this is a Phase III double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus. The Package Leaflet is updated accordingly.

In addition the MAH took the opportunity to implement minor editorial changes throughout the product information.

☒is recommended for approval.

Amendments to the marketing authorisation

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0446/2021 and the results of these studies are reflected in the SmPC and, as appropriate, the Package Leaflet.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Trajenta-H-C-002110-II-0049'

For more information, please refer to the Summary of Product Characteristics.

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

5. Introduction

Linagliptin is a potent inhibitor of DPP-4 activity and prolongs the half-life of GLP-1. It is an orally available compound with a low risk for hypoglycaemic episodes. Linagliptin for the treatment of T2DM in adults is approved in over 90 countries, including the European Union, the USA, and Japan.

The company evaluated clinical data on the use of linagliptin in children and adolescents with type 2 diabetes mellitus (T2DM) who were treated with metformin and/or insulin or who were not tolerating metformin. This clinical overview summarises the results from trials 1218.91 and 1218.56.

6. Clinical Pharmacology aspects

The clinical development program for linagliptin in children and adolescents 10-17 years of age with T2DM consisted of two clinical trials.

The Phase I study 1218-0056 [c02827550-01] was a double-blind, placebo–controlled, 12-week, parallel-group trial to evaluate the PK and PD of linagliptin after single and multiple doses of 1 and 5 mg linagliptin. Sparse and rich PK/PD (Haemoglobin A1c (HbA1c), DPP–4 inhibition, and Fasting Plasma Glucose (FPG)) sampling up to 24 hours post-drug administration was performed in 39 patients. Based on the results of this study, the dose of 5 mg linagliptin for the subsequent Phase III DINAMO study (1218-0091, [c38245139]) was selected.

The Phase III DINAMO study was a double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of 5 mg linagliptin over 26 weeks, with a double-blind, active treatment safety extension period up to 52 weeks in children and adolescents 10-17 years of age with T2DM. As a measure of systemic exposure to linagliptin, steady state trough and 1.5 h post-dose PK samples were taken. The DINAMO study also included the administration of the selective sodium-glucose cotransporter-2 inhibitor empagliflozin in separate treatment arms.

6.1. Methods – analysis of data submitted

Analysis of linagliptin

Specific and sensitive HPLC-MS/MS (high-performance liquid chromatography coupled to tandem mass spectrometry) methods were developed and validated to support the clinical linagliptin development program.

Sufficiently validated methods [n00194391, n00240725] were used for studies 1218-0056 and 1218-0091. While method n00194391 had been validated for the determination of linagliptin and its metabolite CD 1750 XX, it was used for the analysis of linagliptin alone in Phase I trial 1218-0056. Method n00240725 had been validated for the determination of linagliptin alone using unchanged extraction procedure and LC-MS/MS conditions and was employed for Phase III trial 1218-0091.

Overall (inter-) assay performance data for linagliptin are shown in Table 1.

Table 1. Overall (inter-) assay performance data for linagliptin

Matrix	Human plasma			
	Pre-study[a]	1218-0056 In-study[b]	Pre-study[c]	1218-0091 In-study[d]
Concentration range	0.100 – 100 nmol/L	0.100 – 20.0 nmol/L	0.100 – 20.0 nmol/L	0.100 – 20.0 nmol/L
LLOQ Accuracy (dev)	0.0%	n/a	5.0%	n/a
LLOQ Precision CV	5.4% (n=18)	n/a	7.8 % (n=18)	n/a
Low QC Accuracy (dev)	0.4%	2.5%	0.3%	1.3%
Low QC Precision CV	3.6% (n=10)	6.8% (n=27)	3.2% (n=24)	4.7% (n=31)
Mid QC Accuracy (dev)	4.4%	2.2%	-0.5%	2.0%
Mid QC Precision CV	1.9% (n=10)	4.2% (27)	2.1% (n=24)	3.7% (n=31)
High QC Accuracy (dev)	-3.4%	0.4%	-1.9%	-0.6%
High QC Precision CV	1.8% (n=10)	4.1% (n=27)	1.7% (n=24)	2.9% (n=31)

a assay validation report linagliptin in human plasma [n00194391]
b bioanalytical report, Appendix 16.1.9.1 of study 1218-0056 [c02827550]
c assay validation report linagliptin in human plasma [n00240725]
d bioanalytical report, Appendix 16.1.9.1 of study 1218-0091 [c38245139]

The accuracy and precision of all validated bioanalytical assays used during the paediatric clinical development of linagliptin were within the acceptance criteria of ≤ 20% for the lower limit of quantification (LLOQ) and ≤ 15% for all other concentrations, in line with The FDA Guidance for industry: bioanalytical method validation and the EMA guideline on bioanalytical method validation.

Linagliptin proved to be stable in human plasma for at least 24 h at room temperature, 4 freeze/thaw cycles and 416 days freezer storage at -20°C.

The incurred samples reanalysis (ISR) pass rate was 97.1% for Study 1218-0056 and 94.8% for Study 1218-0091 and, therefore, demonstrates good assay reproducibility.

Population PK analysis

Data manipulation, visualization, and simulations were conducted using version 4.1 of R. Population PK and ER analyses for repeated-measures endpoints were conducted via nonlinear mixed effects modelling with a qualified installation of the NONMEM® software, Version 7.5 (ICON PLC, Ireland). All code was maintained using the version control system Subversion. All analyses were conducted on a computer grid with multiple compute nodes. Each node runs the Linux operating system that utilized the gfortran® Fortran Compiler (version 7.5.0 for Linux).

Data from Phase III Study 1218-0091 was used to develop the popPK model (c39218172), starting from a popPK model (c37380493) that was previously developed with data from several studies in adults and from the multiple-dose Phase IIb study 1218-0056 in children and adolescents with T2DM from 10 to 17 years of age. This structural model c37380493 was re-estimated using the data from study 1218-0091 under a Bayesian framework in study c39218172.

The parameter estimates from the previous linagliptin population PK model were used as priors to inform the model parameters without direct support from the sparse paediatric data. For parameters of primary interest, namely apparent clearance after oral dosing (CL/F), apparent central volume of distribution after oral dosing (V_2/F), and CL/F by sex, weakly informative priors were used. All parameter estimates were reported as point estimates from NONMEM® with 95% credible intervals derived from the posterior distribution of the parameter estimates. Additional effects for covariates were explored graphically and estimated as necessary to explain potential biases in the characterization of PK observed in the paediatric population.

A two-compartment model with first-order absorption and a saturable binding sub-model in the central compartment was used based on the results of previous analyses. The model was parameterized with CL/F, V_2/F, apparent (oral) intercompartmental clearance (Q/F), the apparent peripheral volume of distribution after oral dosing (V_3/F), absorption rate constant (k_a), and parameters relating to saturable binding (binding affinity (KSS) and total DPP-4 concentration (RMAX)). Weight (WT) was used to scale clearances and volumes according to fixed allometric exponents between adult and paediatric study patients. The final PopPK model parameters are shown in Table 2. The structure of the two-compartment model with first-order absorption and a saturable binding submodel in the central compartment, as described before, was retained in the final model, and no additional covariates were included.

The previous model estimated interindividual variability (IIV) on CL/F and k_a. IIV could not be estimated on k_a in the current model due to the limited number of PK observations available in the absorption phase. Interoccasion variability was estimated in the previous model but not estimated in the current model, given the limited number of observations per sampling occasion. Therefore, using an exponential variance model, the final model only included IIV on CL/F. The residual error model was also adjusted to include two separate error terms, with one for outlier PK trough observations, which was defined as concentrations more than 5-fold smaller than the median concentration 24 hours post-dose at steady state, and one for all remaining observations. The residual error was described with an additive error model in the logarithmic scale, which corresponds to using proportional error in the linear scale.

Table 2. PK model: Final model parameter estimates (Study c39218172).

			Median	95% CDI	Bulk ESS	Tail ESS	$\hat{R}$	Shrinkage (%)
Structural model								
CL/F (L/hr)	$\exp(\theta_1)$	Apparent clearance	81.5	(58.1, 118)	1662	4374	1.00	
V2/F (L)	$\exp(\theta_2)$	Apparent central volume of distribution	578	(434, 732)	3443	5090	1.00	
Q3/F (L/hr)	$\exp(\theta_3)$	Apparent intercompartmental clearance	227	(180, 285)	5021	8121	1.00	
V3/F (L)	$\exp(\theta_4)$	Apparent peripheral volume of distribution	1340	(1170, 1540)	5725	8827	1.00	
KA (1/hr)	$\exp(\theta_5)$	Absorption rate constant	0.848	(0.710, 1.01)	3864	5797	1.00	
KSS (nmol/L)	$\exp(\theta_6)$	DPP-4 binding affinity	0.0522	(0.0443, 0.0615)	5922	7725	1.00	
RMAX (nmol/L)	$\exp(\theta_7)$	Total DPP-4 concentration	4.18	(3.85, 4.51)	3815	6436	1.00	
Covariate effects								
CL/F ~ SEX	$\exp(\theta_8)$	Proportional shift in CL/F for female relative to male	1.46	(0.944, 2.26)	1019	2089	1.00	
Interindividual variability								
$\Omega_{CL/F}(CV(\%))$	$\Omega_{1,1}$	IIV-CL/F	81.3	(58.2, 118)	8295	15060	1.00	22.2
Residual variability								
$\Sigma_{11}(CV(\%))$	$\Sigma_{1,1}$	RUV - non-outliers	34.8	(31.0, 39.3)	22819	32691	1.00	
$\Sigma_{22}(CV(\%))$	$\Sigma_{2,2}$	RUV - outliers	278	(192, 451)	44077	46093	1.00	

Parameters estimated in the log-domain were back-transformed for clarity
Abbreviations: CDI: credible interval; ESS: effective sample size; R^ : Gelman-Rubin diagnostic; IIV: interindividual variability; RUV: residual unexplained
variability; DPP-4: dipeptidyl peptidase IV activity
Credible intervals calculated from Bayesian posteriors
CV% of omegas = sqrt(exp(estimate) - 1) * 100, CV% of sigma = sqrt(estimate) * 100

The final model provided a reasonable description of the data, as judged by visual inspection of model diagnostic plots. No systemic bias was noted in expected weighted residual (EWRES) or NPDE versus time and population predicted concentration or time after dose. There were also no obvious trends in plots of IIV random effects versus continuous or categorical covariates. Visual predictive checks (VPCs)

indicated that the current model reasonably fit steady-state concentrations in paediatric patients across covariates of interest in Study 1218.56 and 1218-0091 (DINAMO).

Exposure response analysis

In a previous analysis, a population ER model was developed for longitudinal HbA_{1c} using data from several studies in adults and from the multiple-dose Phase IIb study 1218-0056 in children and adolescents with T2DM from 10 to 17 years of age. This ER model was re-estimated for the new paediatric data from study 1218-0091 using full Markov chain Monte Carlo (MCMC) Bayesian estimation methods, with prior distributions defined from the point estimates and uncertainty of the adult ER model for model parameters without direct support from the paediatric data. Specifically, the AUC_{ss} producing half maximal inhibitory effect (AUC50) was estimated with an informative prior, while all other parameters were estimated with weakly informative priors. Additional effects for covariates were explored graphically and estimated as necessary to explain potential biases in the characterization of change in HbA_{1c} observed in the paediatric population.

The previous model was used as a starting point and consisted of a simple HbA_{1c} turnover process with an effect of a wash-out as an additive zero-order process. Linagliptin was allowed to inhibit the production of HbA_{1c} through an inhibitory maximum effect (E_{max}) model. Linagliptin AUC_{ss} was simulated for all PK patients to drive the ER model using their individual parameter estimates. Specifically, AUC_{ss} were derived by integrating over the individual concentration-time profile for an interval of 24 hours, under steady-state conditions, and their assigned linagliptin dose. Metformin and insulin were modelled as simple time-invariant effects that proportionally adjusted the zero-order production of HbA_{1c} and baseline HbA_{1c}. Given Study 1218-0091 includes a 2-week run-in period with an open-label placebo, the effect of washout was not estimated in the current analysis (i.e., no wash-out effect in current data).

The final ER model parameters are shown in Table 3. Model performances were evaluated by using predictive checks and Bayesian diagnostics with prior insulin co-therapy than those without.

The final model provided a reasonable description of the data, as judged by visual inspection of model diagnostic plots. VPCs demonstrated that the model provided an adequate description of HbA1c over time across all dose levels, treatment arms, and covariates of interest in Study 1218.56 and 1218-2019 (DINAMO).

Parameter estimates were compared between the previous and current models with paediatric data from Study 1218.91. Using the previous and current models, Monte Carlo simulations were performed to compare population-level placebo-adjusted HbA1c change from baseline at 26 weeks in adults and paediatric patients.

Table 3. Exposure-effect model: Final model parameter estimates (Study c39218172).

			Median	95% CDI	Bulk ESS	Tail ESS	$\hat{R}$	Shrinkage (%)
Structural model								
BASE (%)	$\exp(\theta_1)$	Baseline HbA1c	7.39	(7.10, 7.70)	679	1189	1.01	
kin (%/hr)	$\exp(\theta_2)$	HbA1c synthesis rate constant	0.0209	(0.0137, 0.0320)	828	1627	1.00	
IMAX	$\frac{\exp(\theta_3)}{(1+\exp(\theta_3))}$	Maximum inhibition	0.0959	(0.0485, 0.159)	1841	3520	1.00	
AUC50 (nmol*hr/L)	$\exp(\theta_4)$	AUC at 50% IMAX	145	(74.8, 282)	3035	5005	1.00	
PROG (%/hr/hr)	$\exp(\theta_6)$	Zero-order disease progression rate constant for prior insulin subjects	6.36e-07	(3.46e-07, 1.05e-06)	977	1850	1.00	
Covariate effects								
INS_{BASE}	$\exp(\theta_5)$	Prior insulin effect on BASE	1.16	(1.09, 1.22)	634	1195	1.01	
Interindividual variability								
Ω_{BASE} (CV(%))	$\Omega_{1,1}$	IIV-BASE	13.8	(11.9, 16.3)	29203	56326	1.00	6.30
Ω_{PROG} (SD)	$\Omega_{2,2}$	IIV-PROG	6.49e-07	(4.45e-07, 9.81e-07)	1016	2215	1.00	23.3
$\Omega_{PROG-BASE}$ (correlation)	$\Omega_{2,1}$	Covariance on PROG-BASE	0.286	(0.0126, 0.547)	10689	19892	1.00	
Residual variability								
Σ_{11} (CV(%))	$\Sigma_{1,1}$	RUV - exponential	6.59	(5.98, 7.31)	18531	36378	1.00	

Parameters estimated in the log-domain were back-transformed for clarity
Abbreviations: CDI: credible interval; eGFR: estimated glomerular filtration rate; ESS: effective sample size; HbA1c: hemoglobin A1c; $R\hat{}$: Gelman-Rubin diagnostic; RUV: residual unexplained variability, Credible intervals calculated from Bayesian posteriors
CV% of omega(1,1) = sqrt(exp(estimate) - 1) * 100
SD of omega(2,2) = sqrt(estimate) / 100000
CV% of sigma = sqrt(estimate) * 100

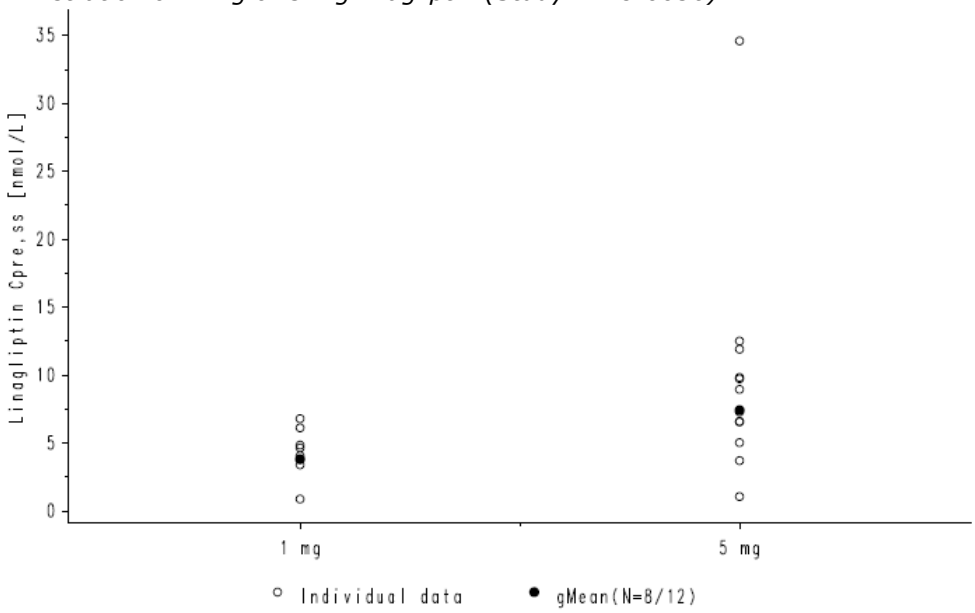
6.2. Results

Descriptive and population PK (popPK) analysis

The PK results in children and adolescents from Phase III study 1218-0091 and Phase I study 1218-0056 were compared to the data previously obtained in adult T2DM patients by (i) descriptive analysis and (ii) based on a population PK (popPK) model, which included data from both studies in paediatric T2DM patients as well as several studies in adult T2DM patients [c39218172].

In Study 1218-0056, steady-state linagliptin trough levels in the linagliptin 5 mg group were higher than in the linagliptin 1 mg group, with gMean trough levels of 7.42 nmol/L (gCV 98.5%) and 3.80 nmol/L (gCV 69.9 %), respectively (see Figure 1). Linagliptin plasma levels increased less than dose proportional. For the 4 patients in the linagliptin 5 mg group for whom rich PK sampling data were available for non-compartmental PK analysis, $AUC_{\tau,ss}$ values were between 152 nmol·h/L and 306 nmol·h/L. The accumulation-based half-lives ranged from 8.15 h to 29.4 h. For the 2 patients in the linagliptin 1 mg group with rich PK sampling the $AUC_{\tau,ss}$ values were 142 nmol·h/L and 148 nmol·h/L. The accumulation-based half-lives were 29.1 h and 108 h, respectively.

Figure 1. Individual and gMean trough concentrations of linagliptin at steady state after once daily oral administration of 1 mg or 5 mg linagliptin (Study 1218-0056)



In Phase III Study 1218-0091, in total, there were 164 valid plasma samples available for the PK analysis of linagliptin. Variability of linagliptin plasma concentrations was considerably higher for samples taken pre-dose (week 26: gCV 124%; week 52: gCV 213%) than for samples taken post-dose (week 26: gCV 42.3%; and week 52: gCV 53.2%); hence, post-dose levels may better reflect potential inter-patient variability. Plasma concentrations at Week 52 were used for all descriptive subgroup analyses.

Influence of intrinsic and extrinsic factors on linagliptin exposure.

The effect of demographic and baseline characteristics, including renal function (eGFR calculated by the Zappitelli-formula), age, body weight, BMI, sex, race, ethnicity, geographical region, and country on linagliptin exposure was investigated descriptively in Study 1218-0091.

In addition, the impact of the most relevant co-medications, such as metformin and insulin, on linagliptin plasma concentrations was evaluated. Furthermore, the relationship between drug plasma concentrations and the occurrence of certain AEs was analysed descriptively.

Despite slight differences in gMean plasma concentrations, individual exposure values were largely overlapping between subgroups, suggesting no influence of renal function, age, sex, race, and region on linagliptin exposure within the investigated range. Exposure slightly increased with a body weight below 70 kg (see Figure 2). There was no influence of baseline medication on linagliptin exposure. Linagliptin exposure did not seem to have an influence on the occurrence of hypoglycaemia (see Figure 3).

Figure 2. Steady state trough plasma concentrations of linagliptin stratified by different covariates (Study 1218-0091)

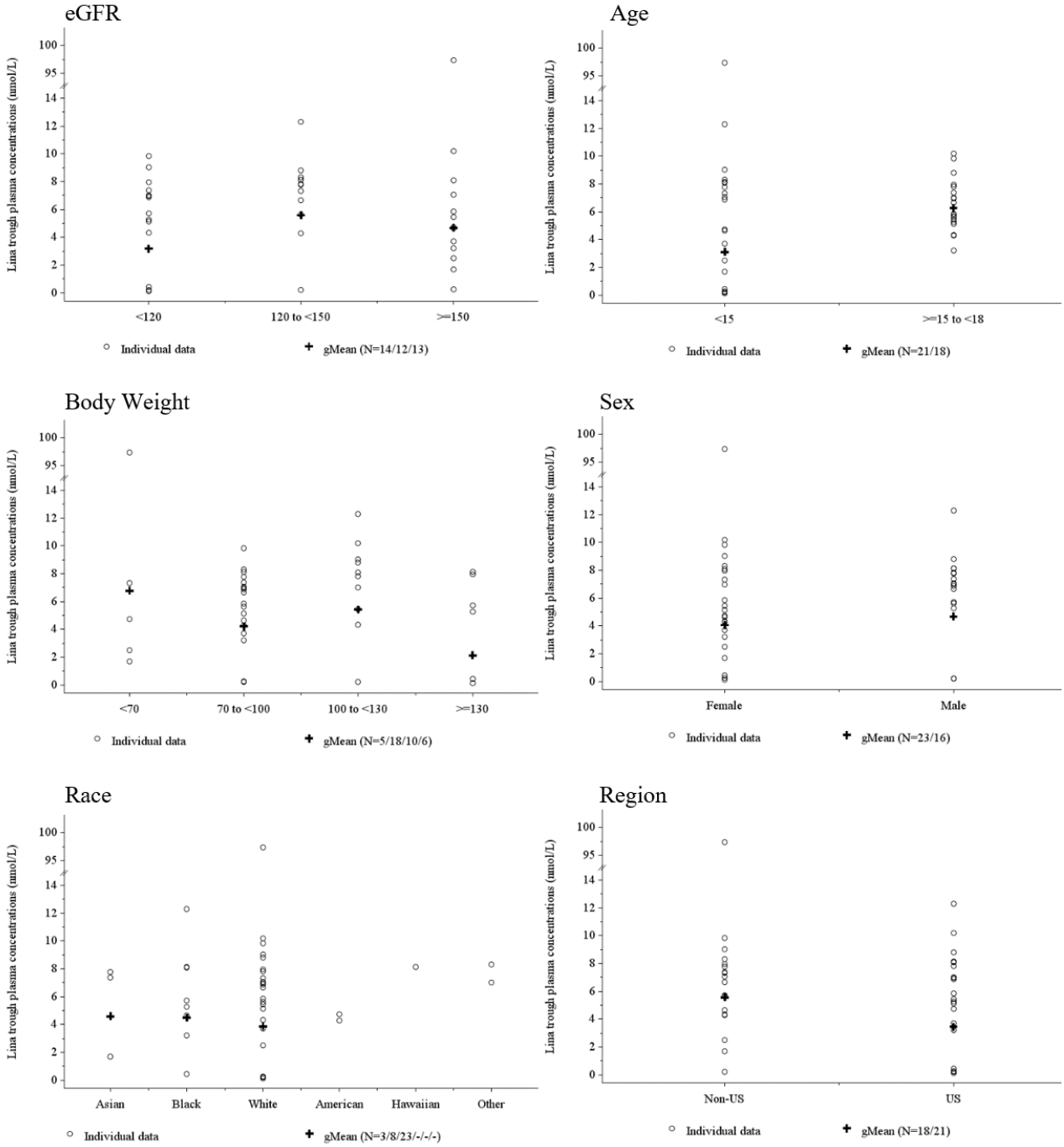
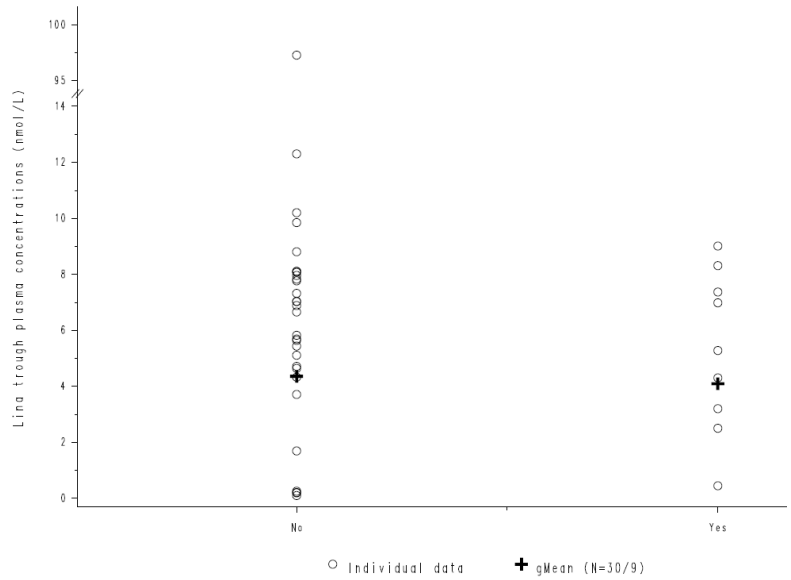


Figure 3. Steady state trough plasma concentrations of linagliptin after administration of 5 mg linagliptin once daily stratified by occurrence of hypoglycaemia (yes or no) (Study 1218-0091)



Plasma concentrations of linagliptin in children and adolescents with T2DM were generally comparable to those previously observed in adult patients with T2DM.

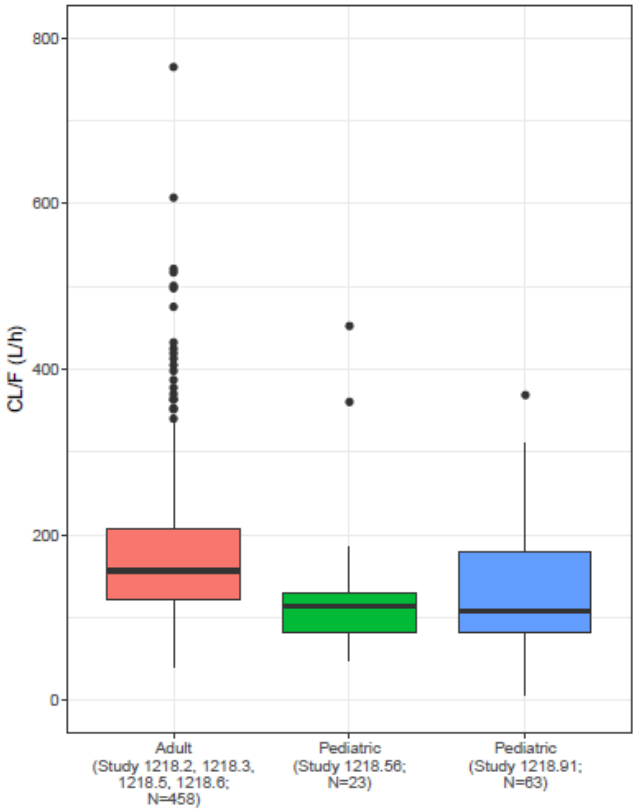
Population PK model c39218172

The popPK model c39218172 for paediatric patients with T2DM included the following covariates with an influence on the PK: linagliptin exposure was characterized as increasing with decreasing weight following allometric scaling; The parameter estimate for sex effect on CL/F suggested that linagliptin CL/F appeared to be higher in females, but the 95% CDIs included the null value (146 (94.4, 226)%) (Table 2).

Individual *CL/F* estimates for paediatric patients in the current model were consistent with individual *CL/F* estimates for paediatric patients in the previous model (Figure 4). Both groups of paediatric patients had lower individual *CL/F* estimates relative to adult patients in the previous model. Consistent with lower *CL/F* estimates for paediatric patients, Monte Carlo simulations indicated paediatric patients had slightly higher *AUC*ss values (19.9% higher) relative to adults. However, there was substantial overlap in the distribution of *AUC*ss between adult and paediatric patients, indicating that generally similar exposure can be achieved in the two patient populations given a linagliptin 5 mg dose (Figure 5).

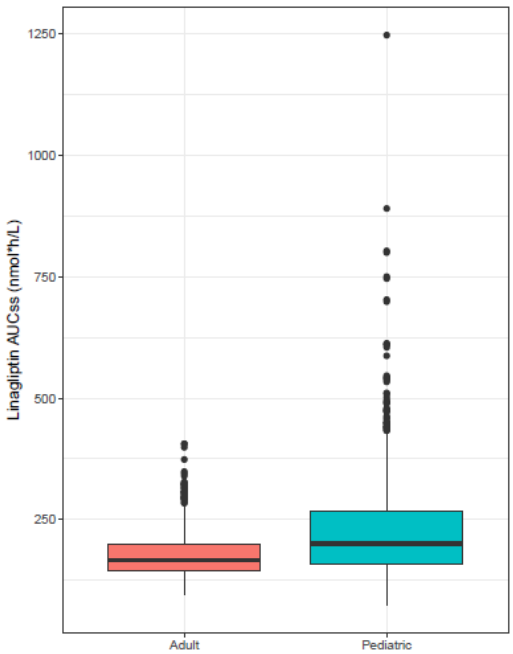
The results of the popPK analysis were in line with the results from the descriptive analysis.

Figure 4. PopPK model: Distributions of individual CL/F values from adults and paediatric patients in the previous model, and paediatric patients from Study 1218.91 (PopPK model c39218172).



Median values are designated by a solid line in the center of the box. Boxes indicate the inter-quartile range (IQR) with whiskers extending to 1.5*IQR. Abbreviations: N = number of patients.

Figure 5. PopPK model: Distributions of AUCss values from Monte Carlo simulations in adults and paediatric patients using the previous model and the current model, respectively (PopPK model c39218172).



Median values are designated by a solid line in the center of the box. Boxes indicate the inter-quartile range (IQR) with whiskers extending to 1.5*IQR. Abbreviations: N = number of patients.

Descriptive comparison of exposure by subgroups of covariates suggested no difference of the PK between children/adolescents and adults with respect to body weight, sex, and antidiabetic background therapy at baseline.

In summary, these analyses support the comparability of the PK between paediatric and adult T2DM patients.

Exposure-response (ER) analysis

The final, re-estimated ER model was a disease progression model, and linagliptin effect was assumed to inhibit k_{in} via an Emax model. The model was parameterized with a zero-order HbA1c synthesis rate (k_{in}), and a constant HbA1c first-order degradation rate (HbA1c degradation rate constant (k_{out})). Paediatric patients requiring insulin showed higher HbA1c baseline as well as a more pronounced disease progression. This resulted in a larger simulated magnitude of placebo-adjusted change of HbA1c in patients requiring insulin. To account for the apparent disease progression observed in the paediatric data, the model was updated by including a time-dependent change in the synthesis process. Specifically, the synthesis rate (k_{in}) changed over time by a zero-order process. Linagliptin effect was parameterized to inhibit k_{in} via an E_{max} model. Insulin was included as a covariate, and insulin co-therapy at baseline was associated with a higher baseline HbA1c and a faster disease progression. Inter-individual variability (IIV) was included on baseline HbA1c and the disease progression parameter. A proportional residual error was also included.

In the comparison of paediatric and adult patients, paediatric patients had slightly lower maximum inhibition (I_{max}) compared to adults. In Monte Carlo simulations, the simulated placebo-adjusted change from baseline HbA1c in adults was larger than that of paediatric patients both without prior insulin use (median adult: -0.614%; paediatric: -0.409%), and with prior insulin use (median adult: -0.647%; paediatric: -0.527%), thus indicating a smaller drug effect for paediatric compared to adult patients. Variability in response was higher in paediatric patients.

At week 26 (timepoint of primary efficacy endpoint in 1218-0091), the difference in response between patients with and without prior insulin use was much larger in paediatric subjects compared to adults (median difference placebo corrected change from baseline adult: 0.033%; paediatric: 0.118%).

6.3. Discussion

In support of the variation, linagliptin PK was assessed in the two studies (1218-0056 and 1218-0091 (DINAMO)). The methods used for the quantification of linagliptin in plasma have been sufficiently validated. Method n00194391, used for analysis of samples from Phase I study 1218-0056, was also used in studies provided with the initial MAA for linagliptin. The robustness of the analysis was shown by the ISR results. In response to an initial OC, it was indicated that the stability period covers the maximum storage period of the samples.

Linagliptin PK was assessed using descriptive analysis per study, and also by the use of a popPK model. The popPK model was developed based on a prior model containing PK data in adults and appears sufficiently validated.

Based on information from Phase II Study 1218-0056, total linagliptin exposure increased less than dose-proportional between the 1 and 5 mg dose. This has also been observed for adults, and is thought to be due to the concentration dependent binding of linagliptin to DPP-4. As discussed and accepted in a previous Type II variation EMEA/H/C/WS1162, linagliptin 5 mg in the paediatric population showed superiority over 1 mg about trough DPP-4 inhibition and a numerically larger reduction concerning the adjusted mean change from baseline in HbA_{1c}.This provided support for the use of the 5 mg dose in the subsequent Phase III Study 1218-0091.

The effect of demographic and baseline characteristics, including renal function, age, body weight, BMI, sex, race, ethnicity, geographical region, and country, on linagliptin exposure was investigated descriptively in Study 1218-0091. Despite slight differences in mean plasma concentrations, individual exposure values were largely overlapping between subgroups, suggesting no influence of renal function, age, sex, race, and region on linagliptin exposure within the investigated range. Exposure slightly increased with a body weight below 70 kg. There was no influence of baseline medication on linagliptin exposure, and linagliptin exposure did not seem to have an influence on the occurrence of hypoglycaemia.

Of note, renal function was determined using the Zappitelli formula. This CysC-based GFR prediction equation is not often used but is reported to provide accurate estimations of GFR in comparison with the Schwartz method. It is known that the Cockcroft-Gold formula is suboptimal for estimating GFR in children. Also, in light of the limited importance of renal excretion for linagliptin (only 5% eliminated in urine), this aspect will not be pursued.

In the popPK model, descriptive comparison of exposure by subgroups of covariates suggested no difference in the PK between children/adolescents and adults concerning body weight, sex, and antidiabetic background therapy at baseline. In summary, these popPK analyses support the comparability of the linagliptin PK between paediatric and adult T2DM patients.

Exposure-effect

The relationship between linagliptin exposure and HbA1c was investigated using a PK/PD model, which was modified from a previously developed model to which the new paediatric data were added. The model appears sufficiently validated.

In the comparison of paediatric and adult patients, paediatric patients had lower maximum inhibition (Imax) compared to adults. In Monte Carlo simulations, the simulated placebo-adjusted change from baseline HbA1c in adults was larger than that of paediatric patients both without prior insulin use (median adult: -0.614%; paediatric: -0.409%), and with prior insulin use (median adult: -0.647%; paediatric: -0.527%), thus indicating a smaller drug effect for paediatric compared to adult patients. Variability in response was higher in paediatric patients.

In summary, there was a smaller effect of linagliptin treatment observed in children compared to adults.

7. Clinical Efficacy aspects

This overview summarises the results from trials 1218.91 and 1218.56 (Table 1: 1). Trial 1218.91 (DINAMO™) was a Phase III randomised, double-blind, placebo-controlled parallel-group trial with 3 treatment arms (placebo, 5 mg linagliptin, 10 mg empagliflozin) lasting 26 weeks in children from 10 to ≤17 years of age (

Figure 1: 1). Patients on empagliflozin who did not achieve HbA_{1c} <7.0% at Week 12 (i.e., non responders) were re-randomised at Week 14 to either continue with 10 mg empagliflozin or increase to 25 mg empagliflozin. The trial included a double-blind, active treatment safety extension period up to 52 weeks: patients on placebo were re-randomised at Week 26 to receive either linagliptin or empagliflozin (10 mg or 25 mg). Trial 1218.91 includes the main trial DINAMO™ (presented in this dossier), and the ancillary trial DINAMO™ Mono which is still ongoing. DINAMO™ Mono includes treatment-naïve patients or patients who are not on active treatment and are treated with trial drug as monotherapy. The recruitment for DINAMO™ Mono has been terminated early in agreement with the FDA due to recruitment challenges and because current information suggested no clinically meaningful difference between monotherapy versus add-on to metformin and/or insulin.

Trial 1218.56 was a Phase II b randomised, double-blind, placebo-controlled parallel group dose-finding trial of linagliptin (1 mg or 5 mg administered orally once daily) over 12 weeks in children and adolescents from 10 to ≤17 years of age, with T2DM.

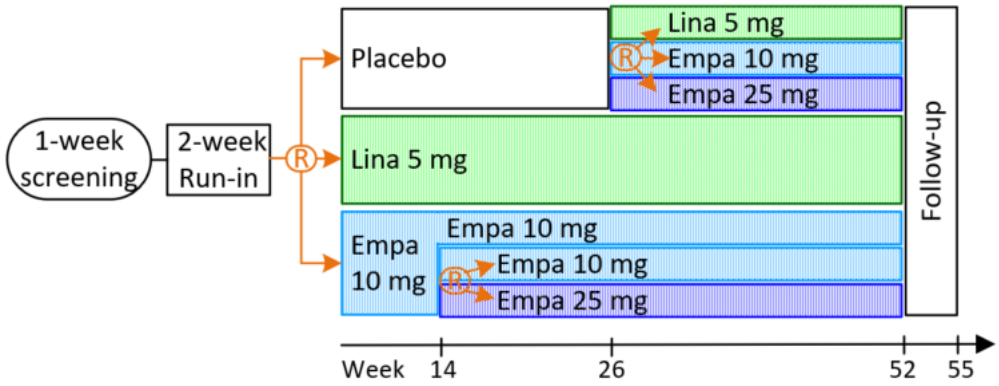
The majority of the treated patients in 1218.91 (91.1%, 143 of 157) and 29.7% of the treated patients (11 of 37) in 1218.56 took metformin as background antidiabetic medication at baseline. In trial 1218.91, 63 of the 143 patients on metformin also took insulin as an antidiabetic background medication (in total 63 of 157 treated patients, 40.1%). In addition, 5 of 157 patients (3.2%) had only insulin as background antidiabetic medication.

Based on the results of the paediatric clinical programme, BI intends to seek to include results into the product information (information on clinical trials) for linagliptin and linagliptin/metformin for the treatment of paediatric patients with T2DM.

Table 1: 1 Trials included in this submission

	Trial 1218.91	Trial 1218.56
Clinical phase	III	II b
Sample size	158 randomised patients (157 treated)	39 randomised patients (39 treated)
Design	Randomised, double-blind, placebo-controlled, parallel group trial	Randomised, double-blind, placebo-controlled dose-finding trial
Duration of treatment	52 weeks	12 weeks
Active substances	Linagliptin (5 mg) and empagliflozin (10 mg and 25 mg)	Linagliptin (1 mg and 5 mg)
Insufficient glycaemic control	HbA_{1c} ≥6.5% and ≤10.5% at screening	HbA_{1c} >6.5% and ≤10.5% at screening
Background therapy	○ Patients treated with diet and exercise plus metformin and/or insulin ○ Patients not tolerating metformin, treated only with diet and exercise	Patients treated with diet and exercise and/or metformin with or without concomitant stable basal insulin
Age group	10 to ≤17 years	10 to ≤17 years
Diagnosis of T2DM	At least 8 weeks before screening	At least 3 months before randomisation
Primary endpoint	Change in HbA_{1c} from baseline to the end of 26 weeks	Change in HbA_{1c} from baseline to the end of 12 weeks

Figure 1: 1 Overview of the trial design for 1218.91



Data of these 2 trials were not pooled for efficacy analyses. Reasons were the different time point of primary endpoint assessment (1218.91: at 26 weeks; 1218.56: at 12 weeks) and because trial 1218.56 was discontinued prior to complete recruitment based on a predefined interim analysis to allow early elimination of the potentially ineffective lowest dose of linagliptin 1 mg.

Assessors comments

Trial 1218.91 (DINAMO™) was a Phase III randomised, double-blind, placebo-controlled parallel-group trial with 3 treatment arms (placebo, 5 mg linagliptin, 10 mg empagliflozin) lasting 26 weeks in children from 10 to ≤17 years of age. The design is complex but acceptable because it answered the call from regulators and experts for multi-arm efficacy and safety studies in paediatric patients, given the recruitment challenges in this population.

Patients on empagliflozin who did not achieve HbA_{1c} <7.0% at Week 12 (i.e., non-responders) were re-randomised at Week 14 to either continue with 10 mg empagliflozin or increased to 25 mg empagliflozin. The trial also included a double-blind, active treatment safety extension period up to 52 weeks: patients on placebo were re-randomised at Week 26 to receive either linagliptin or empagliflozin (10 mg or 25 mg).

Trial 1218.56 was a Phase II b randomised, double-blind, placebo-controlled parallel group dose-finding trial of linagliptin (1 mg or 5 mg administered orally once daily) over 12 weeks in children and adolescents from 10 to ≤17 years of age, with T2DM.

In addition to the safety analyses of trials 1218.91 and 1218.56 presented in the CTRs, safety data of the 2 trials were pooled into 2 groupings:

- SAF-p1 (all patients treated with linagliptin 5 mg up to Week 52) provides a complete account of observed safety data for linagliptin 5 mg over the entire treatment duration
- SAF-p2 (placebo-controlled trials up to Week 26) provides a comprehensive comparison of linagliptin 5 mg vs placebo

Bayesian analysis

In December 2021, BI performed a blinded variability assessment of the primary endpoint in trial 1218.91 with available data for 141 patients. The observed blinded standard deviation (SD = 1.65%) was considerably higher than the anticipated covariate-adjusted SD = 0.9% in the sample size determination in the CTP. Consequently, reduced power could be expected for the primary analysis of DINAMO™ unless a greater treatment effect than anticipated was to be observed. Therefore, BI

performed supplemental analyses to trial 1218.91 using Bayesian borrowing from simulated paediatric patients with T2DM based on exposure-response analyses of historical adult and paediatric patients with T2DM treated with linagliptin [c39218174]. The objective was to provide supportive evidence for the effectiveness of linagliptin in paediatric patients. Linagliptin has been extensively studied in adult populations, and well-developed PK/PD models supported inference in a paediatric population.

Bayesian analyses were performed using 2 different methods to derive the prior distribution for the placebo-corrected treatment effect. One method was to use pharmacometric modelling of the exposure-response relationship of linagliptin based on available historical data in adult and paediatric patients with T2DM by simulating individual and placebo-corrected mean changes in HbA_{1c} in a paediatric population with baseline characteristics matching the DINAMO™ population in relevant covariates.

The second approach used the placebo-corrected treatment effects reported for paediatric populations with T2DM treated with sitagliptin to inform the prior distribution. In both approaches, the prior distribution was robustified with a weakly-informative mixture component to allow for the possibility of prior-data conflict. The decision rule to conclude superior efficacy was a posterior probability of 97.5% of the placebo-corrected treatment effect being less than 0, as measured by the change in HbA_{1c}.

EMA and compliance with the PIP

The PIP (EMEA-000498-PIP01-08-M10) for linagliptin contains waivers for children <10 years and requires clinical trials to investigate T2DM in the paediatric population. For trial 1218.56, the PDCO confirmed that BI had conducted and performed the trial according to the agreed PIP 000498-PIP01-08 and the respective key binding elements. A statement of compliance with the agreed completed PIP is pending at the time of finalisation of this document.

FDA and compliance with the post-marketing requirement and written request

Based on the medical need of paediatric patients with T2DM and to address the Pediatric Research Equity Act requirements, trials in paediatric patients have been agreed with the FDA as post-marketing requirements (1218.91 and 1218.56). Furthermore, the FDA issued a written request (trial 1218.91). All trial elements are met as agreed with the FDA as part of the paediatric post-marketing requirements and written request.

All trials were performed in compliance with GCP and in accordance with applicable regulatory requirements and BI standard operating procedures. All CTPs were approved by institutional review boards or independent ethics committees. In accordance with GCP and according to the local regulatory and legal requirements, informed consent/assent was obtained from all patients/parent(s) or the patient's legally accepted representative.

7.1. Methods – analysis of data submitted

Efficacy endpoints and analysis methods

Trial 1218.91

The following efficacy endpoints were defined for the pivotal phase III trial 1218.91 (DINAMO™). All HbA_{1c} values were obtained from an NGSP-certified laboratory.

Primary confirmatory endpoint: the change in HbA_{1c} (%) from baseline to the end of 26 weeks

Secondary endpoints:

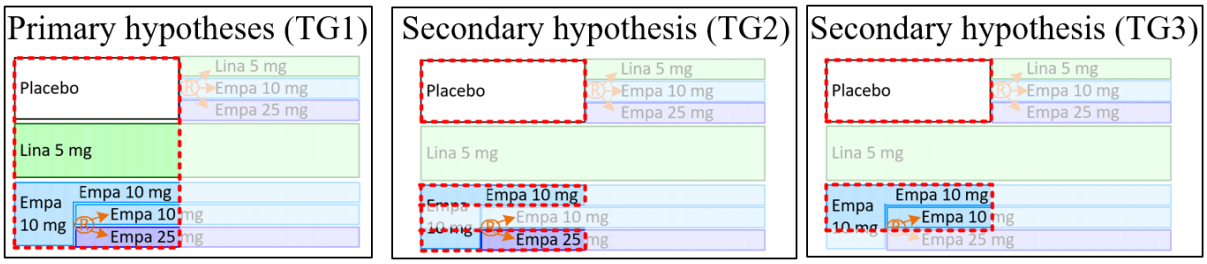
- Change in FPG (mg/dL) from baseline to the end of 26 weeks
- Change in body weight (kg) from baseline to the end of 26 weeks
- Change in SBP (mmHg) from baseline to the end of 26 weeks
- Change in DBP (mmHg) from baseline to the end of 26 weeks
- Proportion of patients who achieve HbA_{1c} <6.5% at the end of 26 weeks
- Proportion of patients who achieve HbA_{1c} <7.0% at the end of 26 weeks

Further endpoints:

- Change in HbA_{1c} (%) from baseline to the end of 12 and 52 weeks
- Change in FPG (mg/dL) from baseline to the end of 52 weeks
- Change in body weight (kg) from baseline to the end of 12 and 52 weeks
- Change in SBP (mmHg) from baseline to the end of 12 and 52 weeks
- Change in DBP (mmHg) from baseline to the end of 12 and 52 weeks
- Proportion of patients who achieve HbA_{1c} <6.5% at the end of 52 weeks
- Proportion of patients who achieve HbA_{1c} <7.0% at the end of 52 weeks
- Proportion of patients who achieve HbA_{1c} reduction of >0.5% at the end of 26 and 52 weeks (introduced with Global Amendment 1)
- Proportion of patients who initiate glycaemic rescue therapy up to 26 weeks and 52 weeks. Any new antidiabetic therapy, any dose increase of basal insulin of more than 0.1 IU/kg above the baseline prescribed dose for more than 21 consecutive days was considered rescue therapy
- Change in fasting serum C-peptide from baseline to the end of 26 and 52 weeks
- Change in urine albumin creatinine ratio (UACR) (mg/g creatinine) from baseline to the end of 26 and 52 weeks
- Change in eGFR (mL/min/1.73m²) from baseline to the end of 26 and 52 weeks
- Change in HbA_{1c} (%) from Week 12 to the end of 26 weeks in patients randomised to empagliflozin 10 mg and not achieving glycaemic target at Week 12

The primary endpoint was analysed based on an ANCOVA model using multiple imputation with consecutive 'wash-out' (primary hypotheses for TG1; see Figure 4: 1 box with dashed red borderline) and 'inverse probability weighting' approaches (secondary hypotheses for TG2 and TG3; see Figure 4: 1 box with dashed red borderline). The 'wash-out' approach imputed missing off-treatment values in active treatment groups based on the primary endpoint distribution in the placebo group. The hypotheses were tested hierarchically in a confirmatory setting. The primary family of hypotheses consisted of 2 pairwise comparisons of the treatment effect of empagliflozin pooled doses versus placebo and linagliptin versus placebo (TG1), followed by the secondary family of hypothesis comparing the effect of each empagliflozin dose regimen with placebo (TG2 and TG3). To test the primary hypotheses, the effect of linagliptin and of empagliflozin was compared with placebo at an overall α of 0.05 (2-sided) using the Hochberg method to account for multiple testing. Only after achieving statistically significant results for both comparisons in the 'wash-out' approach, were the secondary hypotheses (ANCOVA with 'wash-out' plus 'inverse probability weighting' approach) tested to compare the individual empagliflozin doses versus placebo.

Figure 4: 1 Primary endpoint testing in trial 1218.91 with primary (TG1) and secondary hypotheses (TG2 and TG3)



Unless otherwise specified, efficacy analyses were based on the mITT set and included all treated patients who had a baseline HbA_{1c} value. Patients were analysed as randomised and including all HbA_{1c} measurements regardless of adherence to treatment or the use of rescue medication.

Baseline was defined as the last observed measurement prior to administration of any initially randomised trial medication at Day 1.

Assessors comments

In trial 1218.56, the primary endpoint of the final analysis was the change from baseline in HbA_{1c} (%) after 12 weeks of treatment. The key secondary endpoint of the final analysis was the PD endpoint DPP-4 inhibition (%) at the trough at steady state.

In trial 1218.91, the primary confirmatory endpoint was the change in HbA_{1c} (%) from baseline to the end of 26 weeks. Secondary endpoints include the change in fasting glucose (mg/dL) and change in body weight (kg) from baseline to the end of 26 weeks.

Trial 1218.56

The primary endpoint of the final analysis was the change from baseline in HbA_{1c} (%) after 12 weeks of treatment. The key secondary endpoint of the final analysis was the PD endpoint DPP-4 inhibition (%) at trough at steady state. The secondary efficacy endpoint was the change from baseline in FPG after 12 weeks of treatment.

Patient characteristics

Although this clinical overview focuses on data for linagliptin compared with placebo, the entire patient population is described in this section, including the empagliflozin pooled group, to provide the characteristics of all patients in this trial.

Trial 1218.91

Trial 1218.91 was carried out at 78 clinical sites in 13 countries in Asia, Europe, North and South America. In total, 158 patients were randomised to double-blind linagliptin (53 patients), empagliflozin pooled (52 patients), or placebo (53 patients) once daily treatment (

Figure 1: 1). The initial randomisation was stratified by age and sex. The re-randomisations at Week 14 and Week 26 were stratified by the age documented at the initial randomisation. All but 1 randomised patient (linagliptin group, withdrawal from trial) were treated with at least 1 dose of trial medication.

The majority of patients (140 patients, 89.2%) completed the planned observation time of 55 weeks (regardless of completion of planned treatment with trial medication). The majority of patients remained on treatment with trial drug up to Week 26 (140 patients, 89.2%) and up to Week 52 (130 patients, 82.8%). The frequencies of patients with premature treatment discontinuations were generally comparable across treatment groups. The most common reason for premature discontinuation of trial medication was the withdrawal by the patient (Week 26: 10 patients, 6.4%; Week 52: 16 patients, 10.2%). Based on TG6 (complete active treatment period excluding placebo), the median exposure to active trial medication up to Week 52 was 362 days (about 12 months; min: 1 day, max: 393 days), with 58.3% of patients treated for at least 46 weeks with active trial medication.

As intended, between 30% and 70% of randomised patients were <15 years of age (i.e., 76 patients, 48.4%) and between 30% and 70% of randomised patients were female (i.e., 97 patients, 61.8%). The mean age of the patient population was 14.5 years (SD 1.9). More than half of the patient population participated in North America (mostly USA). Most patients were White (78 patients, 49.7%) or Black/African American (49 patients, 31.2%).

About half of the patients (80 patients, 51.0%) took only metformin, 63 patients (40.1%) took metformin plus insulin, and 5 patients (3.2%) had only insulin as background antidiabetic medication, with balanced distribution across treatment groups. Thus, the majority of the treated patients in trial 1218.91 (91.1%, 143 of 157) took metformin as antidiabetic background medication at baseline.

Patients with insufficient glycaemic control of HbA_{1c} ≥6.5% and ≤10.5% could participate in this trial. About half of the patients had baseline HbA_{1c} values of <8% (83 patients, 52.9); for the remaining patients, approximately similar proportions had either HbA_{1c} values of 8.0% to 9.0% (40 patients, 25.5%) or of >9% (34 patients, 21.7%). The mean baseline FPG was 158.70 mg/dL (SD 55.56). As per the inclusion criteria, patients had to be negative for both islet cell antigen auto-antibodies and glutamic acid decarboxylase auto-antibodies. Most patients had been diagnosed with T2DM for 1 to 3 years (66 patients, 42.0%). The mean BMI was 36.04 kg/m^2 (SD 8.33). The mean body weight was 99.92 kg (SD 26.78), with a maximum weight of 171.0 kg observed in this paediatric population. The mean fasting C-peptide values at baseline were 0.9932 nmol/L. The mean eGFR was 129.79 mL/min/1.73 m^2. Normal UACR (<30 mg/g crea) was reported for 73.9% of patients, while 21.0% of patients had microalbuminuria (30 to 300 mg/g crea), and 3.8% had macroalbuminuria (>300 mg/g crea). The modified Tanner staging was used to assess the patient's pubertal stage; a total of 93 patients (59.2%) had a Tanner stage of 5 (i.e., fully developed) and 64 patients (40.8%) had a Tanner stage of 2 to 4 (i.e., partially developed). Demographic and clinical characteristics were generally balanced between the randomised treatment groups.

Trial 1218.56

Overall, 83 patients were enrolled. Of those, 39 patients were randomised and treated (placebo: 15 patients; linagliptin 1 mg: 10 patients; linagliptin 5 mg: 14 patients). Three of the treated patients (7.7%) prematurely discontinued trial medication; none of these patients discontinued because of AEs.

Of the 39 patients, 21 patients (53.8%) were female. Most of the patients were from study centres in Europe (18 patients, 46.2%) or South America (12 patients, 30.8%). The majority of patients were White (23 patients, 59.0%). The mean age at screening was 14.0 years (SD 1.9 years). The mean baseline weight was 79.8 kg (SD 22.2 kg; range: 47 to 139 kg); Almost all patients were obese (BMI

SDS ≥2: 25 patients, 64.1%) or overweight (BMI SDS 1.28 to <2: 8 patients, 20.5%). The mean HbA_{1c} at baseline was 7.86% (SD 0.95%). The mean baseline FPG was 152.7 mg/dL (SD 45.6 mg/dL). Demographic and baseline characteristics were generally balanced across treatment groups. Mean baseline HbA_{1c} (%) was numerically greater in the linagliptin 1 mg group (8.22 [SD 0.93]) than in the placebo group (7.60 [SD 0.92]) and linagliptin 5 mg group (7.87 [SD 0.98]). Slight differences between treatment groups were not unexpected due to the small sample size.

Overall, 29.7% of the treated patients (11 of 37) in 1218.56 took metformin as background antidiabetic medication at baseline.

Assessors comments

Trial 1218.91

In total, 158 patients were randomised to double-blind linagliptin (53 patients), empagliflozin pooled (52 patients), or placebo (53 patients) once daily treatment. The majority of patients remained on treatment with trial drug up to Week 26 (140 patients, 89.2%) and up to Week 52 (130 patients, 82.8%).The frequencies of patients with premature treatment discontinuations were generally comparable across treatment groups.

As intended, between 30% and 70% of randomised patients were <15 years of age (i.e., 76 patients, 48.4%) and between 30% and 70% of randomised patients were female (i.e., 97 patients, 61.8%). The mean age of the patient population was 14.5 years (SD 1.9).About half of the patients (80 patients, 51.0%) took only metformin, 63 patients (40.1%) took metformin plus insulin, and 5 patients (3.2%) had only insulin as background antidiabetic medication, with balanced distribution across treatment groups.

Although the study was done in multiple geographic regions (North America, South America, Europe, and Asia), most participants were enrolled in the Americas, which limits generalizability to the broader worldwide population of children and adolescents with type 2 diabetes.

About half of the patients had baseline HbA1c values of <8% (83 patients, 52.9); for the remaining patients, approximately similar proportions had either HbA1c values of 8.0% to 9.0% (40 patients, 25.5%) or of >9% (34 patients, 21.7%). The mean BMI was 36.04 kg/m2 (SD 8.33). The mean body weight was 99.92 kg (SD 26.78), with a maximum weight of 171.0 kg observed in this paediatric population.

Trial 1218.56

Overall, 83 patients were enrolled. Of those, 39 patients were randomised and treated (placebo: 15 patients; linagliptin 1 mg: 10 patients; linagliptin 5 mg: 14 patients). Three of the treated patients (7.7%) prematurely discontinued trial medication; none of these patients discontinued because of AEs.

Of the 39 patients, 21 patients (53.8%) were female. The mean age at screening was 14.0 years (SD 1.9 years). The mean baseline weight was 79.8 kg (SD 22.2 kg; range: 47 to 139 kg); Almost all patients were obese (BMI SDS ≥2: 25 patients, 64.1%) or overweight (BMI SDS 1.28 to <2: 8 patients, 20.5%). The mean HbA1c at baseline was 7.86% (SD 0.95%). The mean baseline FPG was 152.7 mg/dL (SD 45.6 mg/dL). Demographic and baseline characteristics were generally balanced across treatment groups. Mean baseline HbA1c (%) was numerically greater in the linagliptin 1 mg group (8.22 [SD 0.93]) than in the placebo group (7.60 [SD 0.92]) and linagliptin 5 mg group (7.87 [SD 0.98]). We agree with the MAH that slight differences between treatment groups were not unexpected due to the small sample size.

Overall, 29.7% of the treated patients (11 of 37) in 1218.56 took metformin as background antidiabetic medication at baseline.

Several subgroups may be too small to establish efficacy.

7.2. Results

Trial 1218.91 (DINAMO™)

Although this clinical overview focuses on data for linagliptin compared with placebo, the entire patient population (including the empagliflozin pooled group) is described for certain endpoints in this section to mirror the primary analyses which included testing of both active substances versus placebo.

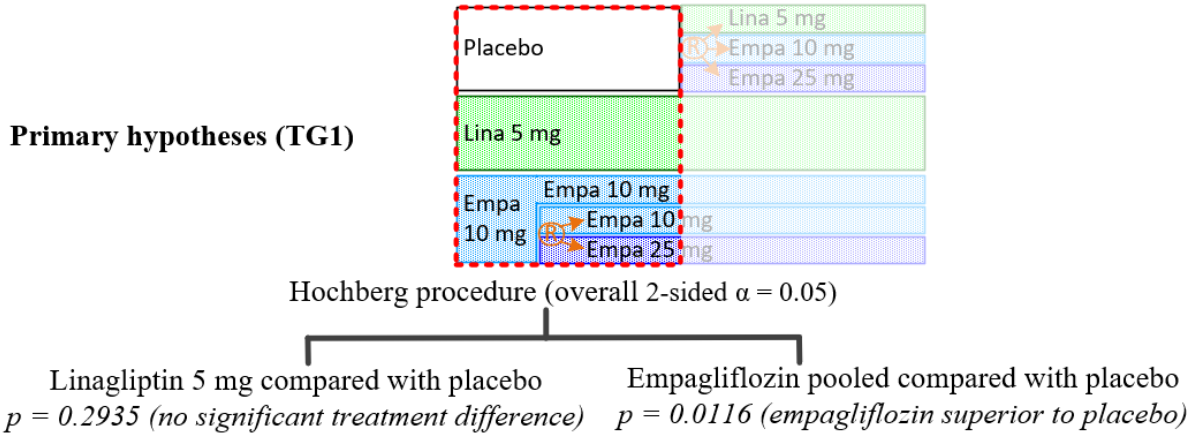
Primary confirmatory endpoint

The hierarchical testing results for DINAMO™ are shown in Figure 4: 2. Based on TG1 (box with dashed red borderline in Figure 4: 2), the treatment effect of linagliptin 5 mg compared with placebo was not statistically significant, while the effect of empagliflozin treatment (pooled) was clinically meaningful and statistically superior to placebo in lowering HbA_{1c} from baseline after 26 weeks (

Table 4: 1). Since the primary hypotheses based on TG1 could not be both rejected, the hierarchical testing for TG2 and TG3 was not continued (

Table 4: 1).

Figure 4: 2 Hierarchical testing results, trial 1218.91



Source data: [c38245139, Table 15.2.1.1.1: 1]

Table 4: 1 HbA_{1c} [%] change from baseline at Week 26, ANCOVA – mITT (OC-AD), trial 1218.91

Treatment	N analysed	Baseline		Change from baseline			Comparison vs placebo			
		Mean	SD	Adjusted mean	95% CI		Adjusted mean	95% CI		p-value
Primary hypotheses based on TG1, multiple imputation with wash-out approach										
Placebo	53	8.05	1.23	0.68	0.23	1.13				
Lina 5	52	8.05	1.11	0.33	−0.13	0.79	−0.34	−0.99	0.30	0.2935
Empa pooled	52	8.00	1.29	−0.17	−0.64	0.31	−0.84	−1.50	−0.19	0.0116

Source data: [c38245139, Tables 15.2.1.1.1: 1]

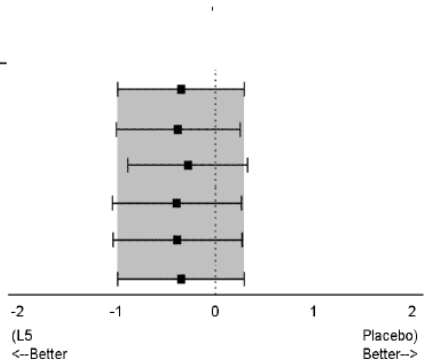
Sensitivity and subgroup analyses of the primary endpoint

Sensitivity analyses of the primary endpoint showed results consistent with the primary analyses (Figure 4: 3). For linagliptin 5 mg vs placebo, the primary analysis results were consistent across the subgroups, as the point estimates of all subgroups were included in the 95% CI of the overall population [c38245139, Figure 15.2.1.3: 1].

Linagliptin (5 mg) vs placebo (TG1)

Figure 4: 3 Sensitivity analyses for the primary endpoint (TG1), trial 1218.91

Analysis – Analysis set (Data type)	L5 (N)	Pbo (N)	Adjusted mean (95%-CI) Comparison vs. Placebo	p-value
Primary analysis: MI - mITT (OC-AD)	52	53	-0.34 (-0.99 0.30)	0.2935
Sensitivity analysis: MMRM at Wk 26 - mITT (OC-AD)	49	50	-0.38 (-1.00 0.25)	0.2409
Sensitivity analysis: MMRM at Wk 26 - mITT (OC)	46	42	-0.28 (-0.89 0.33)	0.3674
Sensitivity analysis: MI – PPS (OC-AD)	49	44	-0.39 (-1.05 0.27)	0.2460
Sensitivity analysis: MI COVID-19 – mITT (OC-AD)	51	53	-0.38 (-1.04 0.27)	0.2534
Sensitivity analysis: MI non-NGSP – mITT (OC-AD)	52	53	-0.34 (-0.99 0.30)	0.2935



MI = multiple imputation with wash-out approach; MMRM at Wk 26 = mixed model for repeated measurement at timepoint Week 26; MI COVID-19 = multiple imputation with wash-out approach according to COVID-19 related intercurrent events; MI non-NGSP = multiple imputation with wash-out approach for non-NGSP certified HbA_{1c} values at Week 26

Source data: [c38245139, Figure 15.2.1.2.7: 1]

Bayesian borrowing analysis

Population simulations based on the previously-fitted pharmacometric models resulted in a population mean treatment effect estimate for linagliptin of −0.64%, with a standard error of the mean of 0.02%.

Prior standard deviations were set at values in excess of the simulation-based standard errors in order to conform to the prespecified effective sample size constraint. Prior distributions were updated with the DINAMO™ data (trial 1218.91) to obtain posterior distributions.

The posterior mean of the placebo-corrected treatment effect for linagliptin was −0.51% (95% credible interval: −0.92%, −0.05%), and there was a 98% posterior probability of superior efficacy. This result provided evidence for superior efficacy at the prespecified evidence threshold using the prespecified weight (65%) for the informative component of the prior based on the pharmacometric simulation results. In the tipping point sensitivity analysis, the posterior probability of superior efficacy decreased with decreasing weight used for the informative component of the prior, but point estimates showed a numerically beneficial effect across all sensitivity analyses.

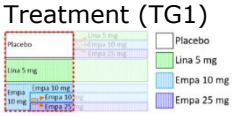
In conclusion, the Bayesian borrowing analysis based on the exposure-response provided evidence for superior efficacy of linagliptin with an overall probability for superiority of 0.98, with a point estimate of −0.51% and 95% credible interval (−0.92%, −0.05%) [c39218174].

Fasting plasma glucose, body weight, and blood pressure

All secondary endpoints were exploratory; a summary of the results is provided in Table 4: 2. The trend for changes in FPG was consistent with HbA_{1c}. For linagliptin, the analysis of FPG did not show a relevant difference at Week 26 when compared with baseline values. The sensitivity analysis for FPG based on OC instead of OC-AD-BOCF showed the same trend [c38245139, Table 15.2.2: 7].

No obvious changes over time in body weight, SBP, and DBP were observed for linagliptin versus placebo (Table 4: 2).

Table 4: 2 Secondary endpoints FPG, body weight, SBP and DBP: change from baseline at Week 26 − mITT (TG1), trial 1218.91

Treatment (TG1) 	N analysed	Baseline		Change from baseline			Comparison vs placebo			
		Mean	SD	Adjusted mean	95% CI		Adjusted mean	95% CI		Nominal p-value
Fasting plasma glucose (FPG) [mg/dL], ANCOVA (OC-AD-BOCF)										
Placebo	52	158.62	53.80	15.70	−0.53	31.93				
Lina 5	51	162.81	56.01	10.29	−6.12	26.69	−5.41	−28.49	17.67	0.6438
Body weight [kg], MMRM (OC-AD)										
Placebo	52	98.87	29.62	−0.04	−1.40	1.32				
Lina 5	50	102.73	26.81	1.42	0.04	2.81	1.46	−0.48	3.41	0.1394
Systolic blood pressure (SBP) [mmHg], MMRM (OC-AD)										
Placebo	52	118.34	11.87	1.30	−1.01	3.61				
Lina 5	50	122.39	11.13	2.21	−0.14	4.56	0.91	−2.40	4.22	0.5870
Diastolic blood pressure (DBP) [mmHg], MMRM (OC-AD)										

Placebo	52	72.60	8.94	0.76	−1.01	2.53				
Lina 5	50	74.01	8.13	2.26	0.46	4.05	1.50	−1.03	4.02	0.2433

Although not shown in this table, the empagliflozin pooled group was included in the models.

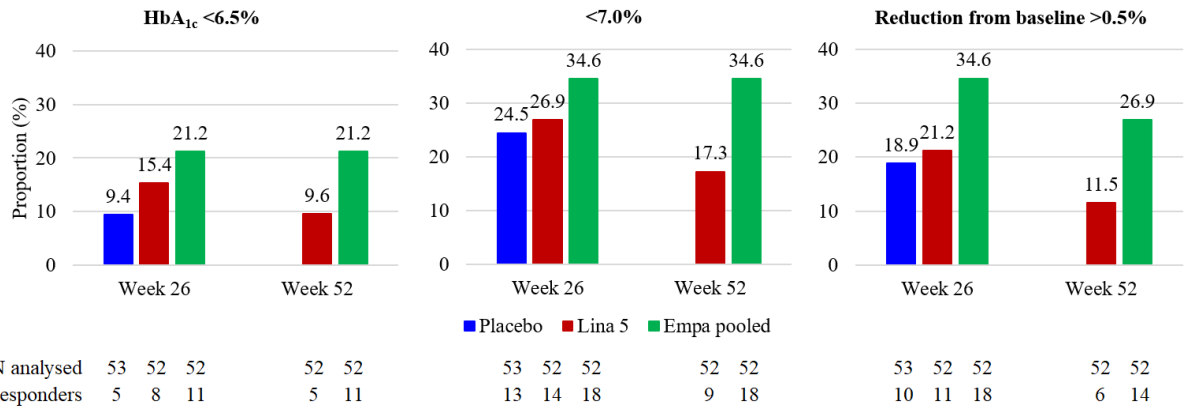
Source data: [c38245139, Tables 15.2.2: 1 to 4]

Endpoints related to HbA_{1c}

The proportion of patients who achieved HbA_{1c} <6.5% or <7.0% at the end of 26 weeks and 52 weeks and the proportion of patients who achieved HbA_{1c} reduction of >0.5% in absolute value at the end of 26 and 52 weeks are summarised in Figure 4: 4.

At Week 26, there were only small differences between linagliptin 5 mg and placebo in the proportion of patients reaching a response based on HbA_{1c} (<6.5% or <7.0%).

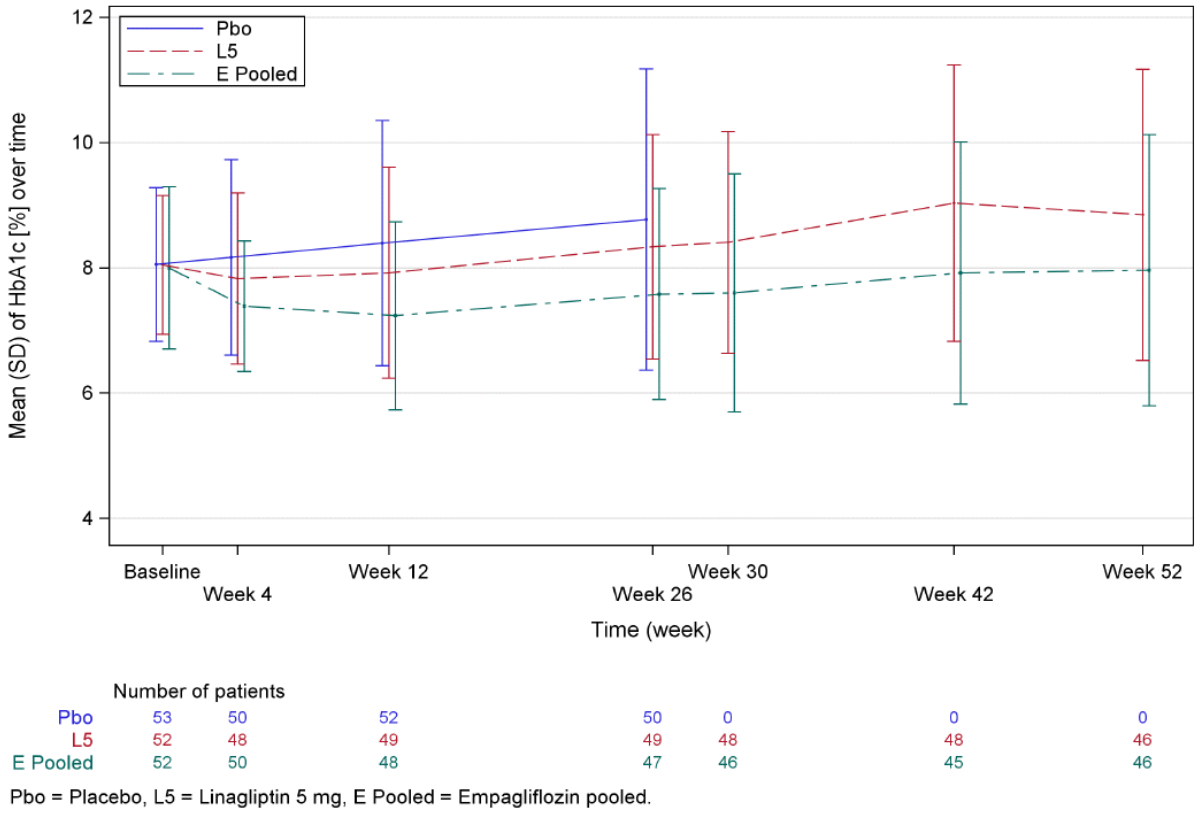
Figure 4: 4 Proportion of patients who achieved a response based on HbA_{1c} – mITT (TG1, TG5) (NCF), trial 1218.91



Source data: [c38245139, Tables 15.2.2: 5 and 6; Appendix 16.1.13.1, Tables 8.2 to 8.5]

In the placebo group, mean HbA_{1c} increased over the 26 weeks by 0.68%, indicating rapid disease progression despite that the majority of patients (94.3%) had background metformin and/or insulin treatment at baseline. The reduction in HbA_{1c} in the linagliptin group was apparent at the first assessment (Week 4) and the difference to placebo appeared to be maintained up to Week 26. From Week 26 to 52, no control using placebo was available due to the trial design; the trend in the linagliptin group was consistent with that from Week 12 to 26 (Figure 4: 5).

Figure 4: 5 Descriptive statistics of HbA_{1c} [%] over time up to Week 52 – mITT (TG1, TG5) (OC-AD), trial 1218.91



Source data: [c38245139, Figure 15.2.3: 1]

Glycaemic rescue therapy

The use of rescue therapy was defined as meeting at least one of the following criteria:

- Any new addition of antidiabetic therapy introduced after the first dose of study treatment
- Any total daily dose increase of basal insulin of more than 0.1 IU/kg above the baseline prescribed dose for more than 21 consecutive days

Up to Week 26, the proportion of patients who initiated glycaemic rescue therapy was comparable between placebo (6 patients, 11.3%) and linagliptin 5 mg (4 patients, 7.7%). Up to Week 52 (long-term analysis for the active substances based on the initial randomisation), 11 patients (21.2%) in the linagliptin 5 mg group initiated glycaemic rescue therapy; 7 of these 11 patients initiated glycaemic rescue after Week 26.

C-peptide, UACR, and eGFR

No obvious changes over time in fasting serum C-peptide, UACR, or eGFR were observed for any treatment group in this trial.

Assessors comments

For the primary end point, the adjusted mean change in HbA1c from baseline was −0.34% (95% CI −0.99 - 0.30, p=0.2935).

For the secondary outcomes, the adjusted mean change in FPG was -5.4 mg/dL (-0.3 mmol/L; -28-49 to 17.67 [-1-58 to 0-98)) for linagliptin versus placebo. At Week 26, there were only small differences between linagliptin 5 mg and placebo in the proportion of patients reaching a response based on HbA1c (<6.5% or <7.0%).

The adjusted mean change in bodyweight from baseline to week 26 was 1.46 kg (-0.48 to 3.41 in the linagliptin versus placebo group. The adjusted mean change in systolic blood pressure with linagliptin versus placebo was 0.91 mm Hg (-2.40 to 4.22). No decreases in diastolic blood pressure from baseline were observed.

Trial 1218.56

There was a dose-dependent, placebo-corrected median HbA_{1c} change from baseline at Week 12 of -0.55% with linagliptin 1 mg and of -0.80% with linagliptin 5 mg in trial 1218.56 [c02827550]. Furthermore, there was a placebo-corrected median FPG change from baseline at Week 12 of +10.0 mg/dL with linagliptin 1 mg and of -24.5 mg/dL with linagliptin 5 mg; the reduction in FPG in the linagliptin 5 mg group is considered clinically meaningful.

Linagliptin at a dose of 5 mg once daily showed an inhibition of DPP-4. In the linagliptin 5 mg group, median DPP-4 inhibition at trough at steady-state was 78.9% (interquartile range 67.7 to 84.0%). This degree of DDP-4 inhibition is in line with the data obtained for linagliptin in adults at the therapeutic dose regimen of 5 mg once daily. In studies 1218.5 [U08-3761] and 1218.6 [U08-1056], the median DPP-4 inhibition after 12 weeks of treatment at 5 mg once daily was 82.5% and 85.0%, respectively. In trial 1218.56, the degree of DPP-4 inhibition by linagliptin 1 mg once daily (median inhibition: 38.4% [interquartile range 26.9 to 48.8%]) was clearly lower than by linagliptin 5 mg once daily. The inhibition observed for the 1 mg dose in the current trial was lower than the inhibition observed in 2 studies in adults evaluating the 1 mg dose level. In trial 1218.6 [U08-1056] and trial 1218.2 [U06-1139], the median DPP-4 inhibition at trough at steady-state was 62.0% and 60.0%, respectively.

Assessors comments

There was a dose-dependent, placebo-corrected median HbA1c change from baseline at Week 12 of -0.55% with linagliptin 1 mg and of -0.80% with linagliptin 5 mg. In addition, in the linagliptin 5 mg group, median DPP-4 inhibition at trough at steady-state was 78.9% (interquartile range 67.7 to 84.0%). This degree of DDP 4 inhibition is in line with the data obtained for linagliptin in adults. Overall, the efficacy and PD data obtained in the paediatric trial 1218.56 were consistent with those in adults with T2DM.

7.3. Discussion

Dose finding study

Trial 1218.56 was a Phase II b randomised, double-blind, placebo-controlled parallel group dose-finding trial of linagliptin (1 mg or 5 mg administered orally once daily) over 12 weeks in children and adolescents from 10 to ≤17 years of age, with T2DM.

In trial 1218.56, the primary endpoint of the final analysis was the change from baseline in HbA_{1c} (%) after 12 weeks of treatment. The key secondary endpoint of the final analysis was the PD endpoint DPP-4 inhibition (%) at trough at steady state. Trial 1218.91

Overall, 83 patients were enrolled. There was a dose-dependent, placebo-corrected median HbA1c change from baseline at Week 12 of -0.55% with linagliptin 1 mg and of -0.80% with linagliptin 5 mg.

In addition, in the linagliptin 5 mg group, median DPP-4 inhibition at trough at steady-state was 78.9% (interquartile range 67.7 to 84.0%). This degree of DDP 4 inhibition is in line with the data obtained for linagliptin in adults.

Design phase 3 trial

Trial 1218.91 (DINAMO™) was a Phase III randomised, double-blind, placebo-controlled parallel group trial with 3 treatment arms (placebo, 5 mg linagliptin, 10 mg empagliflozin) lasting 26 weeks in children from 10 to ≤17 years of age. The design is complex, but acceptable, because it answered the call from regulators and experts for multi-arm efficacy and safety studies in paediatric patients, given the challenges of recruitment in this population.

Patients on empagliflozin who did not achieve HbA_{1c} <7.0% at Week 12 (i.e., non responders) were re-randomised at Week 14 to either continue with 10 mg empagliflozin or increase to 25 mg empagliflozin. The trial also included a double-blind active treatment safety extension period up to 52 weeks: patients on placebo were re-randomised at Week 26 to receive either linagliptin or empagliflozin (10 mg or 25 mg).

Endpoints

In trial 1218.91, primary confirmatory endpoint was the change in HbA_{1c} (%) from baseline to the end of 26 weeks. Secondary endpoints include the change in fasting glucose (mg/dL) and change in body weight (kg) from baseline to the end of 26 weeks.

Patients

In total, 158 patients were randomised to double-blind linagliptin (53 patients), empagliflozin pooled (52 patients), or placebo (53 patients) once daily treatment.

As intended, between 30% and 70% of randomised patients were <15 years of age (i.e., 76 patients, 48.4%) and between 30% and 70% of randomised patients were female (i.e., 97 patients, 61.8%). The mean age of the patient population was 14.5 years (SD 1.9).About half of the patients (80 patients, 51.0%) took only metformin, 63 patients (40.1%) took metformin plus insulin, and 5 patients (3.2%) had only insulin as background antidiabetic medication, with balanced distribution across treatment groups.

Although the study was done in multiple geographic regions (North America, South America, Europe, and Asia), most participants were enrolled in the Americas, which limits generalizability to the broader worldwide population of children and adolescents with type 2 diabetes.

About half of the patients had baseline HbA1c values of <8% (83 patients, 52.9); for the remaining patients, approximately similar proportions had either HbA1c values of 8.0% to 9.0% (40 patients, 25.5%) or of >9% (34 patients, 21.7%). The mean BMI was 36.04 kg/m2 (SD 8.33). The mean body weight was 99.92 kg (SD 26.78), with a maximum weight of 171.0 kg observed in this paediatric population.

Results

For the primary end point, the adjusted mean change in HbA1c from baseline was −0.34% (95% CI −0.99 - 0.30, p=0.2935).

For the secondary outcomes, the adjusted mean change in FPG was -5.4 mg/dL (-0.3 mmol/L; -28-49 to 17.67 [-1-58 to 0-98)) for linagliptin versus placebo. At Week 26, there were only small differences

between linagliptin 5 mg and placebo in the proportion of patients reaching a response based on HbA1c (<6.5% or <7.0%).

The adjusted mean change in bodyweight from baseline to week 26 was 1.46 kg (-0.48 to 3.41 in the linagliptin versus placebo group. The adjusted mean change in systolic blood pressure with linagliptin versus placebo was 0.91 mm Hg (-2.40 to 4.22). No decreases in diastolic blood pressure from baseline were observed.

Several factors might explain the reduced responsiveness to Linagliptin in young people with type 2 diabetes. First, there is a combination of the early development of insulin resistance and more rapid deterioration of beta-cell function in children and adolescents compared with adults with type 2 diabetes. Further, the added physiological insulin resistance of puberty is present in adolescents and not adults. Last, BMI in youth¬onset type 2 diabetes is often higher than in adults with type 2 diabetes.

Conclusion

The 12-week dose-finding trial 1218.56 showed clinically meaningful reductions in HbA_{1c} at Week 12 in the linagliptin 5 mg group. However, in the 26-week Phase III trial 1218.91, treatment with 5 mg linagliptin was not associated with a relevant reduction in HbA1c (−0.34%, p = 0.2935).

8. Clinical Safety aspects

8.1. Methods – analysis of data submitted

Analyses for SAF-p1 and SAF-p2

In addition to the safety analyses in the individual trials (see Table 1: 1), the safety data of the 2 trials were pooled as SAF-p1 and SAF-p2 and described below with a focus on SAF-p2 (placebo-controlled trials up to Week 26).

Safety analyses followed the 'treatment-emergent' principle and included all treated patients. Unless otherwise specified, treatment was assigned as randomised, and the analyses of AEs were based on the number of patients with AEs. AE analyses were restricted to on-treatment AEs, defined as AEs with an onset date between the first trial medication intake and 7 days after the last intake, unless otherwise stated. Exposure-adjusted AEs were also displayed as incidence rates per 100 patient-years.

Standard AE summaries

In SAF-p2, the median exposure to the trial medication was 181.5 days for placebo and 180.5 days for linagliptin 5 mg, in the placebo-controlled period. In SAF-p1, the median exposure to linagliptin 5 mg was 359.0 days, with a maximum of 378 days. Total exposure to linagliptin 5 mg was 58.5 years. Most patients in SAF-p1 (82.9%) and SAF-p2 (78.4%) came from trial 1218.91.

In SAF-p2, the rates of any AEs in the placebo and linagliptin 5 mg groups were generally comparable, as were the rates of severe AEs, AEs leading to discontinuation, drug-related AEs, and SAEs (Table 5: 1).

Table 5: 1 Overall summary of adverse events up to the end of the placebo-controlled period – SAF–p2 – TS

Category of AEs	Placebo			Lina 5 mg		
	N	%	Rate/100 py	N	%	Rate/100 py
Number of patients	68	100.0		66	100.0	
Patients with any AEs	41	60.3	268.7	43	65.2	345.1
Severe AEs	3	4.4	10.6	1	1.5	3.6
Investigator defined drug-related AEs	7	10.3	26.7	9	13.6	37.1
AEs leading to discontinuation of trial medication	2	2.9	7.1	0		
Serious AEs	3	4.4	10.6	2	3.0	7.3
Results in death	0			0		
Is life threatening	1	1.5	3.5	0		
Persistent or significant disability/incapacity	0			0		
Requires or prolongs hospitalisation	3	4.4	10.6	0		
Congenital anomaly or birth defect	0			0		
Other medically important serious event	0			2	3.0	7.3

Percentages calculated using total number of patients per treatment as the denominator; py = patient-years. A patient may be counted in more than one seriousness criterion.

Source data: [c39747995, Table 5.1.2.1]

The results for linagliptin 5 mg based on SAF-p1 were generally comparable with those based on SAF-p2 (Table 5: 2).

Table 5: 2 Overall summary of adverse events – SAF–p1 – TSactive

Category of AEs	Lina 5 mg		
	N	%	Rate/100 py
Number of patients	82	100.0	
Patients with any AEs	57	69.5	267.9
Severe AEs	4	4.9	6.9
Investigator defined drug-related AEs	17	20.7	34.4
AEs leading to discontinuation of trial medication	1	1.2	1.7
Serious AEs	8	9.8	14.1
Results in death	0		

Is life threatening	0		
Persistent or significant disability/incapacity	0		
Requires or prolongs hospitalisation	5	6.1	8.5
Congenital anomaly or birth defect	0		
Other medically important serious event	3	3.7	5.2

Source data: [c39747995, Table 5.1.1.1]

Most frequently reported AEs

In SAF-p2, on the PT level, the most frequently reported AEs for patients on placebo were headache (8 patients, 11.8%) and hypoglycaemia, vitamin D deficiency, diarrhoea, and cough (each reported for 5 patients, 7.4%). In the linagliptin 5 mg group, the most frequently reported AEs by PT were headache (13 patients, 19.7%), hypoglycaemia (11 patients, 16.7%), vomiting (5 patients, 7.6%), and abdominal pain and increased blood ketone body (each 4 patients, 6.1%).

The only imbalance in rates of AEs by PT between the placebo and linagliptin 5 mg groups was in the rate of hypoglycaemia, which was higher on linagliptin 5 mg than on placebo. For other AEs, by PT, there were no relevant differences in rates for placebo compared with the linagliptin 5 mg group.

The rates and pattern of AEs reported for the linagliptin 5 mg group (by SOC and PT) in SAF-p1 were comparable with the rates of AEs reported for the linagliptin 5 mg group in SAF-p2.

Adverse events by intensity

In SAF-p2, the majority of adverse events were of mild or moderate intensity, and rates of AEs by intensity were generally comparable between placebo and the linagliptin 5 mg groups. Severe AEs were reported for 3 patients (4.4%) on placebo and 1 patient (1.5%) in the linagliptin 5 mg group. In the linagliptin 5 mg group, the severe AE abdominal pain was not considered to be drug-related and was not an SAE. No severe AE was reported for >1 patient in either treatment group. The results based on SAF-p1 were generally comparable with SAF-p2.

Drug-related adverse events

In SAF-p2, few AEs were reported as drug-related AEs and there were no relevant differences between the treatment groups with regard to rates or the pattern of reporting of drug-related AEs. On the PT level, few drug-related AEs were reported by >1 patient. On placebo, hypoglycaemia and hyperglycaemia were each reported for 2 patients (2.9%). Drug-related AEs reported for >1 patient in the linagliptin 5 mg group were: hypoglycaemia (5 patients, 7.6%) and nausea and vulvovaginal mycotic infection (each reported for 2 patients, 3.0%). The results based on SAF-p1 were generally comparable with SAF-p2.

AEs leading to discontinuation

In SAF-p2, there were no AEs leading to discontinuation for patients in the linagliptin 5 mg group and 2 patients (2.9%) discontinued from placebo (PTs: acute pancreatitis, polyuria, and irregular menstruation, each reported for 1 patient [1.5%]). The results based on SAF-p1 were generally comparable with SAF-p2.

SAEs

Based on SAF-p2, there was no relevant difference between groups with regard to SAEs.
Three patients (4.4%) on placebo and 2 patients (3.0%) in the linagliptin 5 mg group had SAEs. Hyperglycaemia was reported as an SAE for 2 patients (2.9%) on placebo. No other SAE (on the PT level) was reported for >1 patient in either treatment group.

No patient had any fatal AE (Table 5: 1). One patient (on placebo) had 6 SAEs that were considered to be life-threatening (PTs: acute pancreatitis [onset Day 24], and systemic inflammatory response syndrome, diabetic ketoacidosis, acute kidney injury, acute respiratory failure, and hypovolaemic shock; all with an onset on Day 25).

Based on SAF-p1, SAEs were reported for 8 patients (9.8%) on linagliptin 5 mg. Diabetic ketoacidosis was reported in 2 patients (2.4%); all other SAEs were each reported for 1 patient (1.2%) (PTs: asthma, increased blood glucose, breast abscess, chorioretinitis, hyperglycaemia, and pneumomediastinum).

Assessors comments

Exposure

The median exposure to the trial medication was 181.5 days for placebo and 180.5 days for linagliptin 5 mg, in the placebo-controlled period.

AEs

The rates of any AEs in the placebo and linagliptin 5 mg groups were generally comparable. The most frequently reported AEs for patients on placebo were headache (8 patients, 11.8%) and hypoglycaemia, vitamin D deficiency, diarrhoea, and cough (each reported for 5 patients, 7.4%). In the linagliptin 5 mg group, the most frequently reported AEs by PT were headache (13 patients, 19.7%), hypoglycaemia (11 patients, 16.7%), vomiting (5 patients, 7.6%), and abdominal pain and increased blood ketone body (each 4 patients, 6.1%).

The only imbalance in rates of AEs by PT between the placebo and linagliptin 5 mg groups was in the rate of hypoglycaemia, which was higher on linagliptin 5 mg than on placebo.

The majority of adverse events were of mild or moderate intensity, and rates of AEs by intensity were generally comparable between placebo and the linagliptin 5 mg groups.

Severe AEs

Severe AEs were reported for 3 patients (4.4%) on placebo and 1 patient (1.5%) in the linagliptin 5 mg group.

Drug-related AEs

Few AEs were reported as drug-related AEs and there were no relevant differences between the treatment groups with regard to rates or the pattern of reporting of drug-related AEs. On the PT level, few drug-related AEs were reported by >1 patient. On placebo, hypoglycaemia and hyperglycaemia were each reported for 2 patients (2.9%). Drug-related AEs reported for >1

patient in the linagliptin 5 mg group were: hypoglycaemia (5 patients, 7.6%) and nausea and vulvovaginal mycotic infection (each reported for 2 patients, 3.0%).

AEs leading to discontinuation

There were no AEs leading to discontinuation for patients in the linagliptin 5 mg group and 2 patients (2.9%) discontinued from placebo

SAEs

There was no relevant difference between groups with regard to SAEs. Three patients (4.4%) on placebo and 2 patients (3.0%) in the linagliptin 5 mg group had SAEs. Hyperglycaemia was reported as an SAE for 2 patients (2.9%) on placebo. No other SAE (on the PT level) was reported for >1 patient in either treatment group.

No patient had any fatal AE

AESIs and specific AEs

AESIs (adverse events of special interest) and specific AEs that represent medical concepts were analysed in trials 1218.91 and 1218.56. Those AESIs common to both trials were analysed for the pooled safety. In addition, specific AEs for the pooled safety analyses were defined in the SCS SAP. For SAF-p1 and SAF-p2, these medical concepts were analysed by MedDRA queries (SMQ, BIcMQ, HLGT, or HLT; or identified by the investigators.

In SAF-p2, with the exception of hypoglycaemia, the rates of AESIs and specific AEs up to the end of the placebo-controlled period were comparable in the placebo and linagliptin 5 mg groups (Table 5: 3). In SAF-p2, the rate of hypoglycaemic events was higher on linagliptin 5 mg than on placebo. However, based on data from trial 1218.91 (which comprised the majority of patients included in SAF-p2), there was no relevant difference between treatment groups with regard to rates of symptomatic hypoglycaemia. In SAF-p2, most patients with hypoglycaemic events had at least 1 event with plasma glucose values <54 mg/dL. No patient had an event that required assistance. Note that most of the patients in SAF-p2 were on background antidiabetic medication. In SAF-p1, there was no relevant increase in rates of investigator-defined hypoglycaemia for patients on linagliptin 5 mg (16 patients, 19.5%) when compared with SAF-p2 (11 patients, 16.7%). No patient had any severe event that required assistance.

In SAF-p2, no events were reported in the linagliptin group for pemphigoid in bullous conditions (HLT-primary path) and for pancreatitis (Table 5: 3).

Table 5: 3 AESIs and specific AEs up to the end of the placebo-controlled period – SAF–p2 – TS

Category of AEs	Placebo			Lina 5 mg		
	N	%	Rate/100 py	N	%	Rate/100 py
Number of patients	68	100.0		66	100.0	
Hypersensitivity reactions (SMQ)	2	2.9	7.2	3	4.5	11.1
Skin lesions (SMQ)	0			0		
Pemphigoid in bullous conditions (HLT)	0			0		
Pancreatitis (SMQ)	1	1.5	3.5	0		
Pancreatic cancer (BIcMQ)	0			0		
Hepatic injury (SMQ)	1	1.5	3.5	2	3.0	7.3
Decreased renal function (SMQ)	1	1.5	3.5	0		
Investigator-defined hypoglycaemic AE	5	7.4	18.8	11	16.7	44.8
PG <54 mg/dL and/or severe hypoglycaemia AE	4	5.9		8	12.1	
Required assistance	0			0		
Any hypoglycaemia	7	10.3		16	24.2	
PG <54 mg/dL and/or severe hypoglycaemia AE	4	5.9		8	12.1	
Required assistance	0			0		
Arthralgia (HLGT)	1	1.5	3.6	2	3.0	7.2

Source data: [c39747995, Tables 5.2.2.1, 5.2.2.2, 5.2.2.4 to 5.2.2.12]

In SAF-p1, the rates of AESIs and specific AEs for linagliptin 5 mg were generally comparable with the rates of such events for linagliptin 5 mg in SAF-p2 (Table 5: 4).

Table 5: 4 AESIs and specific AEs – SAF–p1 – TSactive

Category of AEs	Lina 5 mg		
	N	%	Rate/100 py
Number of patients	82	100.0	
Hypersensitivity reactions (SMQ)	4	4.9	6.9
Skin lesions (SMQ)	0		
Pemphigoid in bullous conditions (HLT)	0		
Pancreatitis (SMQ)	0		
Pancreatic cancer (BIcMQ)	0		
Hepatic injury (SMQ)	5	6.1	8.7
Decreased renal function (SMQ)	1	1.2	1.7
Investigator-defined hypoglycaemic AE	16	19.5	32.1
PG <54 mg/dL and/or severe hypoglycaemia AE	11	13.4	
Required assistance	0		
Any hypoglycaemia	19	23.2	
PG <54 mg/dL and/or severe hypoglycaemia AE	11	13.4	
Required assistance	0		
Arthralgia (HLGT)	5	6.1	8.6

Source data: [c39747995, Tables 5.2.1.1, 5.2.1.2, 5.2.1.4 to 5.2.1.12]

CEC-adjudicated events in trial 1218.91

Up to Week 26, 4 patients had events that met the criteria for adjudication for ketoacidosis and 1 event was confirmed as certain ketoacidosis (placebo). Four patients had events that met the criteria for adjudication for myocardial infarction and hospitalisation for heart failure; in all cases the outcome was not confirmed. No events met the criteria for adjudication for stroke or TIA, death, or hepatic injury.

Up to Week 52, 2 patients on linagliptin 5 mg had events that met the criteria for adjudication for ketoacidosis and were confirmed by the CEC (a further 5 patients had events that were not confirmed as diabetic ketoacidosis). One confirmed event was an AESI (the patient had a BMI of 42.9 kg/m^2 and had missed a week of insulin treatment before the diabetic ketoacidosis) and the other confirmed event was identified on the basis of elevated beta-hydroxybutyrate. No corresponding AE of increased beta-hydroxybutyrate or AESI of diabetic ketoacidosis was reported for this event. No further details, including laboratory results, therapy, and action taken with the trial medication, were available in the eCRF. This laboratory-related event was confirmed by the CEC as certain, moderate ketoacidosis.

One event met the criteria for adjudication for hepatic injury and was confirmed as mild to moderate hepatic injury (linagliptin 5 mg active); the CEC assessed the causality of hepatic injury as unlikely, and the event was mild, did not lead to treatment discontinuation, and the patient recovered. Three patients had events that met the criteria for adjudication for myocardial infarction and hospitalisation for heart failure; no event was confirmed by the CEC. No events met the criteria for adjudication for stroke or TIA, or death.

Clinical laboratory evaluation

The pooled analysis of safety laboratory data was limited to frequency of possibly clinically significant abnormalities (PCSAs) based on BI standard criteria. There were no relevant differences between placebo and linagliptin 5 mg with regard to changes in safety laboratory parameters.

In trial 1218.91, there were no notable changes in cholesterol or triglyceride values from baseline to Week 52 in any treatment group and there were no relevant differences among the treatment groups. There were no notable changes in IGF-1, IGF-BP3, and markers of bone turnover from baseline to Week 52 in any treatment group and there were no relevant differences among the treatment groups. NTx, P1NP, IGF-1, and IGF-BP3 were analysed in subgroups according to sex and Tanner staging score at baseline. There were no relevant differences among treatment groups in subgroup analyses by sex and baseline Tanner score. For other safety laboratory parameters, differences between placebo and active treatment were consistent with the known safety profile of linagliptin. There were no notable differences with regard to frequencies of PCSAs between placebo and linagliptin.

In trial 1218.56, there were no clinically relevant findings concerning laboratory assessments.

Vital signs

SBP and DBP are described as efficacy endpoints in trial 1218.91. No obvious changes over time in body SBP or DBP were observed for linagliptin versus placebo. There were no relevant differences between placebo and linagliptin in trial 1218.91 with regard to heart rate and growth assessments (weight, height, BMI, and growth velocity).

In trial 1218.56, there were no clinically relevant findings concerning vital signs.

Safety in special situations

Drug interactions

In trial 1218.91, descriptive analysis did not show any influence of baseline antidiabetic medication on linagliptin exposure.

Drug interactions were not specifically studied in the paediatric trials. See the currently approved product information of linagliptin for adults for more information.

Use in pregnancy and lactation

The use of linagliptin during pregnancy and lactation was not specifically studied in the paediatric trials. See the currently approved product information of linagliptin for adults for more information. In the paediatric clinical trials, no pregnancies were reported.

Overdose

Overdose of linagliptin was not specifically studied in the paediatric trials. See the currently approved product information of linagliptin for adults for more information.

Drug abuse

Linagliptin is not a controlled substance. Abuse of linagliptin was not specifically studied in the paediatric trials.

Withdrawal and rebound

Withdrawal and rebound effects of linagliptin were not specifically studied in the paediatric trials.

Effects on ability to drive or operate machinery or impairment of mental ability

Linagliptin's effect on ability to drive or operate machinery or impairment of mental ability were not specifically studied in the paediatric trials.

Post-marketing experience

Linagliptin is not registered for commercial use in paediatric patients in any part of the world. Information on the post-marketing experience in adults is provided in the current PBRER.

Until the data lock point of 02 May 2022, off-label use of linagliptin in paediatric patients was documented for 44 patients. Off-label use of linagliptin/metformin (fixed-dose combination) in paediatric patients was documented for 9 patients. No relevant difference in the safety profile was observed between adults and paediatric patients below 18 years of age.

Assessors comments

AEs of special interest and specific AEs

AEs of special interest and specific AEs were hypersensitivity reactions (such as angioedema, angioedema like events, and anaphylaxis), skin lesions, pancreatitis, pancreatic cancer, hepatic injury, decreased renal function, hypoglycaemia, arthralgia, and pemphigoid in bullous conditions.

Except for hypoglycaemia, the rates of AESIs and specific AEs up to the end of the placebo-controlled period were comparable in the placebo and linagliptin 5 mg groups.

The rate of hypoglycaemic events was higher on linagliptin 5 mg than on placebo. However, based on data from trial 1218.91, there was no relevant difference between treatment groups concerning rates of symptomatic hypoglycaemia. No patient had an event that required assistance.

One event was confirmed as certain ketoacidosis (placebo).

No events were reported in the linagliptin group for pemphigoid in bullous conditions (HLT-primary path) and for pancreatitis.

One event met the criteria for adjudication for hepatic injury and was confirmed as mild to moderate hepatic injury (linagliptin 5 mg active); the CEC assessed the causality of hepatic injury as unlikely, and the event was mild, did not lead to treatment discontinuation, and the patient recovered.

Safety laboratory parameters

There were no relevant differences between placebo and linagliptin 5 mg with regard to changes in safety laboratory parameters In trial 1218.91, there were no notable changes in cholesterol or triglyceride values from baseline to Week 52 in any treatment group, and there were no relevant differences among the treatment groups. There were no notable changes in IGF-1, IGF-BP3, and

markers of bone turnover from baseline to Week 52 in any treatment group, and there were no relevant differences among the treatment groups.

8.2. Discussion

Exposure

The median exposure to the trial medication was 181.5 days for placebo and 180.5 days for linagliptin 5 mg, in the placebo-controlled period.

AEs

The rates of any AEs in the placebo and linagliptin 5 mg groups were generally comparable. The most frequently reported AEs for patients on placebo were headache (8 patients, 11.8%) and hypoglycaemia, vitamin D deficiency, diarrhoea, and cough (each reported for 5 patients, 7.4%). In the linagliptin 5 mg group, the most frequently reported AEs by PT were headache (13 patients, 19.7%), hypoglycaemia (11 patients, 16.7%), vomiting (5 patients, 7.6%), and abdominal pain and increased blood ketone body (each 4 patients, 6.1%).

The only imbalance in rates of AEs by PT between the placebo and linagliptin 5 mg groups was in the rate of hypoglycaemia, which was higher on linagliptin 5 mg than on placebo.

Severe AEs

Severe AEs were reported for 3 patients (4.4%) on placebo and 1 patient (1.5%) in the linagliptin 5 mg group.

Drug-related AEs

Few AEs were reported as drug-related AEs and there were no relevant differences between the treatment groups with regard to rates or the pattern of reporting of drug-related AEs. On the PT level, few drug-related AEs were reported by >1 patient. On placebo, hypoglycaemia and hyperglycaemia were each reported for 2 patients (2.9%). Drug-related AEs reported for >1 patient in the linagliptin 5 mg group were: hypoglycaemia (5 patients, 7.6%) and nausea and vulvovaginal mycotic infection (each reported for 2 patients, 3.0%).

AEs leading to discontinuation

There were no AEs leading to discontinuation for patients in the linagliptin 5 mg group and 2 patients (2.9%) discontinued from placebo

SAEs

There was no relevant difference between groups with regard to SAEs. Three patients (4.4%) on placebo and 2 patients (3.0%) in the linagliptin 5 mg group had SAEs. Hyperglycaemia was reported as an SAE for 2 patients (2.9%) on placebo. No other SAE (on the PT level) was reported for >1 patient in either treatment group. No patient had any fatal AE.

AEs of special interest and specific AEs

AEs of special interest and specific AEs were hypersensitivity reactions (such as angioedema, angioedema like events, and anaphylaxis), skin lesions, pancreatitis, pancreatic cancer, hepatic injury, decreased renal function, hypoglycaemia, arthralgia, and pemphigoid in bullous conditions.

With the exception of hypoglycaemia, the rates of AESIs and specific AEs up to the end of the placebo-controlled period were comparable in the placebo and linagliptin 5 mg groups.

The rate of hypoglycaemic events was higher on linagliptin 5 mg than on placebo. However, based on data from trial 1218.91, there was no relevant difference between treatment groups with regard to rates of symptomatic hypoglycaemia. No patient had an event that required assistance.

No events were reported in the linagliptin group for pemphigoid in bullous conditions (HLT-primary path) and for pancreatitis.

One event met the criteria for adjudication for hepatic injury and was confirmed as mild to moderate hepatic injury (linagliptin 5 mg active); the CEC assessed the causality of hepatic injury as unlikely, and the event was mild, did not lead to treatment discontinuation, and the patient recovered.

Safety laboratory parameters

There were no relevant differences between placebo and linagliptin 5 mg with regard to changes in safety laboratory parameters In trial 1218.91, there were no notable changes in cholesterol or triglyceride values from baseline to Week 52 in any treatment group and there were no relevant differences among the treatment groups.

Conclusion

The rates of any AEs in the placebo and linagliptin 5 mg groups were generally comparable, as were the rates of severe AEs, AEs leading to discontinuation, drug-related AEs, and SAEs. Except for hypoglycaemia, the rates of AESIs and specific AEs up to the end of the placebo-controlled period were comparable in the placebo and linagliptin 5 mg groups. No unexpected safety concerns were identified for linagliptin in the paediatric programme.

9. Changes to the Product Information

As a result of this variation, section(s) 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated to indicate the outcome of Study 1218-0091 in the paediatric population. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1, which includes all changes to the Product Information.

10. Request for supplementary information

10.1. Major objections

N/A

10.2. Other concerns

Clinical aspects

1. Regarding bioanalysis of linagliptin, samples were demonstrated to be stable for up to 416 days. However, in Study 1218-0091, the maximum storage time was 1090 days, which is longer than the determined long-term stability period. Stability of linagliptin in plasma over 1090 days should be shown.
2. Regarding the SmPC section 5.2, the sentence '*The observed exposure-response relationship was overall comparable in paediatric and adult patie*nts' is not in line with the finding of a lesser effect on HbA1c in the paediatric population compared to adults. It is requested to either delete the sentence or substantiate this statement. Further, the mean concentration of 12.6 nmol/l is based only on a single 1.5 h trough sample per subject and is not considered representative for a real mean concentration. The trough concentration should be indicated.

11. Assessment of the responses to the request for supplementary information

11.1. Major objections

Clinical aspects

N/A

11.2. Other concerns

Clinical aspects

Question 1

Regarding bioanalysis of linagliptin, samples were demonstrated to be stable up to 416 days. However, in Study 1218-0091, the maximum storage time was 1090 days, which is longer than the determined long-term stability period. Stability of linagliptin in plasma over 1090 days should be shown.

Summary of the MAH's response

Stability of linagliptin has meanwhile been demonstrated for up to 2986 days freezer storage:

Analyte	BI 1356 BS
Species	Human
Analytical matrix	K_3 EDTA Plasma
Internal standard (ISTD)	$^{13}C_3$ BI 1356 BS
Validated method	HB-14-038
Validated range	0.100 to 20.0 nmol/L
Quality Control levels	LQC: 0.300 nmol/L MQC: 2.00 nmol/L HQC: 16.0 nmol/L
Analytical technique/method of detection	Solid-phase extraction / LC-MS/MS
Sample volume	150 µL
Calibration model	Linear regression
Weighting factor	$1/x^2$
Run blanks	Passes acceptance criteria
Carryover	Passes acceptance criteria
Matrix frozen stability	2986 days (approximately 100 months) at -10°C to -30°C

The corresponding report with all details is attached to this response (n00300900-01).

Assessment of the MAH's response

Additional stability information was provided that indicate stability up to 2986 days. This covers the maximum storage period of 1090 days.

Conclusion

Issue resolved

Question 2

Regarding the SmPC section 5.2, the sentence 'The observed exposure-response relationship was overall comparable in paediatric and adult patients' is not in line with the finding of a lesser effect on HbA1c in the paediatric population as compared to adults. It is proposed either to delete the sentence or to indicate this difference. Further, the mean concentration of 12.6 nmol/l is based only on a single 1.5 h and trough sample per subject and is therefore not considered representative for a real mean concentration. Only the trough concentration should be indicated.

Summary of the MAH's response

In the comparison of pediatric and adult patients, pediatric patients exhibited a lower estimated maximum inhibition (Imax) compared to adults, with some overlap based upon the precision of the parameter estimates (0.0959 (0.0485, 0.159) vs. 0.141 (0.111, 0.200)). Consequently, simulations for placebo-adjusted change from baseline HbA1c indicated a smaller drug effect for pediatric compared to adult patients. However, variability in response was larger for pediatric patients, resulting in an overlap with the response in adult patients (see Figure 1). The tendency of a larger placebo-adjusted change from baseline HbA1c in patients requiring insulin was consistent in pediatric and adult patients. To indicate the difference in maximum inhibition, we suggest modifying the statement as follows:

The observed exposure-response relationship was generally comparable between pediatric and adult patients, however, with a smaller drug effect estimated in children.

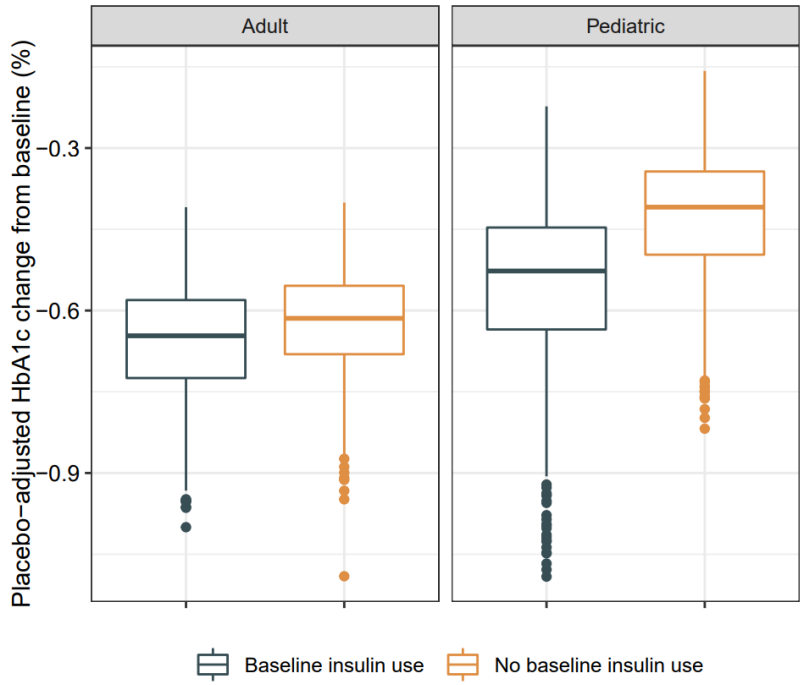


Figure 1: Box plot of placebo-adjusted HbA1c change from baseline values at 26 weeks after treatment start from Monte Carlo simulations in adults and pediatric patients using the previous ER model and the current model, respectively

In addition to the geometric Mean (gMean) trough plasma concentration (N=39), the gMean plasma concentration measured at 1.5 hours post administration (N=46) was also included as it represents a concentration around tmax. The aim was to add information on absorption, rather than limiting the information to elimination.

Assessment of the MAH's response

The proposed text on the comparison of the paediatric and adult exposure-response, indicating a smaller effect in children, is agreed.

With respect to the proposed mean concentration of 12.6 nmol/l, it is acknowledged that information on exposure around tmax may be beneficial for the prescriber. However, in order to increase clarity, the Applicant should modify the sentence as follows:

The observed geometric mean trough concentrations and geometric mean concentrations at 1.5 hours post-administration ***(assumed to approximate the tmax)*** *at steady state were 4.30 nmol/L and 12.6 nmol/L, respectively.*

Further, providing more data on absorption is supported, however, it is noticeable that no Cmax nor Ctrough for adults is indicated in section 5.2. In order to be able to put the provided paediatric 'Cmax' and Ctrough information in perspective, the adult Cmax and Ctrough at steady-state should be provided in section 5.2 as well.

Conclusion

Issue not resolved

12. 2nd Request for supplementary information

12.1. Major objections

N/A

12.2. Other concerns

Clinical aspects

1. With respect to the proposed mean concentration at 1.5 hours post-administration of 12.6 nmol/l, it is acknowledged that information on exposure around tmax may be beneficial. However, in order to increase clarity, the Applicant should modify the sentence as follows:

   *The observed geometric mean trough concentrations and geometric mean concentrations at 1.5 hours post-administration **(assumed to approximate the tmax)** at steady state were 4.30 nmol/L and 12.6 nmol/L, respectively.*

   Further, providing more data on absorption, as indicated by the Applicant, is supported, however, it is noticeable that no Cmax nor Ctrough for adults is indicated in section 5.2. In order to be able to put the provided paediatric 'Cmax' and Ctrough information in perspective, the adult Cmax and Ctrough at steady-state should be provided in section 5.2 as well.

13. Assessment of the responses to the 2nd request for supplementary information

13.1. Major objections

Clinical aspects

N/A

13.2. Other concerns

Clinical aspects

Question 1

With respect to the proposed mean concentration at 1.5 hours post-administration of 12.6 nmol/l, it is acknowledged that information on exposure around tmax may be beneficial. However, in order to increase clarity, the Applicant should modify the sentence as follows:

*The observed geometric mean trough concentrations and geometric mean concentrations at 1.5 hours post-administration **(assumed to approximate the tmax)** at steady state were 4.30 nmol/L and 12.6 nmol/L, respectively.*

Further, providing more data on absorption, as indicated by the Applicant, is supported, however, it is noticeable that no Cmax nor Ctrough for adults is indicated in section 5.2. In order to be able to put the provided paediatric 'Cmax' and Ctrough information in perspective, the adult Cmax and Ctrough at steady-state should be provided in section 5.2 as well.

Summary of the MAH's response

BI acknowledges that the relation between time to maximum plasma concentration and 1.5 hours post drug administration should be made clear. Therefore, the following modification is suggested:

The observed geometric mean trough concentrations and geometric mean concentrations at 1.5 hours post-administration ***(representing a concentration around tmax)*** *at steady state were 4.30 nmol/L and 12.6 nmol/L, respectively.*

In addition, it is acknowledged that a direct comparison of paediatric to adult plasma concentrations is of interest for the prescriber. The following addition is suggested:

The observed geometric mean trough concentrations and geometric mean concentrations at 1.5 hours post-administration at steady state were 4.30 nmol/L and 12.6 nmol/L, respectively. ***Corresponding plasma concentrations in adult patients were 6.04 nmol/L and 15.1 nmol/L.*** (Reference: c40364167)

The values were derived from a randomised, double-blind, placebo-controlled, parallel group study investigating the efficacy and safety of linagliptin administered orally once daily over 12 weeks as add-on therapy in patients with type 2 diabetes and insufficient glycaemic control despite metformin therapy as this study matched the DINAMO study design in terms of dose, PK sampling and background medication (1218−0006, U08-1056).

Descriptive statistics of plasma concentrations of linagliptin at steady state after multiple oral administration of 5 mg linagliptin once daily at week 52 [1218−0091, c38245139] in children/adolescents and at week 4 [1218−0006, U08-1056] in adults are displayed in the following Table:

Plasma concentrations of linagliptin (nmol/L)				
	1218−0006 (adult patients)		1218−0091 (paediatric patients)	
	C_{trough}	1.5 h	C_{trough}	1.5 h
N	61	7	39	46
gMean	**6.04**	**15.1**	**4.30**	**12.6**
gCV (%)	48.5	87.3	213	53.2
Mean	6.50	19.0	8.11	15.0
CV (%)	35.8	70.5	185	96.5
SD	2.32	13.4	15.0	14.4
Min	0.353	4.92	0.102	4.62
P10	4.53	4.92	0.257	7.19
Q1	5.35	9.02	4.30	9.37
Median	6.21	15.6	6.66	12.6
Q3	7.32	36.5	8.07	15.4
P90	8.72	38.6	9.85	21.1
Max	18.7	38.6	97.3	105

Source data: c40364167, Table 1.3.1

There were only 7 patients included in the analysis of plasma concentrations at 1.5 h post drug administration for adult patients. Pharmacokinetic parameters of the therapeutic dose of 5 mg linagliptin assessed in several single and multiple dose studies in healthy volunteers and patients were generally consistent across studies and between healthy volunteers and patients. The Cmax,ss value derived from a previously conducted population pharmacokinetic analysis was 13.6 nmol/L [U10-1864] and the Cmax,ss value in study 1218-0033, where the final commercial formulation was administered to healthy volunteers, was 12.9 nM [U10-1139]. This indicates that the cited plasma concentration is representative for adult patients with type 2 diabetes around tmax.

References (already submitted)

c40364167	Rascher J. Meta-analysis of Linagliptin in Children/Adolescents and Adults with Type 2 Diabetes Mellitus. 07 November 2022
c38245139	Drda K, Maass K, Lam T, Rascher J. A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus. 1218.91. 10 Nov 2022.
U08-1056	c01817124. Uhlig-Laske B, Herbach K, Ring A, Gräfe-Mody U, Friedrich C. A randomised, double-blind, placebo-controlled, five parallel groups study investigating the efficacy and safety of BI 1356 (1 mg, 5 mg and 10 mg administered orally once daily) over 12 weeks as add-on therapy in patients with type 2 diabetes and insufficient glycaemic control despite metformin therapy, including an open-label glimepiride treatment arm. 1218-0006. 22 Oct 2009
U10-1864	Module 2.7.2 (Summary of Clinical Pharmacology Studies). 02 June 2010.
U10-1139	Gießmann T, Kurz C, Friedrich C, Ring A. Assessment of dose proportionality of different dose strengths of linagliptin tablets after oral administration to healthy male and female volunteers in an open, randomised, multiple-dose, three period crossover, phase I trial. 10 Feb 2010

Assessment of the MAH's response

The proposed text on the comparison of the paediatric and adult exposure-response, indicating a smaller effect in children, as well as the direct comparison of paediatric to adult plasma concentrations is agreed.

Conclusion

Issue resolved

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance