9 November 2023
EMA/542987/2023
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Jardiance

International non-proprietary name: empagliflozin

Procedure No. EMEA/H/C/002677/II/0076

Note

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

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List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC0-∞	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC0-tz	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
BIcMQ	BI-customised MedDRA query
BMI	Body mass index
CEC	Clinical event committee
CI	Confidence interval
Cmax	Maximum measured concentration of the analyte in plasma
CO	Clinical overview
CTD	Common technical document
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Cardiovascular
DBP	Diastolic blood pressure
DDP-4	Dipeptidyl peptidase 4
DINAMO™	Trial 1218.91 (main trial)
DKA	Diabetic ketoacidosis
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GCP	Good clinical practice
GLP-1	Glucagon-like peptide
HbA1c	Haemoglobin A1c (glycated haemoglobin)
HLGT	High level group term
HLT	High level term

ICH	International Council for Harmonisation
IGF-1	Insulin-like growth factor
IGF-BP3	Insulin-like growth factor binding protein 3
IPW	Inverse probability weighting
LLA	Lower limb amputation
MedDRA	Medical dictionary for drug regulatory activities
MI	Multiple imputation
mITT	Modified intention-to-treat
MMRM	Mixed model for repeated measures
NCF	Non-completers considered failure
NGSP	National Glycohemoglobin Standardization Program
OC	Observed cases
OC-AD	Observed cases - all data
OC-AD-BOCF	Observed cases - all data and baseline observation carried forward
PBRER	Periodic benefit-risk evaluation report
PD	Pharmacodynamic(s)
PDCO	Paediatric committee
PIP	Paediatric investigation plan
PK	Pharmacodynamic(s)
PPS	Per-protocol set
PT	MedDRA preferred term
SAE	Serious adverse event
SBP	Systolic blood pressure
SCS	Summary of clinical safety
SD	Standard deviation
SGLT-2	Sodium-glucose co-transporter 2
SMQ	Standard MedDRA query
SOC	MedDRA system organ class
$t_{1/2}$	Terminal half-life of the analyte in plasma
T2DM	Type 2 diabetes mellitus
TG	Treatment grouping
TIA	Transient ischaemic attack
t_{max}	Time from dosing to the maximum measured concentration of the analyte in plasma

TS	Treated set
TSAP	Trial statistical analysis plan
UACR	Urine albumin creatinine ratio
UTI	Urinary tract infection

1. Background information on the procedure

1.1. Type II variation

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 variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for JARDIANCE to include treatment of children aged 10 years and above with type 2 diabetes based on results from study DINAMO 1218-0091; this is 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. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 21.1 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0283/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0283/2021 was completed.

The PDCO issued an opinion on compliance for the PIP P/0283/2021.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Vrijlandt Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	14 December 2022
Start of procedure:	27 January 2023
CHMP Rapporteur Assessment Report	24 March 2023
PRAC Rapporteur Assessment Report	31 March 2023
PRAC members comments	4 April 2023
PRAC Outcome	14 April 2023
CHMP members comments	17 April 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 April 2023
Request for supplementary information (RSI)	26 April 2023
CHMP Rapporteur Assessment Report	26 June 2023
CHMP members comments	10 July 2023
Updated CHMP Rapporteur Assessment Report	13 July 2023
2nd Request for supplementary information	20 July 2023
CHMP Rapporteur Assessment Report	16 October 2023
CHMP members comments	27 October 2023
Updated CHMP Rapporteur Assessment Report	2 November 2023
Opinion	9 November 2023

2. Scientific discussion

2.1. Introduction

Empagliflozin has been approved in Europe since May 2014. Empagliflozin is indicated in adults from age 18 years with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise to improve glycaemic control, either as monotherapy in patients for whom use of metformin is inappropriate due to intolerance, or as add-on therapy to other glucose lowering medicinal products including insulin.

The purpose of this application is to fulfil the requirement pursuant to Regulation EC No 1901/2006 for a Paediatric Investigation Plan as agreed by the Paediatric Development Committee and adopted by the European Medicines Agency, and to seek the extension of the indication for empagliflozin in T2DM to include treatment of children aged 10 years and above based on clinical data on the use of empagliflozin in children and adolescents with T2DM who were treated with metformin and/or insulin or who were not tolerating metformin.

This application is supported by data from study DINAMO 1218-0091, "*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*".

2.1.1. Problem statement

The incidence of T2DM in children is increasing worldwide, and the main driver is the increased prevalence and degree of childhood obesity. Childhood T2DM is still relatively rare in Europe, with a prevalence of approximately 2.5 per 100 thousand.

Disease or condition

As in adults, T2DM in children is characterised by hyperglycaemia driven by insulin resistance and relative insulin deficiency. Developing T2DM at a younger age is associated with a considerably higher risk of long-term cardiovascular disease compared with those who develop T2DM in the middle age. The rapid deterioration in glucose regulation in children as compared with adults may contribute to the greater risk for micro- and macrovascular complications in children with T2DM as they develop into adults.

State the claimed the therapeutic indication

The requested indication is an extension of the T2DM indication as follows (added wording in **bold underlined**):

Jardiance is indicated in adults **and children aged 10 years and above for the treatment of** insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance
- in addition to other medicinal products for the treatment of diabetes

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

Epidemiology

The incidence of T2DM in children is increasing worldwide, and the main driver is the increased prevalence and degree of childhood obesity. Paediatric T2DM, which is more prevalent in populations with low socioeconomic and educational status, is still relatively rare in Europe, with a prevalence of approximately 2.5 per 100 thousand.

Biologic features

As in adults, T2DM in children is characterised by hyperglycaemia driven by insulin resistance and relative insulin deficiency. The physiologic insulin resistance associated with pubertal development may exacerbate glucose dysregulation in susceptible children. Insulin secretion is more impaired in adolescents (approximately 85% reduction) as compared to adults (approximately 50% reduction) at the time of diagnosis of T2DM. Thus, the deterioration in insulin secretion appears to be more rapid in adolescents than in adults.

Clinical presentation and prognosis

Developing T2DM at a younger age is associated with a considerably higher risk of long-term cardiovascular disease compared with those who develop T2DM in the middle age. The rapid deterioration in glucose regulation in children as compared with adults may contribute to the greater risk for micro- and macrovascular complications in children with T2DM as they develop into adults.

Management

Management of T2DM in children involves lifestyle modifications. Pharmacologic glucose-lowering treatment is often necessary and includes metformin, insulin, or a combination of both. Several GLP-1 receptor agonists have already been approved for the use in paediatric patients. In addition, another SGLT2 inhibitor (dapagliflozin) is approved for the use in paediatric patients aged 10 years and above. An ongoing study is investigating the efficacy and safety of canagliflozin in children and adolescents (>=10 to <18 Years) with type 2 diabetes mellitus.

2.1.2. About the product

Empagliflozin is an orally administered, potent, and highly selective SGLT-2 inhibitor developed by BI. Empagliflozin is approved and marketed for the treatment of adults with T2DM, for the prevention of CV events in adults with T2DM and established cardiovascular disease, and in adults with heart failure independent of left ventricular ejection fraction.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development programme supporting the use of empagliflozin in paediatric patients with T2DM includes 2 completed studies:

- Study 1218-0091, "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"

- Study 1245.87, "A Randomised, single-dose, parallel group, study to investigate the pharmacokinetics and pharmacodynamics of empagliflozin in children and adolescents aged 10 to less than 18 years (and adults below 25 years) with type 2 diabetes mellitus"

Both of these studies were part of Jardiance's PIP, as agreed by the PDCO and EMA in decision P/0283/2021.

The MAH did not apply for CHMP scientific advice on the paediatric development of Jardiance.

2.1.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP, as claimed by the MAH.

2.2. Non-clinical aspects

2.2.1. Ecotoxicity/environmental risk assessment

Introduction

In accordance with Article 8 (ca) and (g) of Directive 2001/83/EC as amended, an application for marketing authorization shall be accompanied by an ERA, evaluating any potential risks of the medicinal product to the environment. For Type II variation applications for known substances, for which an ERA is not considered necessary, a rationale for the absence of an ERA should be provided, taking into consideration a possible significant increase of environmental exposure to the drug substance. The present statement, providing this rationale for Jardiance (empagliflozin) 10 and 25 mg film-coated tablets, was carried out according to the following guidance document of the Committee for Medicinal Products for Human Use (CHMP): "Guideline on the environmental risk assessment of medicinal products for human use" (EMA/CHMP/SWP/4447/00, June 2006).

Environmental Risk Assessment (ERA)

An Environmental Risk Assessment (ERA) for empagliflozin [U13-1023-01] was submitted with the initial MAA and an updated ERA after completion of an additional study [q00222007-01]. The risk assessment resulted in the conclusion that no significant impact on the environment is expected.

In the current ERA, the estimation of the predicted environmental concentration (PEC) of empagliflozin in the various environmental compartments is based on the default market penetration factor (Fpen = 0.01), as provided in the EMA guideline, and the highest maximum daily dose of 25 mg. The recommended maximum daily dose of the newly proposed indication (Type 2 Diabetes - paediatric indication) will be 25 mg.

The default Fpen is based on a very conservative worst-case estimation, meaning that 1% of all EU inhabitants are treated 365 d/a with the recommended maximum daily dose. The market penetration factor was not refined though, e.g., by using the much smaller actual amount of substance placed on the market. Therefore, the effects on the environment by adding the new intended Type 2 Diabetes - paediatric indication with a much smaller patient group are considered negligible and well covered by the used Fpen. The ERA tables, including calculations for all proposed indications for Jardiance, were updated (as indicated in tables) as follows:

Table 1 *Maximum daily doses of empagliflozin for all indications for Jardiance*

Treatment	Maximum daily dose
Type 2 Diabetes	25 mg
Heart Failure, reduced ejection fraction	10 mg
Heart Failure, preserved ejection fraction	10 mg
Chronic Kidney Disease	10 mg
Type 2 Diabetes - paediatric indication (new)	25 mg *(max dose applied for)*

To calculate the PEC values, taking into consideration all proposed indications of Jardiance, the default market penetration factor (Fpen) of 0.01 (not refined) and the sum of the maximum daily doses, i.e. 80 mg (see Table 1), have been applied.

For the calculation of the PEC/PNEC ratios in the various environmental compartments the PNEC values as mentioned in the original Environmental Risk Assessment [q00222007-01] have been used (see Table 2 and Table 3).

Table 2 *PEC and PNEC values for empagliflozin*

Compartment	$PEC_{Type\ 2\ Diabetes}$ [µg/L]	$PEC_{all\ indications}$ [µg/L]	PNEC [µg/L]
Surface water	0.125	0.4	240
Microorganisms	0.125[1]	0.4[1]	≥10000
Groundwater	0.03125[2]	0.1[2]	≥10000

[1] $PEC_{microorganisms} = PEC_{surface\ water}$

[2] $PEC_{groundwater} = 0.25 \cdot PEC_{surface\ water}$

Table 3 *PEC/PNEC ratios for empagliflozin*

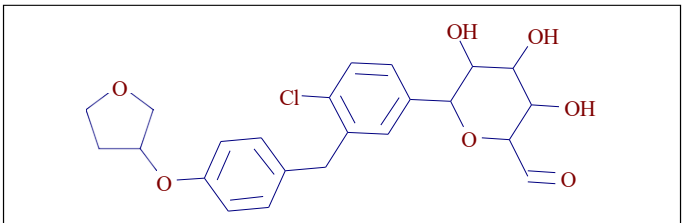
Compartment	PEC/PNEC ratio Type 2 Diabetes	PEC/PNEC ratio all indications	Trigger for Tier B
Surface water	0.00052	0.0017	1
Microorganisms	≤ 0.0000125	≤ 0.00004	0.1
Groundwater	≤ 0.000003125	≤ 0.00001	1

ERA Phase II – Tier A OECD 308 and Tier B OECD 218 studies

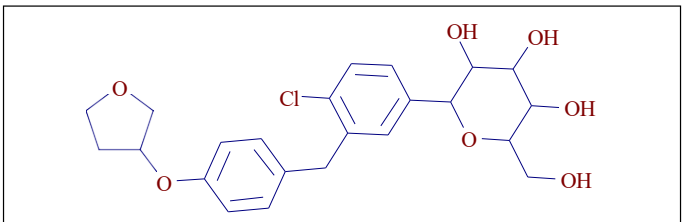
In the water sediment study, the relevant transformation products M3 and M12 generated in the water/sediment study exceeded the P trigger for sediment (M3) and water (M12), but only after conversion to 12°C EU outdoor temperature, and none of the detected transformation products showed continuously increasing concentration during the study.

Consequently, following the 'total residue approach' (EMA/CHMP/SWP/44609/2010 of 17 March 2011) a toxicity study in sediment-dwelling Chironomid larvae (OECD 218) was conducted resulting in the conclusion that the use of empagliflozin and its transformation products can be considered as insignificant environmental risk for the compartment sediment.

However, since the study on identification of metabolites [U13-1652-01] indicates that metabolite M3 may be a stereoisomer of the parent compound, it might be that M3 has certain pharmacologically activity. Therefore, below, information on the structure of M3 and M1 (M12 was instable and could not be further analysed) as well as the DT50 values for total system, sediment and water recalculated to 12 °C for empagliflozin and the relevant transformation products M3, M1 and M12 are given. M3 is very persistent in the sediment (DT50 > 180 days) and M12 is persistent in water (DT50 > 40 days).



Proposal for M1 of BI 10773: C23H25ClO7, MM 448.1289 Da



Proposal for M3 of BI 10773: C23H27ClO7, MM 450.1445 Da (Isomer of BI 10773)

Table 4 *DT50-Values recalculated to 12°C (Arrhenius equation) for empagliflozin and the relevant transformation products M1, M3 and M12*

[^{14}C]BI 10773		Water		Sediment		Total System	
		River	Pond	River	Pond	River	Pond
Parent	DT_{50} (days)	2.5	2.3	5.5	4.1	2.8	2.8
M1	DT_{50} (days)	9.6	13.0	39.3	26.0	13.2	16.9
M3	DT_{50} (days)	27.3	4.7	189.8	140.9	110.4	78.5
M12	DT_{50} (days)	--	79.8	--	88.8	--	80.0

Updated ERA summary table

The ERA summary table which is included in the original authorization of Jardiance (Table 1 in Section 2.3.4 of the EPAR) has been updated accordingly (see Table 5 below).

Table 5 Summary of the main study results

Substance (INN/Invented Name): Empagliflozin					
CAS-number (if available): 864070-44-0					
PBT screening		Result			**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD107	Log K_{ow} = 1.73			Not potentially PBT, nor vPvB
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	Log K_{ow} = 1.73			not B
Persistence	DT50 or ready biodegradability	**Parent:** $DT_{50,\ 12°C\ water}$: 2.6/ 2.3 d $DT_{50,\ 12°C\ sediment}$: 5.5/4.1d Transformation products: **TP M3** (stereoisomer of empagliflozin) $DT_{50,\ 12°C\ sediment}$ =**189.8/140.9 d TP M12**: $DT_{50,\ 12°C\ water}$ =**79.8 d TP M3**: **very persistent** in sediment, **TP M12: very persistent** in water			**vP** (for transformation products M3 in sediment, TP M12 in water)
Toxicity	NOEC or CMR	2.4 mg/L			not T
PBT-statement	The compound is considered not PBT and not vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$ (all indications), default or refined (e.g. prevalence, literature)	0.4	µg/L			> 0.01 threshold
Other concerns (e.g. chemical class)					No
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 51.5 L/kg			Mean of 49 and 54 L/kg for WWTP sludge.
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 1.2/1.1 d (r/p) $DT_{50,\ sediment}$ = 2.6/1.9 d (r/p) $DT_{50,\ whole\ system}$ = 1.3/1.3 d (r/p) shifting to sediment = 26.4/25.0% (r/p)			r = river, p = pond, Significant shifting to sediment observed
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *Pseudokirchneriella subcaptitat*	OECD 201	NOEC	≥100	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥100	mg/L	
Fish, Early Life Stage Toxicity Test / *Danio rerio*	OECD 210	NOEC	2.4	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥100	mg/L	
Phase IIb studies					
Sediment dwelling organism *Chironomus riparius*	OECD 218	NOEC	1010	mg/kg	normalized to 10% Corg

Conclusion

For all three compartments, the PEC/PNEC ratios for all proposed indications of Jardiance are clearly below the trigger values of 1 and 0.1, respectively. Additionally, empagliflozin and its transformation products can be considered as insignificant environmental risk for the compartment sediment.

Hence, the ERA submitted with the initial MAA remains valid for the current type II variation covering the additional proposed indication.

2.2.2. Discussion on non-clinical aspects

The current application concerns an extension of the indication of Jardiance from adult patients to children aged 10 years and above with type 2 diabetes. No new non-clinical data have been submitted in this application, which is considered acceptable for the extension of indication.

The applicant, as requested, updated the ERA and ERA summary table with the new total PEC_{SW} value of all approved indications including the recently approved chronic kidney disease indication.

From a non-clinical view, the proposed extended indication is considered approvable.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of empagliflozin.

- Considering the above data, empagliflozin is not expected to pose a risk to the environment.

From a non-clinical view, the proposed extended indication is considered approvable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The clinical development programme supporting the use of empagliflozin in paediatric patients with T2DM includes 2 completed studies:

- Study 1218-0091, "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"
- Study 1245.87, "A Randomised, single-dose, parallel group, study to investigate the pharmacokinetics and pharmacodynamics of empagliflozin in children and adolescents aged 10 to less than 18 years (and adults below 25 years) with type 2 diabetes mellitus"

2.3.2. Pharmacokinetics

The pharmacokinetic data presented in this application are limited to data that support the extension of indication for empagliflozin to include treatment aged 10 years and above with type 2 diabetes (T2DM). The initial marketing application of empagliflozin was assessed in procedure EMA/CHMP/137741/2014. The current procedure is supported by results from study **1245.87 (c09062077)** and study **1218-0091** (DINAMO). These studies have been specified as key binding elements in PIP (**EMEA-000828-PIP01-09-M09**).

Study **1245.87** was a single-dose trial (n = 27), in which the pharmacokinetics and pharmacodynamics of empagliflozin was evaluated in paediatric patients with T2DM after administration of 5, 10 or 25 mg empagliflozin. Additionally, empagliflozin pharmacokinetics and pharmacodynamics were compared between paediatric and adult patients in an exposure-response analysis (**c37380422-01**). The study results of **1245.87** and exposure-response analysis (**c37380422-01**) have been assessed before in EMEA/H/C/002677/P46.

Study **1218-0091** was a double-blind, randomised, placebo-controlled, parallel group trial that evaluated 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. Further details regarding study design are displayed in section 5.4 (clinical efficacy). In this study, pharmacokinetic samples were collected at pre-dose and after 1.5 hours after drug administration at week 26 and week 52.

An updated population pharmacokinetic analysis and exposure-response analyses (**c39218173-01**) were presented in this procedure, which was based on the previously conducted analyses in adults and **study 1245.87** (**c37380422-01**). This analysis is extensively discussed below.

The initially proposed posology in paediatric patients aged 10 years and older is similar to the adult patients. I.e. the recommended starting dose is 10 mg empagliflozin once daily. In patients tolerating empagliflozin 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily.

Methods

Bioanalytical methods

Samples of study **1218-0091** were analysed using a validated HPLC-MS/MS assay (**SAP.1217**). This is the same bioanalytical method as used in study **1245.87**. The maximum storage duration from collection to extraction was reported as 1090 days at -20°C, which was within the 1327 days long-term stability period. A total of 529 study samples were analysed in twelve runs. One run failed, which was reported as sample preparation error by the analyst. Furthermore, a total of 6 samples were reanalysed, because these were above the upper limit of quantification. 55 of 56 (98.2%) of the samples in the evaluation demonstrated a percent difference within ±20.0%, thus meeting the acceptance criteria.

Population pharmacokinetic and exposure-response analysis (c39218173-01)

Objective

Models for both population pharmacokinetic and population exposure-response were previously developed for empagliflozin (**c37380422-01**). These models were re-estimated using a Bayesian framework to characterise paediatric pharmacokinetics and pharmacodynamic (specifically, glycosylated hemoglobin (HbA1c) lowering) for paediatric patients in Study **1218-0091** and assess any differences in relation to adults. The primary analysis objectives were to:

- Characterize the pharmacokinetics of empagliflozin in paediatric patients with type 2 diabetes mellitus (T2DM) and assess any differences in relation to adult PK.
- Characterize the exposure-response of empagliflozin on HbA1c in paediatric patients with T2DM using data from Study **1218-0091** and assess any differences in relation to adult ER.

Data

A population pharmacokinetic model was previously developed with data from several studies in adults and from the single dose pediatric study 1245-0087. In this update, solely data of study **1218-0091** was used. This study randomised 157 children and adolescents from 10 to 17 years of age with T2DM to either placebo, linagliptin or empagliflozin. Pre-dose and 1.5 hour post-dose pharmacokinetic samples were collected at weeks 26 and 52. HbA1c samples were collected at baseline, week 4, 12, 26, 30, 42, 52, but only data up to 26 weeks was included in the exposure-response analysis.

A total of 74 patients were included in the population pharmacokinetic analysis. Subjects were 62.2% female, had a median age of 14.5 years (ranging from 10 to 17) and had a bodyweight range from 42.5 to 169 kg. In these patients, 278 observations were eligible for inclusion (after exclusion of samples in the control linagliptin arm) in the population pharmacokinetic model. A total of 55 observations (19.8%) were reported as below the lower limit of quantification.

The exposure-response analysis dataset included 103 subjects receiving empagliflozin or placebo treatment and contributing a total of 394 observations. Of these subjects, 39 received 10 mg of empagliflozin during weeks 1 to 26, 13 subjects received 10 mg of empagliflozin from weeks 1 to 14 and 25 mg from weeks 15 to 26, and 51 subjects remained in the placebo arm for weeks 1 to 26. A total of 16 observation records were excluded from the analysis dataset; Ten HbA1c observations were excluded as they were measured >7 days after the last reported dose; two observations were excluded for subjects in the placebo group that were re-randomized to treatment and had their HbA1c measured greater than one day after the start of empagliflozin at week 26; and four subjects were excluded because they had no post-baseline HbA1c records.

Methods – Population pharmacokinetic model

The previous model was a two-compartment model with sequential zero-order and first-order absorption was used, based upon the results of previous analyses. The model was parameterized with CL/F, V2/F, apparent (oral) intercompartmental clearance (Q/F), apparent peripheral volume of distribution after oral dosing (V3/F), absorption rate constant (ka) and zero order absorption duration (D1). Interindividual variability (IIV) on CL/F and V3/F was estimated. Weight (WT) was used to scale clearances and volumes according to fixed allometric exponents between adult and paediatric subjects. Sex, race and eGFR on CL/F were covariates in this model.

This structural model was re-estimated using the data from study **1218-0091** under a Bayesian framework. The final model was fit using the no U-turn sampling (NUTS) method in NONMEM with four chains of 5000 warmup and 1000 sampling iterations. The parameter estimates from the previous empagliflozin 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 CL/F, apparent central volume of distribution after oral dosing (V2/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.

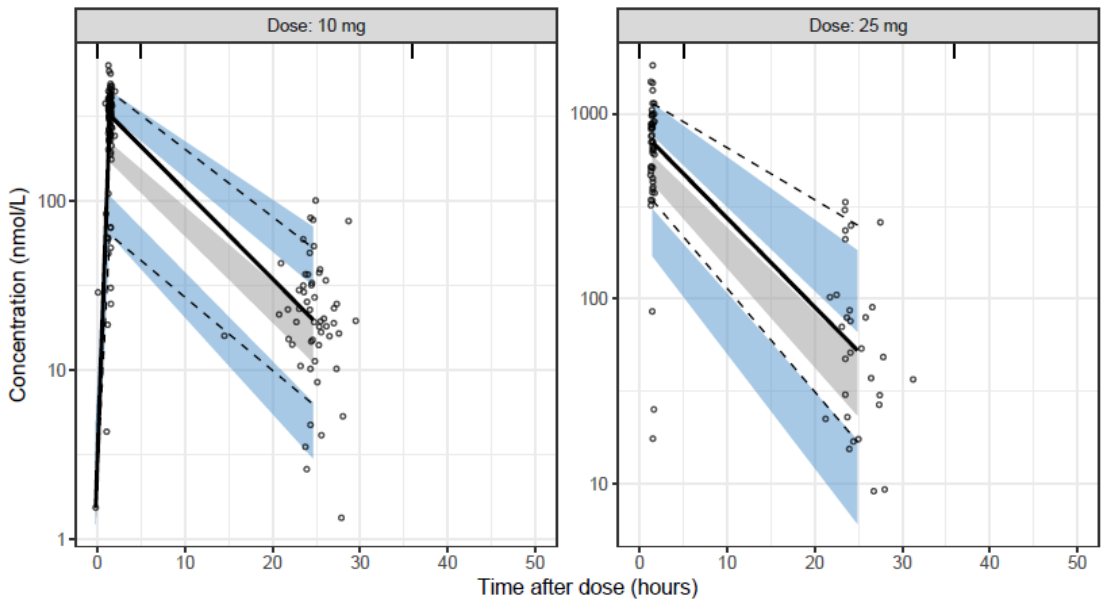
Covariates in the previous model, including the effects of sex, race and eGFR on CL/F and fixed allometric bodyweight effects on CL/F, V2/F, Q/F and V3/F, were retained in the final model, and no additional

covariates were included. The IIV on V3/F was estimated to be highly correlated with CL/F IIV due to the limited number of PK observations available in the distribution phase. Therefore, the final model only included IIV on CL/F using an exponential variance model. The residual error model was also adjusted to include two separate additive residual error terms with one for outlier PK trough observations, which was defined as concentrations that were 7 times larger than the expected paediatric concentration 24 hours post dose at steady state. The residual error was described using a combined proportional and additive error model for normal observations and an additive error model for observation outliers.

Results - Population pharmacokinetic model

A visual predictive check, in which paediatric data of study **1218-0091** was simulated, using the previous population pharmacokinetic model is provided in Figure 1. The data indicated an underprediction of empagliflozin concentrations at both 10 and 25 mg dose levels.

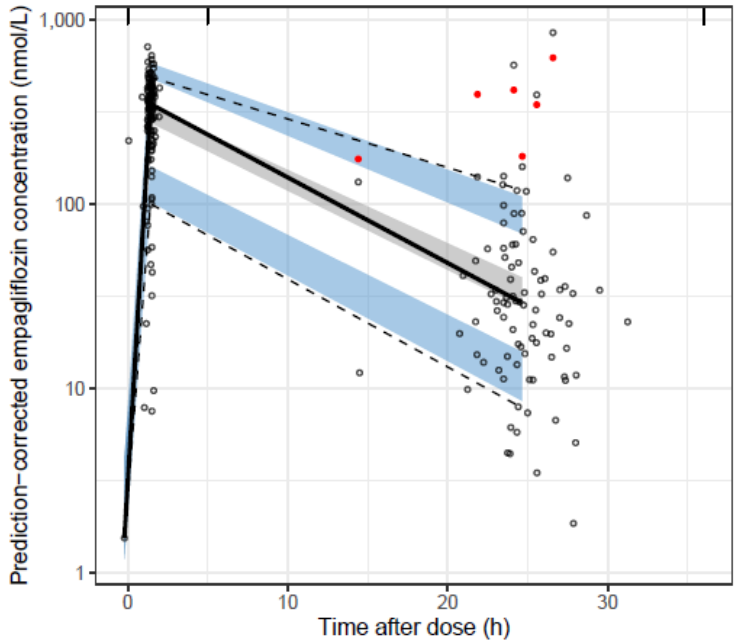
Figure 1. Visual predictive check of previous population pharmacokinetic model on data of study 1218-0091



The lines represent the median (solid) or 10th / 90th (dashed) percentiles of the observed data. The shaded areas represent 90% prediction intervals for median (grey) or 10th / 90th percentiles for data simulated under the model. Circles represent the observed data.

The previous population pharmacokinetic model was then re-estimated using a Bayesian approach, but found to result in unrealistic paediatric CL/F values. The reason was investigated and pinpointed towards the age covariate effect in the adult model, for which there was no support by the paediatric age range. Therefore, the age covariate was removed from the model. This resulted in the final population pharmacokinetic model, which was deemed to provide a reasonable description of the data as indicated by visual inspection of model diagnostics (Figure 2), plausibility of parameter estimates and their precision.

Figure 2. Prediction-corrected visual predictive check - final model



The lines represent the median (solid) or 10th ⁄ 90th (dashed) percentiles of the observed data. The shaded areas represent 90% prediction intervals for median (grey) or 10th ⁄ 90th percentiles for data simulated under the model. Circles represent the observed data (red circles are deemed outliers).

Table 6. Previous model and final population pharmacokinetic model parameter estimates.

		DINAMO model		Previous model	
		Median	95% CDI	Median	95% CDI
Structural model					
CL/F (L/hr)	Apparent clearance	6.74	(5.71, 7.90)	8.45	(8.23, 8.67)
V2/F (L)	Apparent central volume of distribution	4.12	(1.30, 6.63)	5.83	(5.12, 6.66)
KA (1/hr)	First order absorption rate constant	0.239	(0.232, 0.246)	0.237	(0.231, 0.244)
Q/F (L/hr)	Apparent intercompartmental clearance	5.51	(5.22, 5.83)	5.59	(5.29, 5.90)
V3/F (L)	Apparent peripheral volume of distribution	71.7	(67.6, 76.2)	71.9	(68.1, 76.6)
D1 (hr)	Zero order absorption duration	0.326	(0.199, 0.542)	0.297	(0.143, 0.399)
Covariate effects					
$EGFR_{CL/F}$	eGFR effect on CL/F	0.407	(0.363, 0.454)	0.408	(0.362, 0.455)
$BLACK_{CL/F}$	Race=Black effect on CL/F	0.897	(0.834, 0.967)	0.885	(0.817, 0.957)
$ASIAN_{CL/F}$	Race=Asian effect on CL/F	0.934	(0.904, 0.965)	0.933	(0.902, 0.965)
$FEMALE_{CL/F}$	Sex=Female effect on CL/F	1.19	(0.977, 1.45)	1.02	(0.985, 1.05)
$Age_{CL/F}$	Age effect on CL/F	-	-	-0.183	(-0.259, -0.106)
Interindividual variability					
$\Omega_{CL/F}$	IIV-CL/F (CV%)	33.3	(25.3, 44.0)	55.2	(53.6, 56.9)
$\Omega_{V3/F}$	IIV-V3/F (CV%)	-	-	40.5	(33.9, 48.4)
$\Omega_{CL/F-V3/F}$	Covariance CL/F-V3/F	-	-	0.0837	(0.0575, 0.111)
Residual variability					
Σ_{11}	RUV - propotional, non-outliers (CV%)	47.4	(41.9, 54.2)	35.9	(35.4, 36.4)
Σ_{22}	RUV - additive, non-outliers (SD)	1.67	(0.664, 5.94)	2.09	(1.98, 2.22)
Σ_{33}	RUV - additive, outliers (SD)	353	(213, 731)	-	-

Parameters estimated in the log-domain were back-transformed for clarity

Abbreviations: CDI = credible interval; ESS = effective sample size; R^ = Gelman-Rubin diagnostic; IIV =inter-individual variability; RV = residual variability; CV = coefficient of variation; SD = standard deviation

Credible intervals calculated from Bayesian posteriors

*CV% of omegas = sqrt(exp(estimate) - 1) * 100*

*CV% of sigma = sqrt(estimate) * 100*

SD of sigma = sqrt(estimate)

Methods – Exposure-Response analysis

An exposure-response model was previously developed for longitudinal HbA1c using adult data. This model consisted of a turnover model parameterised with HbA1c synthesis rate constant (kin) and HbA1c degradation rate constant (kout), with empagliflozin inhibiting the kin parameter through an inhibitory maximum effect (Emax) relationship, and a placebo effect incorporated on the kout parameter, to describe the change in HbA1c over time in relation with empagliflozin exposure. Baseline HbA1c and eGFR were included as covariates on Imax, and Imax was estimated to increase with increasing baseline HbA1c

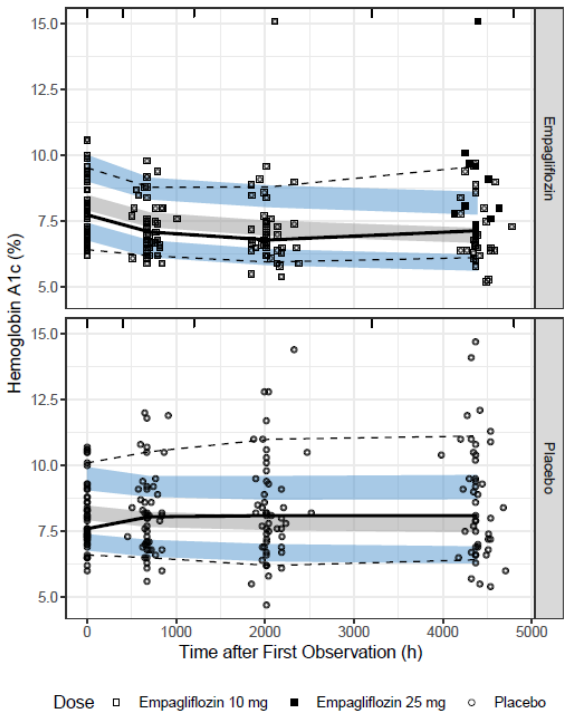
and increasing eGFR, based upon priors from the previously estimated model. Insulin was also included as a covariate, and insulin co-therapy at baseline was associated with a higher baseline HbA1c and a faster disease progression. Inter-individual variability (IIV) was included on baseline HbA1c and the disease progression parameter. A proportional residual error was also included.

This exposure-response 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 exposure-response model for model parameters without direct support from the paediatric data. The AUCss was simulated for paediatric subjects with PK observations to drive the exposure-response model using their individual pharmacokinetic parameter estimates. The estimate of area under the concentration-time curve at 50% of the maximum effect (AUC50) was fixed to the same value the previous adult model had been fixed at. The effects of estimated glomerular filtration rate (eGFR) and baseline HbA1c on Imax were 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 HbA1c observed in the paediatric population.

Exposure-response model

The placebo response was not captured by the previous adult model; the simulations predicted a flat or downward trend over time, while the observed data increased over time (Figure 3). The simulations were underpredictive at the 10th, median and 90th percentiles. The treated cohort exhibited a similar trend, where the simulations underpredicted the observed data overall. This indicated that the previous adult turnover, placebo and drug effect model parameterizations were not adequate for the Study **1218-0091** paediatric patients.

Figure 3. Visual Predictive Check – previous model



This analysis initially began by re-estimating this model using data from Study **1218-0091** in a Bayesian framework. The previous model estimate for the placebo effect was 5.16 (4.25, 6.07) (median, 95% CI), corresponding to the typical reduction in HbA1c relative to that patient's baseline. However, as this stood in contrast with the paediatric data where there was an increase in HbA1c over time, the placebo model was adjusted to capture paediatric disease progression observed with increasing HbA1c over time.

To capture the observed increases in HbA1c over time, a time-dependent change in the synthesis process was used (i.e., increase of HbA1c) over time. Specifically, the synthesis rate (kin) changed over time by a zero-order process. During model development the disease progression term was parameterized in terms of separate parameters conditional on background insulin therapy status. The estimate for patients not requiring insulin consistently pushed towards zero. Subsequently, this parameter was dropped, and the disease progression parameter was only applied to patients requiring background insulin data.

The previous model estimated the covariate effects of eGFR and baseline HbA1c on Imax; these were retained in the current model and estimated using informative priors. The previous model also included the effects of baseline metformin, insulin, and sulfonylurea cotherapy on the placebo response parameter. There were no pediatric patients who received sulfonylureas, and only 10 subjects who didn't receive background metformin therapy (four active treatment and six placebo patients). Consequently, neither covariate effect was included in the final model as their limited availability in the current dataset precluded their estimation. The final model only included the effect of receiving insulin co-therapy on the disease progression parameter (zero-order disease progression rate constant. Similarly, the previous model had also included the effects of age, weight, eGFR, race, gender, and background therapy (metformin, insulin, and sulfonylureas) on baseline HbA1c. Due to the limitations stated above with respect to the number of reference patients not on metformin or sulfonlyureas, these background medication effects were also removed from baseline HbA1c. The age, weight, eGFR, race, and gender covariate effects on baseline HbA1c were also removed from the model. This was for two primary reasons, first, many of these covariate effects were negligible in the previous model; either their point estimates were near the null value and/or their 95% CIs included the null value. Secondly, The EDA also did not indicate any trends or imbalances across these covariates with respect to baseline HbA1c. Thus, it was concluded that their exclusion from the model, would not impact the estimation of our parameter of interest, Imax, and the final model only included the effect of receiving insulin co-therapy on baseline HbA1c. The weakly informative prior variance for kout, baseline HbA1c, and the effect of insulin on baseline HbA1c were set to 0.1, as the planned weakly informative variance of 1 was too wide and allowed non-physiologic samples for the parameters. pcVPCs and model parameters are displayed in Figure 4 and Table 7.

Figure 4. Prediction-corrected visual predictive check - final exposure-response model

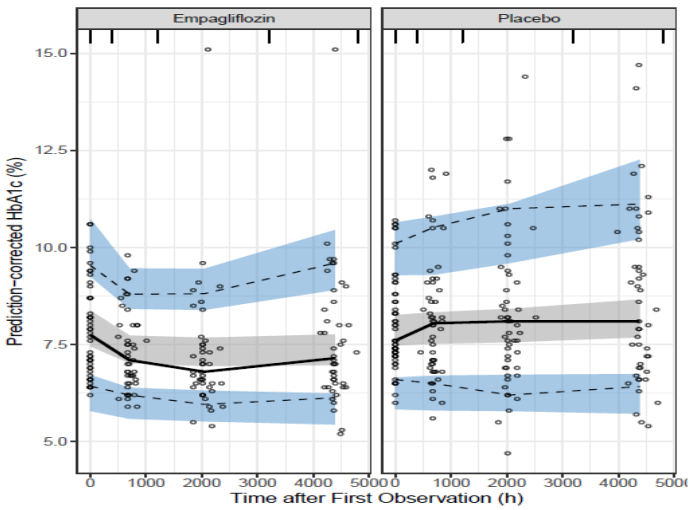


Table 7. Estimates Exposure-response model

		Study 1218.91 model		Previous model	
		Median	95% CDI	Median	95% CI
Structural model					
kout (1/day)	HbA1c degradation rate constant	0.0489	(0.0346, 0.0717)	0.0178	(0.0165, 0.0192)
BASE (%)	Baseline HbA1c	7.35	(6.99, 7.72)	8.17	(8.10, 8.23)
PROG (%/h/h)	Zero-order disease progression rate constant	5.64e-07	(2.94e-07, 9.20e-07)	-	-
IMAX (%)	Maximum inhibition	10.1	(7.39, 12.9)	10.9	(10.3, 11.6)
AUC50 (nmol*hr/L)	AUC at 50% IMAX	703	Fixed	703	(703, 703)
PBO (%)	Placebo effect on kout	-	-	5.16	(4.25, 6.07)
Covariate effects					
INS_{BASE}	Prior insulin effect on BASE	1.15	(1.07, 1.24)	1.02	(1.01, 1.03)
$EGFR_{IMAX}$	eGFR effect on IMAX	1.03	(0.917, 1.15)	1.04	(0.792, 1.30)
$HbA1c_{IMAX}$	Baseline HbA1c effect on IMAX	2.04	(1.86, 2.21)	2.04	(1.46, 2.62)
MET_{BASE}	Prior metformin effect on BASE	-	-	1	(0.994, 1.01)
SU_{BASE}	Sulfonylurea effect on baseline	-	-	1.01	(1.00, 1.02)
MET_{PBO}	Metformin background effect on placebo effect	-	-	1.97	(1.09, 2.85)
INS_{PBO}	Insulin background effect on placebo effect	-	-	-1.22	(-2.67, 0.233)
SU_{PBO}	Sulfonylurea background effect on placebo effect	-	-	-2.49	(-3.44, -1.54)
SEX_{BASE}	Sex = Female effect on baseline HbA1c	-	-	1	(0.995, 1.01)
AGE_{BASE}	Age effect on baseline HbA1c	-	-	-0.0687	(-0.0847, -0.0526)
WT_{BASE}	Body weight effect on baseline HbA1c	-	-	-0.0436	(-0.0579, -0.0294)
$BLACK_{BASE}$	Race = Black effect on baseline HbA1c	-	-	1.02	(1.01, 1.04)
$ASIAN_{BASE}$	Race = Asian effect on baseline HbA1c	-	-	0.992	(0.985, 0.999)
$EGFR_{BASE}$	eGFR effect on baseline HbA1c	-	-	0.00306	(-0.00745, 0.0136)
Interindividual variability					
Ω_{BASE} (CV(%))	IIV-BASE	16.1	(13.9, 19.0)	10.7	(10.4, 10.9)
Ω_{PROG} (CV(%))	IIV-PROG	7.35	(5.33, 10.7)	-	-
$\Omega_{PROG-BASE}$ (Corr)	Covariance on PROG-BASE	0.00112	(-0.00201, 0.00422)	-	-
Ω_{kout} (CV(%))	IIV-KOUT	-	-	171	(153, 191)
$\Omega_{kout-BASE}$ (CV(%))	Covariance on kout-BASE	-	-	0.00993	(0.00357, 0.0163)
$\Omega_{PBO-kout}$ (Corr)	Covariance on kout-PBO-kout	-	-	0.0183	(0.00935, 0.0273)
$\Omega_{PBO-BASE}$ (Corr)	Covariance on PBO-BASE	-	-	0.00541	(0.00444, 0.00637)
Ω_{PBO} (CV(%))	IIV-PBO	-	-	13.1	(12.5, 13.7)
Ω_{IMAX} (CV(%))	IIV-IMAX	-	-	10	(10.0, 10.0)
Residual variability					
$\Sigma_{1,1}$ (CV(%))	Additive RUV on log scale	6.32	(5.71, 7.01)	5.03	(4.90, 5.16)

Parameters estimated in the log-domain were back-transformed for clarity
Abbreviations: CDI: credible interval; CI: confidence interval; eGFR: estimated glomerular filtration rate; HbA1c: glycosylated hemoglobin; IIV: inter-individual variability; RUV: residual variability
Credible intervals calculated from Bayesian posteriors

Simulations

Pediatric and adult patients with T2DM showed comparable CL/F estimates, which resulted in comparable AUCss values for both populations following Monte Carlo simulations (Figure 5, Table 8).

Figure 5. Simulated paediatric exposure in study 1218-0091 and 1245.87 versus adult exposure

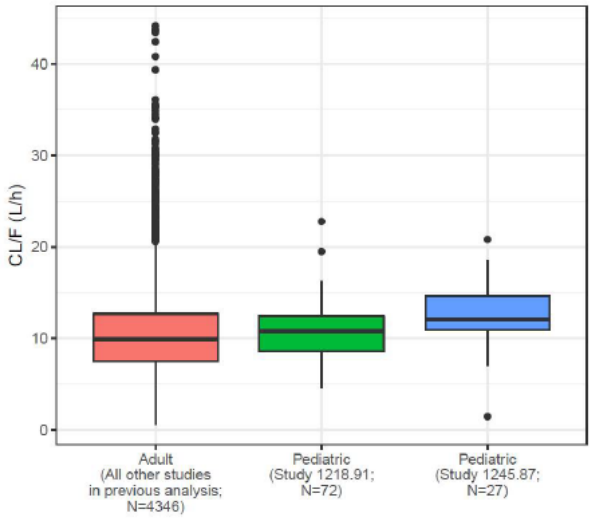


Table 8. Comparison of AUCss values from Monte Carlo simulations in adults and pediatric patients

	Adult	Pediatric
Median AUCss (95% PI)	2.46e+03 (813, 6.77e+03)	2.27e+03 (1.10e+03, 4.44e+03)
Difference	-	-191
Percent Difference	-	-7.76

To compare the exposure-response between paediatrics and adults, Monte Carlo simulations were performed from the previous model for 1000 adult patients and from the current model for 1000 paediatric patients with T2DM (Figure 6 and Table 4). Overall, placebo-adjusted change from baseline in the paediatric population decreased with a larger magnitude than in the adult population. This is primarily due to higher renal function in paediatrics, as the covariate effect of eGFR on Imax produces a higher overall drug effect with increased renal filtration. Overall, insulin cotherapy was associated with a larger simulated magnitude of placebo-adjusted change from baseline in paediatric patients, whereas adults had comparable placebo-adjusted change from baseline independent of insulin background requirements.

Figure 6. Placebo-adjusted HbA1c change from baseline predictions for 10 mg empagliflozin in pediatrics and adults with and without insulin co-therapy at baseline

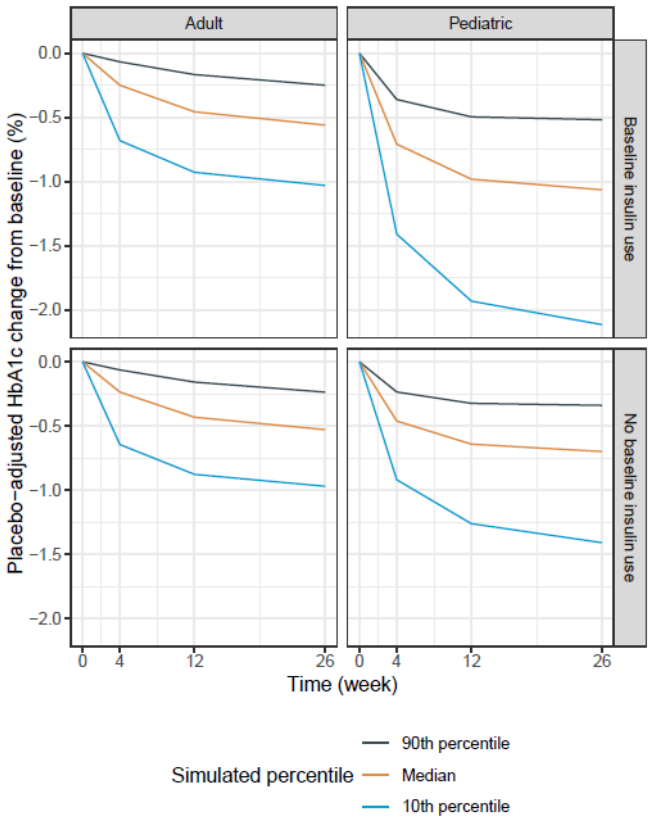


Table 9. Summary statistics of placebo-adjusted HbA1c change from baseline at week 26 from MonteCarlo simulations in adults and pediatric patients using the previous ER model and the current model, respectively.

	Quantiles for simulated placebo-adjusted change from baseline HbA1c (%)		
	10th percentile	Median	90th percentile
Adult			
No baseline insulin use	-0.969	-0.528	-0.236
Baseline insulin use	-1.03	-0.560	-0.249
Pediatric			
No baseline insulin use	-1.41	-0.699	-0.339
Baseline insulin use	-2.11	-1.06	-0.518

2.3.3. Discussion on clinical pharmacology

Overall, the population pharmacokinetic analysis was appropriately conducted.

The analysis was based on a previously conducted population pharmacokinetic analysis already assessed and accepted in procedure EMEA/H/C/002677/P46. This model was updated using a Bayesian approach with study data of 1218-0091. Prior, where applicable, and posterior distributions were compared as model diagnostic. The visual predictive check of the previously developed population pharmacokinetic model on this new dataset showed some deviations between the model predictions and observations. This

was attributed to the age effect that was included in the adult model. The age effect was shown to be only applicable for the adult range. Without this age effect, the population pharmacokinetic model performed adequately and can be used to compare the plasma exposure between paediatrics and adult patients.

The exposure comparison indicated no large differences when comparing the overall paediatric and adult populations. As allometric scaling using fixed exponents is used in the population pharmacokinetic model, an approximate 50% higher exposure can be expected for a patient with a bodyweight of 40 kg compared to a patient with a bodyweight of 70 kg. At weights of 45 kg, 70 kg, 95 kg, and 120 kg the median normalized steady state AUC, relative to a 70 kg individual was 1.39, 1.0, 0.795, and 0.667, respectively.

More adjustments to the adult exposure-response model were needed to describe the paediatric patients of study 1218-0091, but this appeared to be mainly limited to a different placebo response in paediatric patients. In addition, paediatric patients requiring insulin showed higher HbA1c baseline as well as a more pronounced disease progression. This resulted in a larger magnitude of simulated placebo-adjusted change of HbA1c in pediatric patients requiring insulin.

Due to differences in the placebo-effect and/or disease progression between adult and paediatric patients, the observed difference in placebo-corrected HbA1c treatment effects between adult and paediatric patients should be carefully interpreted.

At weights of 45 kg, 70 kg, 95 kg, and 120 kg, the median normalized placebo adjusted changes from baseline in HbA1c were 1.05, 1.00, 0.957, and 0.919 respectively.

2.3.4. Conclusions on clinical pharmacology

The analyses described in this section are considered supportive as efficacy and safety in paediatric patients aged 10 years and older were investigated in study **1218-0091.** The results of study **1245.87** were previously assessed in procedure EMEA/H/C/002677/P46, where it was concluded that the exposure is similar between paediatric and adult T2DM patients. Similarity in exposure can also be concluded in this procedure.

Overall, the pharmacokinetics and pharmacodynamics have been appropriately investigated by the Applicant.

2.4. Clinical efficacy

2.4.1. Dose response studies

The paediatric PK/PD trial 1245.87 showed that, following a single oral dose of empagliflozin 5 mg, 10 mg, or 25 mg, paediatric patients with T2DM had similar exposure-response relationships to those of adults with T2DM after accounting for significant covariates.

In adults, empagliflozin 10 mg and 25 mg once daily are the approved doses for patients with T2DM. Taking into account the consistent PK profile and the comparable exposure-response relationship of empagliflozin in children and adolescents versus adults and based on the various analyses for the individual empagliflozin doses for trial 1218.91 based on TG1, TG2, TG3, TG4, and TG7 the efficacy and safety data from trials 1245.87 and 1218.91 support 10 mg empagliflozin once daily as recommended starting dose for children from 10 to ≤17 years of age. In patients tolerating empagliflozin 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily.

2.4.2. Main study

Title of Study

DINAMO 1281-0091: 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

Methods

Study participants

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

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. 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 withdrawal by 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 background antidiabetic 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.

Treatments

There were 3 treatment arms for this trial:

- placebo,
- 5 mg linagliptin
- 10 mg empagliflozin

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.

Outcomes/endpoints

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:

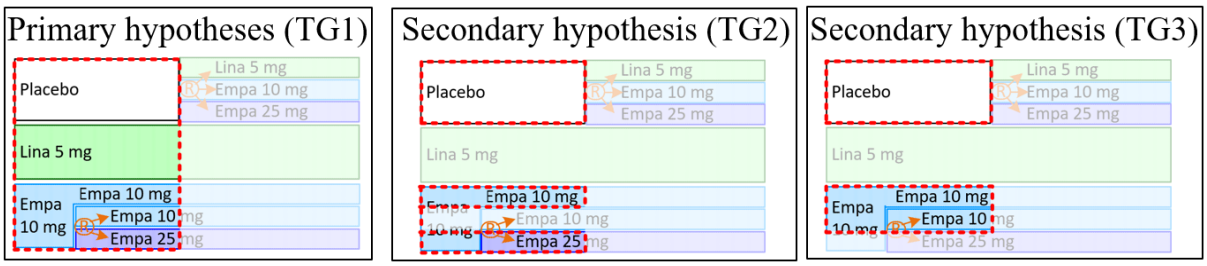
- Change in HbA_{1c} (%) from baseline to the end of 12 and 52 weeks
- Change in FPG (mg/dL) from baseline to the end of 52 weeks
- Change in body weight (kg) from baseline to the end of 12 and 52 weeks
- Change in SBP (mmHg) from baseline to the end of 12 and 52 weeks
- Change in DBP (mmHg) from baseline 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

Statistical methods

The primary endpoint was analysed based on an ANCOVA model using multiple imputation with consecutive 'wash-out' (primary hypotheses for TG1; see Figure 7 box with dashed red borderline) and 'inverse probability weighting' approaches (secondary hypotheses for TG2 and TG3; see Figure 7 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 7 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.

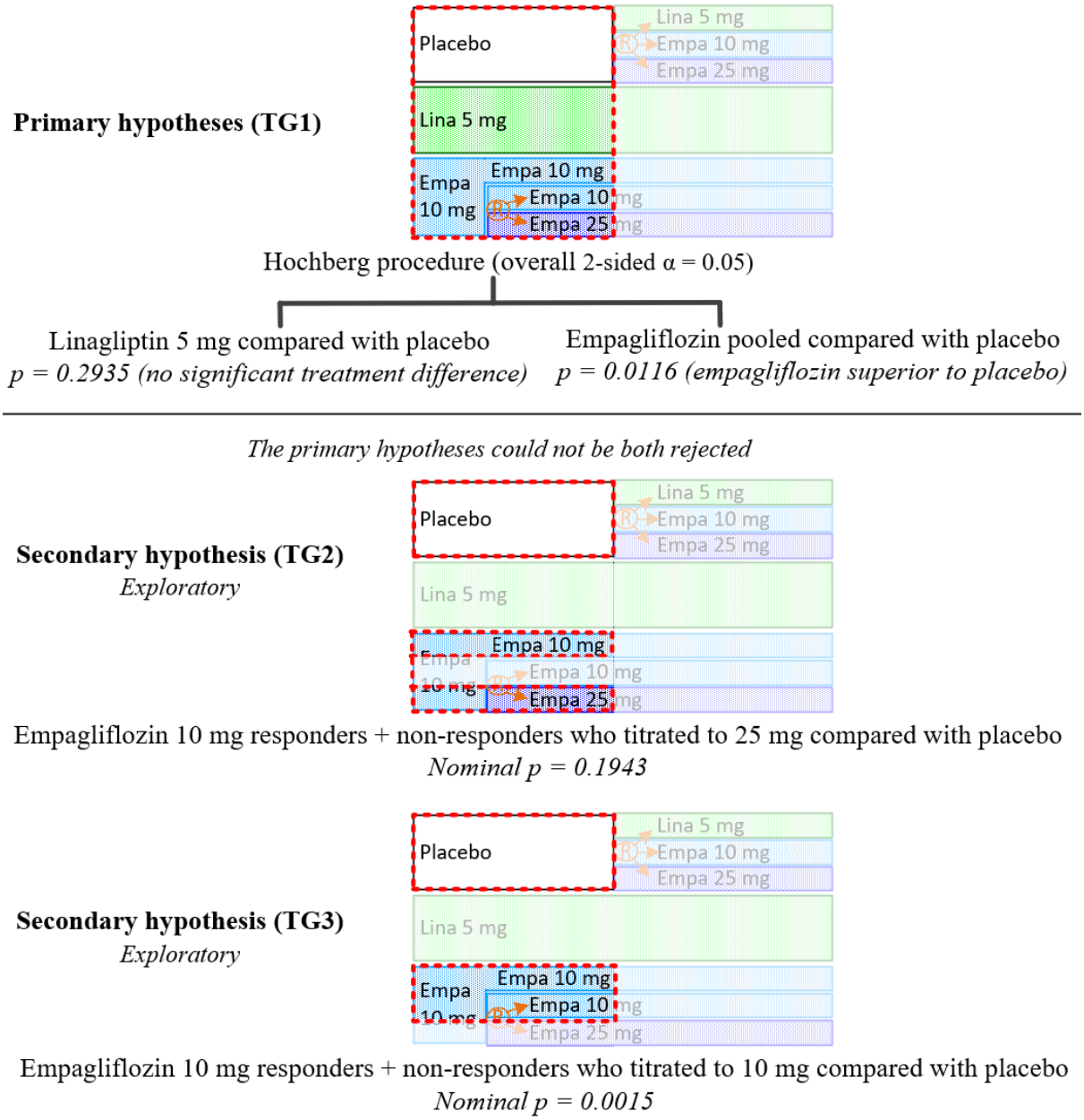
Baseline was defined as the last observed measurement prior to administration of any initially randomised trial medication at Day 1.

Results

Primary confirmatory endpoint

The hierarchical testing results for DINAMO are shown in Figure 8. Based on TG1 (box with dashed red borderline) , 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 10). Since the primary hypotheses based on TG1 could not be both rejected, the hierarchical testing for TG2 and TG3 was not continued. These analyses were considered exploratory, and the p-values regarded as nominal (Table 10).

Figure 8 Hierarchical testing results, trial 1218.91

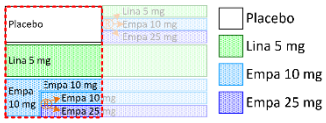
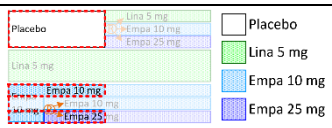
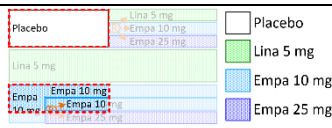


Based on TG2 (box with dashed red borderline in Table 10), empagliflozin 10 mg as a starting dose titrated to 25 mg due to insufficient glycaemic control after 12 weeks or remaining at 10 mg for those with sufficient glycaemic control suggested a clinically meaningful placebo-corrected numerical reduction in HbA_{1c} of −0.52% (95% CI: −1.31% to 0.27%) at Week 26, although the effect had a nominal p-value of 0.1943. In both prespecified sensitivity analyses for TG2, one using MMRM with no multiple imputation or adjusted weighting and another for only patients compliant with the clinical trial protocol, the treatment effect estimates for empagliflozin in TG2 were larger and nominally significant compared with placebo (Figure 9).

Based on TG3 (box with dashed red borderline in Table 10), empagliflozin 10 mg as a starting dose and staying at 10 mg regardless of glycaemic control after 12 weeks suggested a clinically meaningful and

nominally significant reduction in HbA_{1c} compared with placebo at Week 26 (placebo-adjusted mean change from baseline −1.18%, 95% CI −1.90% to −0.45%, nominal p = 0.0015); see Table 10.

Table 10 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
Secondary hypothesis based on TG2, multiple imputation with wash-out inverse probability weighting approach										and
Placebo	53	8.05	1.23	0.66	0.12	1.21				
Empa 10+titr 25	41	7.80	1.26	0.14	−0.42	0.71	−0.52	−1.31	0.27	0.1943 (nominal)
Secondary hypothesis based on TG3, multiple imputation with wash-out inverse probability weighting approach										and
Placebo	53	8.05	1.23	0.68	0.19	1.17				
Empa 10+titr 10	39	7.92	1.36	−0.49	−1.03	0.04	−1.18	−1.90	−0.45	0.0015 (nominal)

The change in HbA1c [%] from Week 12 to the end of 26 weeks in patients randomised to empagliflozin 10 mg and not at glycaemic target (HbA1c <7.0%) at Week 12 was a further endpoint. Based on descriptive analysis (OC-AD), the mean (SD) change from Week 12 to 26 for patients titrated to 10 mg was −0.10% (0.71) and for those titrated to 25 mg 0.52% (0.63).

Table 15.2.3: 9 Descriptive statistics of HbA1c [%] over time from Wk12 up to Wk52 - mITT (TG4) (OC-AD)

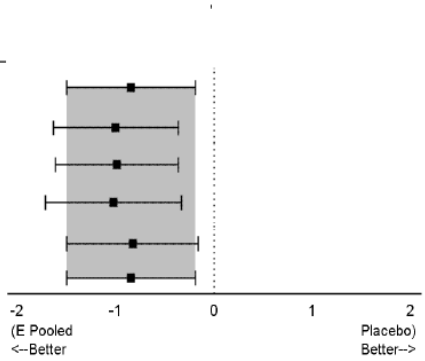
	E10NR/10*								E10NR/25*							
	N	Mean	SD	Min	Q1	Median	Q3	Max	N	Mean	SD	Min	Q1	Median	Q3	Max
OC-AD																
Baseline [1]	11	8.04	0.87	7.0	7.30	7.70	8.70	9.6	13	8.28	2.17	7.0	7.10	7.50	8.60	15.1
Week 26	10	7.87	0.85	6.6	7.10	7.90	8.60	9.0	12	8.89	2.22	7.0	7.50	8.05	9.65	15.1
Week 30	11	7.99	1.05	6.6	7.20	7.80	8.80	9.9	12	8.78	2.45	6.5	7.75	8.30	8.85	16.0
Week 42	11	8.60	1.65	6.5	7.30	8.00	10.40	11.0	12	9.13	2.83	6.6	7.45	8.10	9.70	16.2
Week 52	11	8.65	1.58	6.5	6.90	8.70	10.00	11.2	12	9.21	2.89	6.4	7.30	8.65	10.25	17.2
Change at Week 26	10	-0.10	0.71	-1.1	-0.60	-0.10	0.20	1.4	12	0.52	0.63	-0.5	0.05	0.40	1.05	1.7
Change at Week 30	11	-0.05	0.70	-1.1	-0.50	-0.30	0.30	1.2	12	0.41	0.66	-0.8	0.05	0.45	0.90	1.2
Change at Week 42	11	0.56	1.03	-1.2	-0.10	0.30	1.20	2.5	12	0.75	1.37	-0.9	-0.10	0.45	1.15	4.2
Change at Week 52	11	0.62	0.94	-0.9	-0.50	0.80	1.20	2.0	12	0.83	1.42	-1.2	-0.30	1.10	1.50	3.9

Sensitivity analyses of the primary endpoint showed results consistent with the primary analyses (Figure 9).

Figure 9 Sensitivity analyses for the primary endpoint (TG1, TG2, TG3), trial 1218.91

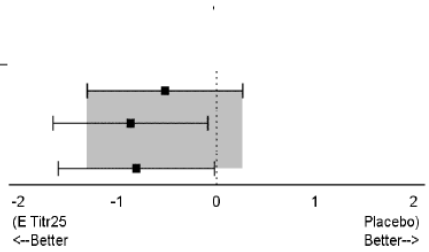
Empagliflozin (10 mg + 25 mg pooled) vs placebo (TG1)

Analysis – Analysis set (Data type)	E Pooled (N)	Pbo (N)	Adjusted mean (95%-CI) Comparison vs. Placebo	p-value
Primary analysis: MI - mITT (OC-AD)	52	53	-0.84 (-1.50 -0.19)	0.0116
Sensitivity analysis: MMRM at Wk 26 - mITT (OC-AD)	47	50	-1.00 (-1.63 -0.37)	0.0022
Sensitivity analysis: MMRM at Wk 26 - mITT (OC)	41	42	-0.99 (-1.61 -0.36)	0.0022
Sensitivity analysis: MI – PPS (OC-AD)	45	44	-1.02 (-1.71 -0.33)	0.0038
Sensitivity analysis: MI COVID-19 – mITT (OC-AD)	52	53	-0.83 (-1.50 -0.16)	0.0153
Sensitivity analysis: MI non-NGSP – mITT (OC-AD)	52	53	-0.84 (-1.50 -0.19)	0.0116



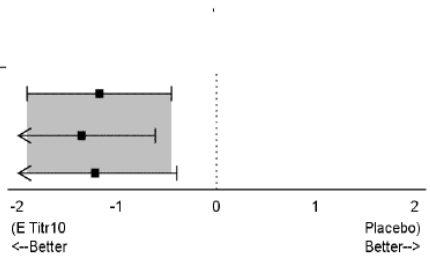
Empagliflozin (10 mg + titration to 25 mg) vs placebo (TG2)

Analysis – Analysis set (Data type)	E Titr25 (N)	Pbo (N)	Adjusted mean (95%-CI) Comparison vs. Placebo	p-value
Primary analysis: MI and IPW – mITT (OC-AD)	41	53	-0.52 (-1.31 0.27)	0.1943
Sensitivity analysis: MMRM at Wk 26 – mITT (OC-AD)	37	50	-0.87 (-1.65 -0.09)	0.0298
Sensitivity analysis: MI and IPW – PPS (OC-AD)	34	44	-0.81 (-1.60 -0.02)	0.0458



Empagliflozin (10 mg + titration to 10 mg) vs placebo (TG3)

Analysis – Analysis set (Data type)	E Titr10 (N)	Pbo (N)	Adjusted mean (95%-CI) Comparison vs. Placebo	p-value
Primary analysis: MI and IPW – mITT (OC-AD)	39	53	-1.18 (-1.90 -0.45)	0.0015
Sensitivity analysis: MMRM at Wk 26 – mITT (OC-AD)	35	50	-1.35 (-2.09 -0.62)	0.0004
Sensitivity analysis: MI and IPW – PPS (OC-AD)	34	44	-1.22 (-2.04 -0.40)	0.0037



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; MI and IPW = multiple imputation with wash-out approach and inverse probability weighting approach

Using TG7, the changes in HbA_{1c} from Week 26 to 52 were analysed for patients initially randomised to placebo and re-randomised at Week 26 to linagliptin 5 mg, empagliflozin 10 mg, or empagliflozin 25 mg (Table 11). The number of patients was relatively low in each group (15 or 16 patients). The mean (SD) change at Week 52 for empagliflozin 10 mg was −0.35% (1.50) and for empagliflozin 25 mg −0.53% (1.13), indicating a numerical benefit for patients treated with either dose of empagliflozin.

Table 11 Descriptive statistics of HbA_{1c} [%] change from Week 26 to 52 – mITT (TG7) (OC-AD), trial 1218.91

Treatment (TG7)	N	Week 26 (baseline), mean (SD)	Change from Week 26, mean (SD)		
			Week 30	Week 42	Week 52
Empagliflozin 10 mg	15	8.43 (2.38)	−0.48 (0.65)	0.12 (1.41)	−0.35 (1.50)
Empagliflozin 25 mg	16	8.53 (2.37)	−0.60 (0.85)	−0.57 (1.05)	−0.53 (1.13)

Subgroup analyses of the primary endpoint

For empagliflozin pooled vs placebo, a trend towards a larger HbA_{1c} reduction in patients with higher baseline HbA_{1c} or FPG was observed. Also, the subgroup with time since diagnosis of T2DM of 1 to 3 years appeared to show a larger treatment effect than the other 2 subgroups. The primary analysis results were consistent across the rest of the subgroups. Efficacy was similar for individuals aged <15 and individuals aged >15-18 years.

Figure 10 Empagliflozin. Subgroup analyses for the primary endpoint (TG1) – mITT (OC-AD)

Subgroup \Category	E Pooled (N)	Pbo (N)	Adjusted mean (95%-CI) Comparison vs. Placebo	p-value
Overall	52	53	-0.84 (-1.50 -0.19)	0.0116
Age [years] at randomisation				
<15	25	26	-1.10 (-2.03 -0.16)	0.0212
>=15 to <18	27	27	-0.61 (-1.53 0.32)	0.1976
HbA1c [%] at baseline				
<8.0	28	29	-0.30 (-1.18 0.58)	0.5001
8.0 to 9.0	12	12	-1.05 (-2.38 0.27)	0.1185
>9.0	12	12	-1.93 (-3.35 -0.50)	0.0080
BMI [kg/m²]				
<34.65 [4]	26	27	-1.23 (-2.12 -0.35)	0.0065
>=34.65 [4]	26	26	-0.46 (-1.40 0.48)	0.3342
BMI z-score				
>2 to <=3 (Class 1 obesity)	21	17	-1.11 (-2.21 -0.01)	0.0487
>3 (Class 2 or 3 obesity)	26	27	-0.81 (-1.80 0.18)	0.1093
FPG [mg/dL] at baseline				
<126	19	13	-0.03 (-1.18 1.12)	0.9565
140 to <200	15	23	-1.21 (-2.24 -0.17)	0.0227
>=200	11	10	-1.79 (-3.13 -0.45)	0.0086
Geographical region				
US	36	33	-0.59 (-1.40 0.22)	0.1555
Non-US	16	20	-1.49 (-2.56 -0.42)	0.0066
Sex				
Male	19	19	-1.04 (-2.14 0.06)	0.0641
Female	33	34	-0.73 (-1.55 0.09)	0.0819
Time since diagnosis of T2DM				
<1 year	17	18	-0.23 (-1.37 0.90)	0.6847
1 year - 3 years	21	24	-1.52 (-2.50 -0.53)	0.0025
>3 years	14	11	-0.31 (-1.73 1.10)	0.6636
Background antidiabetic medication at baseline				
Metformin only	26	28	-1.07 (-1.97 -0.18)	0.0190
Metformin and Insulin	22	19	-0.42 (-1.50 0.66)	0.4473
eGFR [mL/min/1.73m2] (Zappitelli) at baseline				
<120	21	24	-0.77 (-1.79 0.24)	0.1360
120 to <150	19	23	-1.06 (-2.06 -0.06)	0.0373
>=150	12	6	-0.58 (-2.29 1.13)	0.5092
Race				
Black or African American	19	17	-0.78 (-1.89 0.33)	0.1666
White	23	29	-0.63 (-1.50 0.24)	0.1583

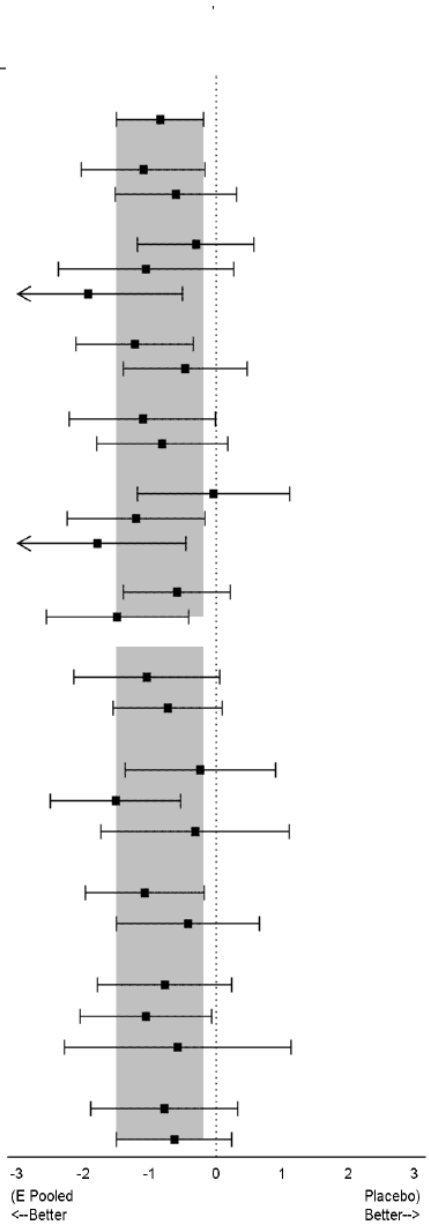
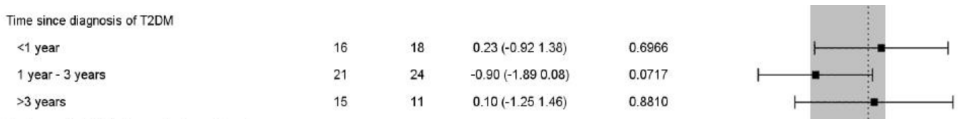


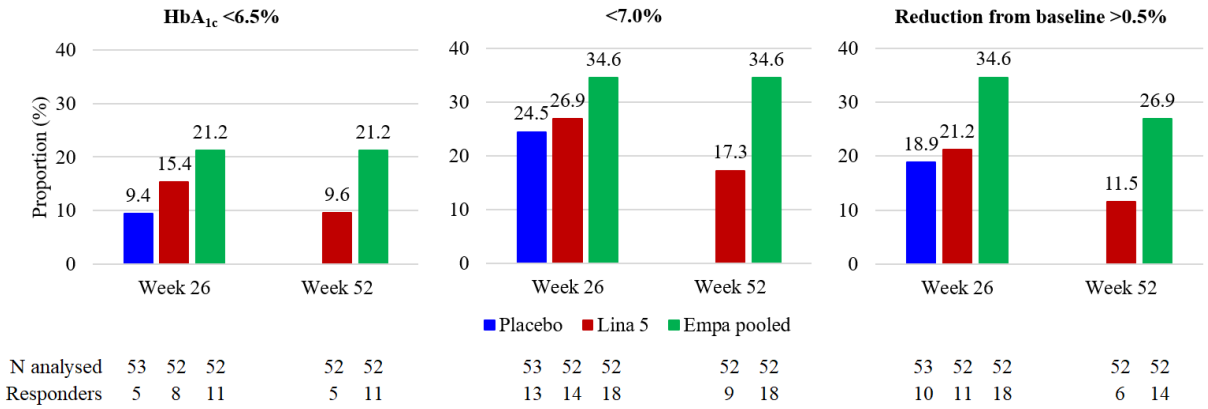
Figure 10 Linagliptin. Subgroup analyses for the primary endpoint (TG1) – mITT (OC-AD)



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

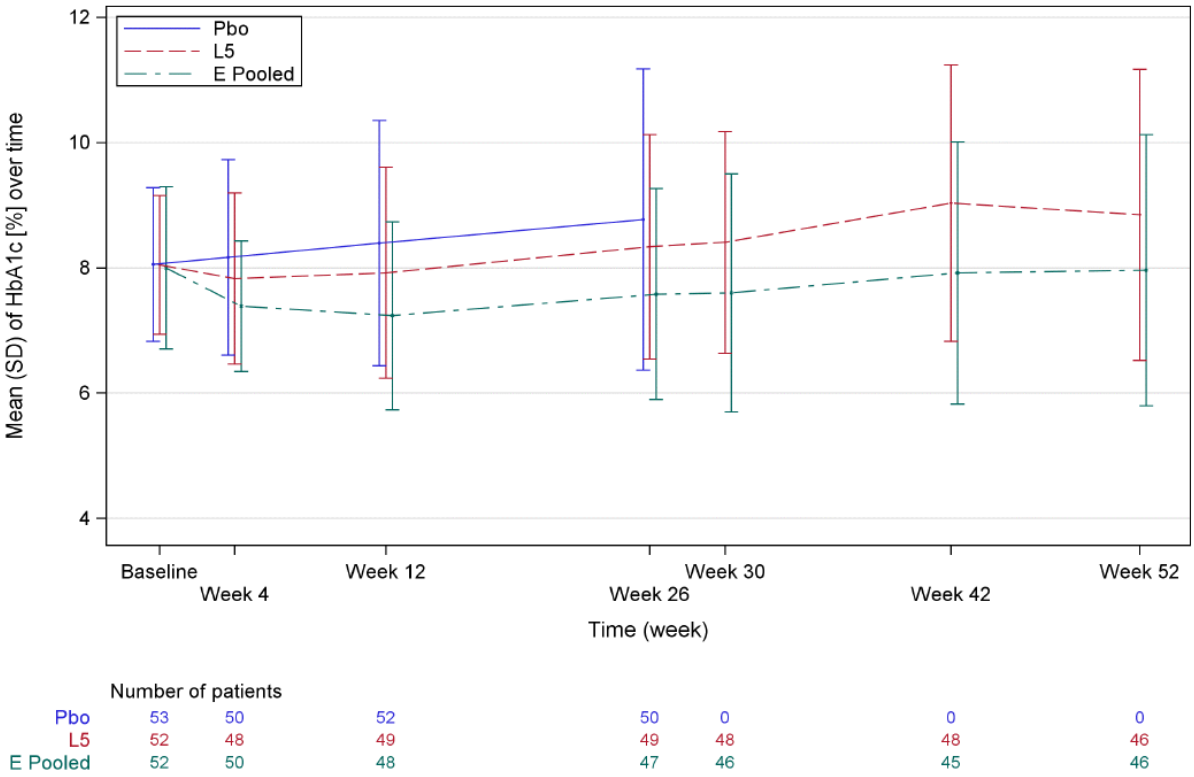
Figure 11. At Week 26, there was a numerical difference between the empagliflozin pooled group and placebo in the proportion of patients reaching a response based on HbA_{1c} (<6.5% or <7.0%).

Figure 11 Proportion of patients who achieved a response based on HbA1c – mITT (TG1, TG5) (NCF), trial 1218.91



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 empagliflozin pooled group was apparent at the first assessment (Week 4) and the difference to placebo was constant up to Week 26. From Week 26 to 52, no control using placebo was available due to the trial design; the trend in the empagliflozin pooled group was consistent with that from Week 12 to 26 (Figure 12).

Figure 12 Descriptive statistics of HbA1c [%] over time up to Week 52 – mITT (TG1, TG5) (OC-AD), trial 1218.91



Pbo = Placebo, L5 = Linagliptin 5 mg, E Pooled = Empagliflozin pooled.

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

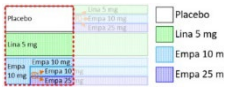
Up to Week 26, the proportion of patients who initiated glycaemic rescue therapy was comparable between placebo (6 patients, 11.3%) and empagliflozin pooled (5 patients, 9.6%). Up to Week 52 (long-term analysis for the active substances based on the initial randomisation), 6 patients (11.5%) in the empagliflozin pooled group initiated glycaemic rescue therapy.

FPG, body weight, SBP, and DBP

All secondary endpoints were exploratory; a summary of the results is provided in Table 12. The trend for changes in FPG was consistent with HbA_{1c}. For empagliflozin, a clinically meaningful and nominally significant lowering of FPG was observed.

No obvious changes over time in body weight, SBP, and DBP were observed for empagliflozin pooled versus placebo (Table 12).In addition, no obvious changes over time in fasting serum C peptide, UACR, or eGFR were observed for any treatment group in this trial.

Table 12 Secondary endpoints FPG, body weight, SBP and DBP: change from baseline at Week 26 – mITT (TG1), trial 1218.91

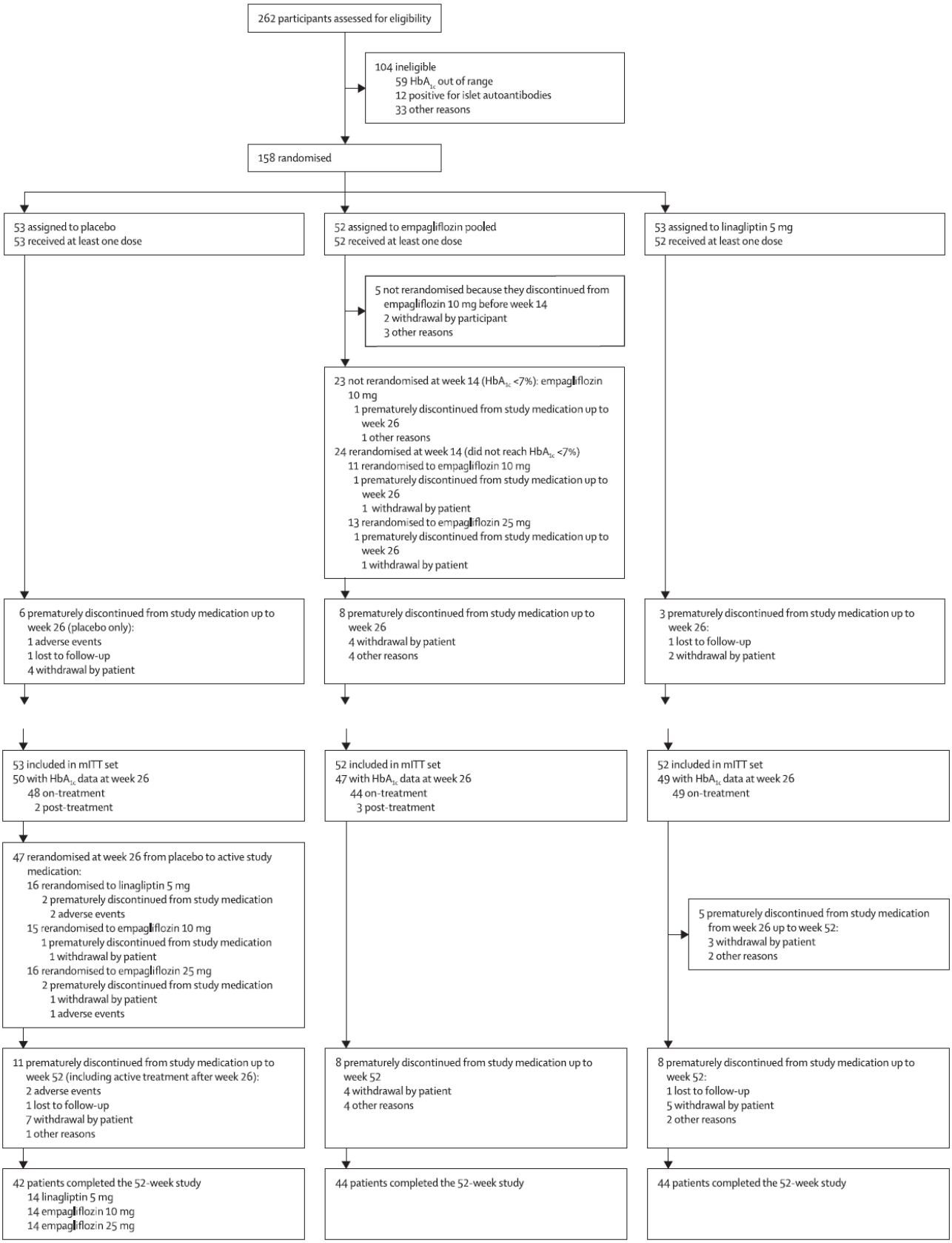
Treatment (TG1)	N analysed	Baseline		Change from baseline			Comparison vs placebo			
		Mean	SD	Adjusted mean	95% CI		Adjusted mean	95% CI		Nominal p-value
Fasting plasma glucose (FPG) [mg/dL], ANCOVA (OC-AD-BOCF)										
Placebo	52	158.62	53.80	15.70	−0.53	31.93				
Empa pooled	48	154.43	57.78	−19.48	−36.39	−2.57	−35.18	−58.61	−11.74	0.0035
Body weight [kg], MMRM (OC-AD)										
Placebo	52	98.87	29.62	−0.04	−1.40	1.32				
Empa pooled	52	98.66	24.35	−0.79	−2.17	0.59	−0.75	−2.68	1.19	0.4476
Systolic blood pressure (SBP) [mmHg], MMRM (OC-AD)										
Placebo	52	118.34	11.87	1.30	−1.01	3.61				
Empa pooled	52	120.23	9.97	−0.12	−2.47	2.24	−1.42	−4.72	1.88	0.3967
Diastolic blood pressure (DBP) [mmHg], MMRM (OC-AD)										
Placebo	52	72.60	8.94	0.76	−1.01	2.53				
Empa pooled	52	72.03	8.38	0.78	−1.04	2.60	0.02	−2.52	2.56	0.9878

Although not shown in this table, the linagliptin 5 mg group was included in the models.

]

Participant flow

Figure 13: participant flow

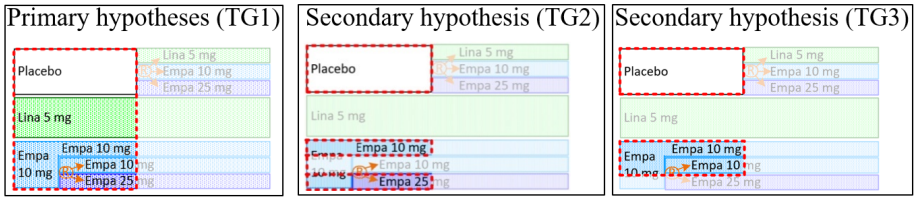

262 participants assessed for eligibility
104 ineligible
59 HbA1c out of range
12 positive for islet autoantibodies
33 other reasons
158 randomised
53 assigned to placebo
53 received at least one dose
52 assigned to empagliflozin pooled
52 received at least one dose
53 assigned to linagliptin 5 mg
52 received at least one dose
5 not rerandomised because they discontinued from empagliflozin 10 mg before week 14
2 withdrawal by participant
3 other reasons
23 not rerandomised at week 14 (HbA1c <7%): empagliflozin 10 mg
1 prematurely discontinued from study medication up to week 26
1 other reasons
24 rerandomised at week 14 (did not reach HbA1c <7%)
11 rerandomised to empagliflozin 10 mg
1 prematurely discontinued from study medication up to week 26
1 withdrawal by patient
13 rerandomised to empagliflozin 25 mg
1 prematurely discontinued from study medication up to week 26
1 withdrawal by patient
6 prematurely discontinued from study medication up to week 26 (placebo only):
1 adverse events
1 lost to follow-up
4 withdrawal by patient
8 prematurely discontinued from study medication up to week 26
4 withdrawal by patient
4 other reasons
3 prematurely discontinued from study medication up to week 26:
1 lost to follow-up
2 withdrawal by patient
53 included in mITT set
50 with HbA1c data at week 26
48 on-treatment
2 post-treatment
52 included in mITT set
47 with HbA1c data at week 26
44 on-treatment
3 post-treatment
52 included in mITT set
49 with HbA1c data at week 26
49 on-treatment
47 rerandomised at week 26 from placebo to active study medication:
16 rerandomised to linagliptin 5 mg
2 prematurely discontinued from study medication
2 adverse events
15 rerandomised to empagliflozin 10 mg
1 prematurely discontinued from study medication
1 withdrawal by patient
16 rerandomised to empagliflozin 25 mg
2 prematurely discontinued from study medication
1 withdrawal by patient
1 adverse events
5 prematurely discontinued from study medication from week 26 up to week 52:
3 withdrawal by patient
2 other reasons
11 prematurely discontinued from study medication up to week 52 (including active treatment after week 26):
2 adverse events
1 lost to follow-up
7 withdrawal by patient
1 other reasons
8 prematurely discontinued from study medication up to week 52
4 withdrawal by patient
4 other reasons
8 prematurely discontinued from study medication up to week 52:
1 lost to follow-up
5 withdrawal by patient
2 other reasons
42 patients completed the 52-week study
14 linagliptin 5 mg
14 empagliflozin 10 mg
14 empagliflozin 25 mg
44 patients completed the 52-week study
44 patients completed the 52-week study

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13 Summary of Efficacy for trial 1218.91 (DINAMO)

Title: 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 (**DINAMO**, **main trial**)		
Study identifier	1218.91 (DINAMO)	
Design	Randomised, placebo-controlled, double-blind, and parallel group trial with 3 treatment arms (placebo, 5 mg linagliptin, 10 mg empagliflozin) lasting 26 weeks. Patients on empagliflozin who did not achieve HbA_{1c} <7.0% at Week 12 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).	
	Duration of main phase	26 weeks
	Duration of Run-in phase	2 weeks placebo
	Duration of Extension phase	26 weeks
Hypothesis	Superiority of linagliptin vs placebo and empagliflozin vs placebo	
Treatment groups	Linagliptin	Linagliptin 5 mg once daily, up to 52 weeks, 53 patients initially randomised
	Empagliflozin	Empagliflozin once daily pooled (10 mg + 25 mg), up to 52 weeks, 52 patients initially randomised
	Placebo	Placebo once daily, up to 26 weeks, 53 patients initially randomised
Endpoints and definitions	Primary endpoint	Change in HbA_{1c} (%) from baseline to the end of 26 weeks
Database lock	10 Aug 2022	
Results and Analysis		
Analysis description	Primary Analysis	

Analysis population and time point description	Primary endpoint, mITT, after 26 weeks of treatment 				
Descriptive statistics and estimate variability (for the primary endpoint)	Treatment group			Placebo	Linagliptin	Empagliflozin
	TG1, number of patients			53	52	52
	Adjusted mean			0.68	0.33	−0.17
	95% CI			0.23, 1.13	−0.13, 0.79	−0.64, 0.31
	TG2, number of patients			53		41
	Adjusted mean			0.66		0.14
	95% CI			0.12, 1.21		−0.42, 0.71
	TG3, number of patients			53		39
	Adjusted mean			0.68		−0.49
	95% CI			0.19, 1.17		−1.03, 0.04
Effect estimate per comparison	Primary endpoint, primary hypothesis (TG1)	Comparison groups	Linagliptin 5 mg vs placebo			
		Adjusted mean	−0.34			
		95% CI	−0.99, 0.30			
		P-value	0.2935			
		Comparison groups	Empagliflozin pooled vs placebo			
		Adjusted mean	−0.84			
		95% CI	−1.50, −0.19			
		P-value	0.0116			
	Primary endpoint, secondary	Comparison groups	Empagliflozin 10 mg + titrated to 25 mg vs placebo			
		Adjusted mean	−0.52			
		95% CI	−1.31, 0.27			

	hypothesis (TG2; exploratory)	Nominal p-value	0.1943
	Primary endpoint, secondary hypothesis (TG3; exploratory)	Comparison groups	Empagliflozin 10 mg + titrated to 10 mg vs placebo
		Adjusted mean	−1.18
		95% CI	−1.90, −0.45
		Nominal p-value	0.0015
Notes	Results for the primary endpoint are included in this table.		

2.4.3. Discussion on clinical efficacy

Phase 3 trial design

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 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).

Patients

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.

Several subgroups may be too small to establish efficacy.

HbA1c: primary outcome

For the primary outcome, the adjusted mean HbA1c change from baseline at week 26 was –0.84 % [-9.2 mmol/mol] in the empagliflozin pooled group versus placebo (95% CI -1.50 to –0.19 (-16.4 to -2.1]; p=0.012); the corresponding change from baseline for linagliptin versus placebo was –0.34% [-3.8 mmol/mol; 95% CI—0.99 to 0.30 [-10.8 to 3.3]; p=0.29).

HbA1c: 10 mg vs 25 mg

The weighted adjusted mean change in HbA1c values at week 26 in the dosing regimen up-titrating non-responders to empagliflozin 25 mg was -0.52% [-5.7 mmol/mol] versus the placebo group (95% C, -1.31 to 0.27 [-14.3 to 2.9]; p=0.19). The corresponding change from baseline in those who remained on 10 mg was -1.18% [-12.9 mmol/mol; 95% Cl -1.90 to -0.45 [-20.8 to -4.9]; p=0.0015).

The change in HbA1c [%] from Week 12 to the end of 26 weeks in patients randomised to empagliflozin 10 mg and not at glycaemic target (HbA1c <7.0%) at Week 12 was a further endpoint. Based on descriptive analysis (OC-AD), the mean (SD) change from Week 12 to 26 for patients titrated to 10 mg was −0.10% (0.71, n=10) and for those titrated to 25 mg +0.52% (0.63, n=12). However, the higher mean baseline HbA1c value in the 25 mg group and one outlier may explain the disappointing results in the 25 mg group.

The changes in HbA1c from Week 26 to 52 were also analysed for patients initially randomised to placebo and re-randomised at Week 26 to linagliptin 5 mg, empagliflozin 10 mg, or empagliflozin 25 mg. The number of patients was relatively low in each group (15 or 16 patients). The mean (SD) change at Week 52 for empagliflozin 10 mg was −0.35% (1.50) and for empagliflozin 25 mg −0.53% (1.13).

HbA1c: subgroups

As could be expected, a trend towards a larger HbA1c reduction in patients with higher baseline HbA1c or FPG was observed for empagliflozin pooled vs placebo. Importantly, the subgroup with time since diagnosis of T2DM of 1 to 3 years appeared to show a larger treatment effect than the other 2 subgroups. 2 patients with HbA1c increases >5% were identified as major contributors to the heterogeneity of the treatment effects in this subgroup analysis. The primary analysis results were consistent across the rest of the subgroups. Efficacy was similar for individuals aged <15 and individuals aged >15-18 years.

Other endpoints

At Week 26, the trend for changes in FPG was consistent with HbA1c. No obvious changes over time in body weight, SBP, and DBP were observed for empagliflozin pooled versus placebo.

2.4.4. Conclusions on the clinical efficacy

In children from 10 to ⩽17 years of age, empagliflozin (10 mg and 25 mg combined) was associated with a clinically relevant decrease in HbA1c compared to placebo. However, the Hba1c change in non-responders on 10 mg was lower in those uptitrated to empagliflozin 25 mg (+0.52% since re-randomisation) compared to those who remained on 10 mg (-0.10% since re-randomisation). However, the higher mean baseline HbA1c value in the 25 mg group and one outlier may explain the disappointing results in the 25 mg group.

2.5. Clinical safety

Patient exposure

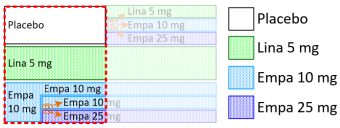
In the paediatric programme for empagliflozin, the pivotal trial 1218.91 represented most of the exposure with a treatment period of up to 52 weeks. Therefore, the main focus in this section is on trial 1218.91. Safety analyses followed the 'treatment-emergent' principle and included all treated patients. 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.

Adverse events

The main analysis of safety in trial 1218.91 focused on TG1 up to Week 26 (box with dashed red borderline in Table 14), for a randomised, placebo-controlled comparison. Up to Week 26, the rate of any AE in the empagliflozin pooled group was slightly higher than on placebo, while the rates of severe AEs, AEs leading to discontinuation, drug-related AEs, and SAEs were generally comparable with the rates on placebo (Table 14).

Table 14 Overall summary of adverse events up to Week 26 – TS (TG1), trial 1218.91

Category of AEs



	Placebo			Empa pooled		
	N	%	Rate/ 100 py	N	%	Rate/ 100 py
Number of patients	53	100.0		52	100.0	
Patients with any AEs	34	64.2	273.9	40	76.9	467.5
Severe AEs	2	3.8	8.0	1	1.9	4.2
Investigator defined drug-related AEs	6	11.3	26.2	9	17.3	42.6
AEs leading to discontinuation of trial medication	2	3.8	8.0	0		
Serious AEs	2	3.8	8.0	2	3.8	8.4
Results in death	0			0		
Is life threatening	1	1.9	4.0	1	1.9	4.2
Persistent or significant disability/incapacity	0			0		
Requires or prolongs hospitalisation	2	3.8	8.0	2	3.8	8.4
Congenital anomaly or birth defect	0			0		
Other medically important serious event	0			1	1.9	4.2

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.

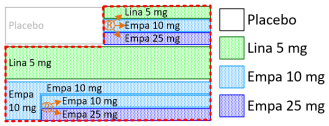
Supportive analysis of safety using TG6 up to Week 52 (box with dashed red borderline in

Table 15) was carried out to investigate safety over the entire active treatment period in the trial. For the empagliflozin active pooled group, the rates of AEs, severe AEs, AEs leading to discontinuation, drug-related AEs, and SAEs up to Week 52 (

Table 15) were similar to the rates reported for empagliflozin pooled group up to Week 26 (Table 14).

Table 15 Overall summary of adverse events up to Week 52 – TSactive (TG6), trial 1218.91

Category of AEs



	Empa active		
	N	%	Rate/ 100 py
Number of patients	83	100.0	
Patients with any AEs	63	75.9	320.4
Severe AEs	3	3.6	4.9
Investigator defined drug-related AEs	14	16.9	26.2
AEs leading to discontinuation of trial medication	1	1.2	1.6
Serious AEs	3	3.6	4.9
Results in death	0		
Is life threatening	1	1.2	1.6
Persistent or significant disability/incapacity	0		
Requires or prolongs hospitalisation	3	3.6	4.9
Congenital anomaly or birth defect	0		
Other medically important serious event	1	1.2	1.6

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.

Most frequently reported AEs in trial 1218.91

Up to Week 26, the most frequently reported AEs for patients on placebo were headache (7 patients, 13.2%) and hypoglycaemia, vitamin D deficiency, and diarrhoea (each reported for 5 patients, 9.4%). In the empagliflozin pooled group, the most frequently reported AEs by PT were hypoglycaemia (11 patients, 21.2%), headache (8 patients, 15.4%), and vitamin D deficiency (5 patients, 9.6%). The only imbalance in rates of AEs by PT between the placebo and empagliflozin was in the rate of hypoglycaemia, which was higher on empagliflozin than on placebo. For other AEs, by PT, there were no relevant differences in rates for placebo compared with the empagliflozin pooled group.

From Week 26 to 52, no control using placebo was available due to the trial design. Up to Week 52, the rates and pattern of AEs reported for the empagliflozin active pooled group (by SOC and PT) were comparable with the rates of AEs reported up to Week 26 for the empagliflozin pooled group.

Adverse events by intensity

Up to Week 26, almost all AEs in the placebo and empagliflozin pooled groups were of mild or moderate intensity. Severe AEs were reported for 2 patients (3.8%) on placebo and 1 patient (1.9%) in the empagliflozin pooled group. In the empagliflozin pooled group, the severe AE suicidal ideation was also an SAE (see below); it was not considered to be drug related. Up to Week 52, the rates of AEs by severity in

the empagliflozin active pooled group were generally comparable with rates in the empagliflozin pooled group at Week 26.

Drug-related adverse events

Up to Week 26, on the PT level, few drug-related AEs were reported by >1 patient and there was no relevant difference between placebo and the empagliflozin pooled group. On placebo, hypoglycaemia was reported for 2 patients (3.8%). Drug-related AEs reported for >1 patient in the empagliflozin pooled group were hypoglycaemia (4 patients, 7.7%), fungal infection and increased blood ketone body (each reported for 2 patients, 3.8%). Up to Week 52, the rates of drug-related AEs in the empagliflozin active pooled group were generally comparable with rates in the empagliflozin pooled group at Week 26.

AEs leading to discontinuation

Up to Week 26, there were no AEs leading to discontinuation of patients in the empagliflozin pooled group and 2 patients (3.8%) discontinued from placebo (PTs: acute pancreatitis, polyuria, and irregular menstruation, each reported for 1 patient [1.9%]). Up to Week 52, the rates of AEs leading to discontinuation in the empagliflozin pooled group were generally comparable with rates at Week 26 in the empagliflozin active pooled group.

Serious adverse event/deaths/other significant events

There was no relevant difference among treatment groups with regard to SAEs reported during this trial. Up to Week 26, 2 patients (3.8%) in each group (placebo and empagliflozin pooled) had SAEs. Up to Week 52, 3 patients (3.6%) in the empagliflozin active pooled group had SAEs. No patient had a fatal AE. Two patients had SAEs that were considered to be life-threatening: 1 patient on placebo (up to Week 26), who had 6 such SAEs (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), and 1 patient on empagliflozin, who was included in both the summary of SAEs up to Week 26 (empagliflozin pooled group) and up to Week 52 (empagliflozin active pooled group). For the patient on empagliflozin, the PT was suicidal ideation; this event was not considered to be drug related and occurred in a patient with a history of suicidal ideation of >5 years at trial entry.

Up to Week 52, no SAE (on the PT level) was reported for >1 patient in either treatment group. Two SAEs were considered to be related to trial medication: hyperglycaemia (1 patient on placebo) and tubulointerstitial nephritis (1 patient on empagliflozin 10 mg). The event of tubulointerstitial nephritis led to interruption of trial treatment rather than discontinuation; the patient recovered. Also, 4 days before the onset of this event, the patient had colitis with vomiting and diarrhoea, and received ciprofloxacin, metronidazole, and ibuprofen as treatment.

Two patients discontinued trial medication due to SAEs: acute pancreatitis (1 patient on placebo, medication code broken) and tubulointerstitial nephritis (1 patient on empagliflozin 10 mg, mentioned above; the medication was interrupted rather than discontinued).

Laboratory findings

Hepatic and renal laboratory parameters were evaluated as part of the AESI evaluation, and no relevant differences were observed for empagliflozin pooled compared with placebo. In the analysis of hepatic laboratory parameters (up to Week 26), the frequency of patients with elevated liver enzyme values was balanced between placebo and empagliflozin pooled. Two patients on empagliflozin pooled had elevated ALT and/or AST ≥3x upper limit of normal; both patients had already elevated liver enzyme values before

first intake of trial medication. None of the patients in trial 1218.91 fulfilled the criteria for potential Hy's Law.

There were no notable changes in total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, or triglyceride values from baseline to Week 26 in either treatment group (placebo or empagliflozin pooled) or to Week 52 for the empagliflozin pooled group. There were also no relevant differences between the treatment groups.

There were no notable changes in IGF-1, IGF-BP3 and markers of bone turnover from baseline to Week 26 in either treatment group (placebo or empagliflozin pooled) or up to Week 52 for the empagliflozin pooled group. There were also no relevant differences between 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 between treatment groups in subgroup analyses by sex and baseline Tanner score.

For other safety laboratory parameters, differences between placebo and empagliflozin were consistent with the known safety profile of empagliflozin. Mean values for uric acid were decreased from baseline to Week 26 in the empagliflozin pooled group compared with baseline values, and haematocrit and haemoglobin values were increased. However, there were no notable differences with regard to frequencies of PCSAs between placebo and empagliflozin pooled.

2.5.1. Discussion on clinical safety

Up to Week 26, the rate of any AE in the empagliflozin pooled group was slightly higher than on placebo, while the rates of severe AEs, AEs leading to discontinuation, drug-related AEs, and SAEs were generally comparable with the rates on placebo.

Up to Week 26, no AEs were leading to discontinuation of patients in the empagliflozin pooled group and 2 patients (3.8%) discontinued from placebo (PTs: acute pancreatitis, polyuria, and irregular menstruation, each reported for 1 patient [1.9%]). There was no relevant difference among treatment groups with regard to SAEs reported during this trial. Up to Week 26, 2 patients (3.8%) in each group (placebo and empagliflozin pooled) had SAEs. Up to Week 52, 3 patients (3.6%) in the empagliflozin active pooled group had SAEs. No patient had a fatal AE. Two patients had SAEs that were considered to be life-threatening: 1 patient on placebo and 1 patient on empagliflozin (suicidal ideation).

Two patients discontinued trial medication due to SAEs: acute pancreatitis (1 patient on placebo, medication code broken) and tubulointerstitial nephritis (1 patient on empagliflozin). The results of the AESIs and specific AEs were consistent with the known safety profile of empagliflozin in patients with T2DM. Up to Week 26, there were few patients with the following AESIs, and no imbalances in rates between placebo and the empagliflozin pooled group: hypersensitivity reactions, pancreatitis, hepatic injury, decreased renal function, diabetic ketoacidosis (DKA), ketone measurements reported as AE, genital infection, arthralgia, and volume depletion. For DKA, there was no patient in the empagliflozin (active) pooled group who was reported with DKA.

For hypoglycaemic events, up to Week 26, there were higher overall rates for patients in the empagliflozin pooled group compared with placebo, but no relevant difference among treatment groups with regard to rates of symptomatic hypoglycaemia. There were no severe hypoglycaemia events. However, there was an increased risk of hypoglycaemia in patients using insulin as a background (14.3 vs. 32.0) as well as in patients without insulin background (6.3 vs. 14.8). There were no relevant differences between placebo and empagliflozin pooled with regard to heart rate and growth assessments (weight, height, BMI, and growth velocity).

There were no relevant safety differences (including hypoglycaemia) between empagliflozin 10 and 25 mg.

Long-term safety data is currently missing, but the MAH has made a commitment to ensure close monitoring of long-term safety via future PSURs, which is acceptable.

2.5.2. Conclusions on clinical safety

In paediatric patients, no unexpected safety concerns were identified for empagliflozin (pooled doses) with regard to AEs, drug-related AEs, AESIs, safety laboratory parameters, and other safety parameters assessed in the paediatric programme. Only for hypoglycaemic events, there were higher overall rates for patients in the empagliflozin pooled group compared with placebo. There were no relevant safety differences (including hypoglycaemia) between empagliflozin 10 and 25 mg. Long-term safety data in the paediatric population needs to be added as missing information in the summary of safety concerns section of the empaglifozin PSUR and systematically reported in all upcoming PSURs. The MAH has made a commitment in this regard, which is acceptable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 21.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 21.1 with the following content:

Safety concerns

Table 16 Summary of safety concerns

Important identified risks	Complicated urinary tract infection
	Genital infection
	Diabetic ketoacidosis with atypical presentation
Important potential risks	Urinary tract carcinogenicity
	Liver injury
	Amputation risk
	Pancreatitis
Missing information	None

Pharmacovigilance plan

Table 17 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
PASS 1245-0097 Post-authorisation safety study to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with T2DM: a multi-database European study Ongoing	To evaluate the risk of renal and bladder cancer in empagliflozin-treated patients, compared to users of other antidiabetic treatment.	Urinary tract carcinogenicity	Final report	30 Sep 2023

Risk minimisation measures

Table 18 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Complicated urinary tract infection	*Routine risk minimisation measures* SmPC sections 4.4 and 4.8 PL sections 2 and 4 Prescription only medicine *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* None

		Additional pharmacovigilance activities PASS 1245-0096 (final report 31 Dec 2022)
Genital infection	*Routine risk minimisation measures* SmPC section 4.8 PL section 4 Prescription only medicine *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* None *Additional pharmacovigilance activities* PASS 1245-0096 (final report 31 Dec 2022)
Diabetic ketoacidosis with atypical presentation	*Routine risk minimisation measures* SmPC sections 4.4 and 4.8 PL sections 2 and 4 Prescription only medicine *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form to capture data on patients with DKA *Additional pharmacovigilance activities* PASS 1245-0096 (final report 31 Dec 2022)
Important potential risks		
Urinary tract carcinogenicity	*Routine risk minimisation measures* Prescription only medicine *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* None *Additional pharmacovigilance activities* PASS 1245-0097 (final report 30 Jun 2022)

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important potential risks (cont'd)		
Liver injury	*Routine risk minimisation measures* SmPC sections 4.2 and 4.4 Prescription only medicine *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* None *Additional pharmacovigilance activities* PASS 1245-0096 (final report 31 Dec 2022)
Amputation risk	*Routine risk minimisation measures*	*Routine pharmacovigilance activities beyond adverse*

	SmPC section 4.4 PL section 2 Prescription only medicine *Additional risk minimisation measures* None	*reactions reporting and signal detection* AE follow-up form to capture data on patients with amputation risk *Additional pharmacovigilance activities* PASS 1245-0137 (final report, 31 Mar 2023)
Pancreatitis	*Routine risk minimisation measures* Prescription only medicine *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form to capture data on patients with pancreatitis. *Additional pharmacovigilance activities* None
Missing information		
None		

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the product information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The objective of this variation is to extend the indication of Jardiance for the treatment of type 2 diabetes mellitus in children 10 years and above. As a consequence, the package leaflet is also proposed to be updated with the new indication and use in paediatric patients.

According to the Guidelines on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use (revision 1, 12 January 2009) it is possible to refer to already approved package leaflets for which results of readability testing are available. The package leaflet for Jardiance was subject to a readability user testing with the intial marketing authorisation application. Further, with the indication extension for heart failure with reduced ejection fraction (EMEA/H/C/002677/II/0055) a readablity user test was conducted. In the final report dated February 2021, the package leaflet was rated readable and comprehensive. No further improvement was deemed necessary per this recent report. During procedure EMEA/H/C/002677/II/0055, the package leaflet was updated based on CHMP's request to ensure patient's understanding in the contexts of the side effect 'diabetic ketoacidosis'.

With this proposed indication extension, the update of the package leaflet only concerns sections 1. 'What Jardiance is used for' and 'Children and adolesents'. The design and layout of the printed package leaflet will not change.

In conclusion, given that a readability user test was conducted recently and that changes to be introduced

for the treatment of type 2 diabetes mellitus in children 10 years and above are only very limited in e tent, Boehringer Ingelheim considers it justified to not consult with target patient groups.

3. Benefit-Risk Balance

Empagliflozin is an orally administered, potent, and highly selective SGLT-2 inhibitor. Empagliflozin is approved and marketed for the treatment of adults with T2DM, for the prevention of CV events in adults with T2DM and established cardiovascular disease, and in adults with heart failure independent of left ventricular ejection fraction.

Based on the results of the paediatric clinical programme, the company now intends to seek an indication for empagliflozin for the treatment of paediatric patients with T2DM.

The proposed indication (added text in bold) is : "Jardiance is indicated **in** ~~for the treatment of~~ adults **and children aged 10 years and above** **for the treatment of** ~~with~~ insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance
- in addition to other medicinal products for the treatment of diabetes

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1."

3.1. Therapeutic Context

The incidence of T2DM in children is increasing worldwide, and the main driver is the increased prevalence and degree of childhood obesity. Childhood T2DM is still relatively rare in Europe, with a prevalence of approximately 2.5 per 100 thousand.

3.1.1. Disease or condition

As in adults, T2DM in children is characterised by hyperglycaemia driven by insulin resistance and relative insulin deficiency. Developing T2DM at a younger age is associated with a considerably higher risk of long-term cardiovascular disease compared with those who develop T2DM in the middle age. The rapid deterioration in glucose regulation in children as compared with adults may contribute to the greater risk for micro- and macrovascular complications in children with T2DM as they develop into adults.

3.1.2. Available therapies and unmet medical need

Management of T2DM in children involves lifestyle modifications. Pharmacologic glucose-lowering treatment is often necessary, including metformin, insulin, or a combination of both. Several GLP-1 receptor agonists have already been approved for use in paediatric patients. In addition, the SGLT2 inhibitor (dapagliflozin) has already been approved for use in paediatric patients aged 10 years and above. An ongoing study is investigating the efficacy and safety of canagliflozin in children and adolescents (>=10 to <18 Years) with type 2 diabetes mellitus.

3.1.3. Main clinical studies

PK/PD trial

Trial 1245.87 was a Phase I randomised, single-dose, parallel-group trial with 3 treatment arms with 1 dose of empagliflozin each (5 mg, 10 mg, and 25 mg).

Phase 3 trial design

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 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 increased to 25 mg empagliflozin. The trial also included a double-blind, active treatment safety extension period of up to 52 weeks: patients on placebo were re-randomised at Week 26 to receive either linagliptin or empagliflozin (10 mg or 25 mg).

Patients

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.

3.2. Favourable effects

HbA1c: primary outcome

For the primary outcome, the adjusted mean HbA1c change from baseline at week 26 was –0.84 % [-9.2 mmol/mol] in the empagliflozin pooled group versus placebo (95% CI -1.50 to –0.19 (-16.4 to -2.1]; p=0.012); the corresponding change from baseline for linagliptin versus placebo was –0.34% [-3.8 mmol/mol; 95% CI—0.99 to 0.30 [-10.8 to 3.3]; p=0.29).

Other endpoints

At Week 26, the trend for changes in FPG was consistent with HbA1c. No apparent changes over time in body weight, SBP, and DBP were observed for empagliflozin pooled versus placebo.

3.3. Uncertainties and limitations about favourable effects

HbA1c: 10 mg vs 25 mg

The weighted adjusted mean change in HbA1c values at week 26 in the dosing regimen up-titrating non-responders to empagliflozin 25 mg was -0.52% [-5.7 mmol/mol] versus the placebo group compared to baseline (95% C, -1.31 to 0.27 [-14.3 to 2.9]; p=0.19). The corresponding change from baseline in those who remained on 10 mg was -1.18% [-12.9 mmol/mol; 95% Cl -1.90 to -0.45 [-20.8 to -4.9]; p=0.0015).

The change in HbA1c [%] from Week 12 to the end of 26 weeks in patients randomised to empagliflozin 10 mg and not at glycaemic target (HbA1c <7.0%) at Week 12 was a further endpoint. Based on descriptive analysis (OC-AD) and small groups, the mean (SD) change from Week 12 to 26 for patients titrated to remain on 10 mg was −0.10% (0.71, n=10) and for those titrated to 25 mg was +0.52% (0.63, n=12).

The changes in HbA1c from Week 26 to 52 were also analysed for patients initially randomised to placebo and re-randomised at Week 26 to linagliptin 5 mg, empagliflozin 10 mg, or empagliflozin 25 mg. The number of patients was relatively low in each group (15 or 16 patients). The mean (SD) change at Week 52 for empagliflozin 10 mg was −0.35% (1.50) and for empagliflozin 25 mg −0.53% (1.13).

HbA1c: subgroups

The primary analysis results were consistent across subgroups. Efficacy was similar for individuals aged <15 and individuals aged >15-18 years. However, as expected, a trend towards a larger HbA1c reduction in patients with higher baseline HbA1c or FPG was observed for empagliflozin pooled vs placebo. In addition, the subgroup with time since diagnosis of T2DM of 1 to 3 years appeared to show a larger treatment effect than the other 2 subgroups.

3.4. Unfavourable effects

Up to Week 26, the rate of any AE in the empagliflozin pooled group was slightly higher than on placebo, while the rates of severe AEs, AEs leading to discontinuation, drug-related AEs, and SAEs were generally comparable with the rates on placebo.

Up to Week 26, there were no AEs leading to discontinuation of patients in the empagliflozin pooled group and 2 patients (3.8%) discontinued from placebo (PTs: acute pancreatitis, polyuria, and irregular menstruation, each reported for 1 patient [1.9%]). There was no relevant difference among treatment groups with regard to SAEs reported during this trial. Up to Week 26, 2 patients (3.8%) in each group (placebo and empagliflozin pooled) had SAEs. Up to Week 52, 3 patients (3.6%) in the empagliflozin active pooled group had SAEs. No patient had a fatal AE. Two patients had SAEs that were considered to be life-threatening: 1 patient on placebo and 1 patient on empagliflozin (suicidal ideation).

Two patients discontinued trial medication due to SAEs: acute pancreatitis (1 patient on placebo, medication code broken) and tubulointerstitial nephritis (1 patient on empagliflozin). The results of the AESIs and specific AEs were consistent with the known safety profile of empagliflozin in patients with T2DM. Up to Week 26, there were few patients with the following AESIs, and no imbalances in rates between placebo and the empagliflozin pooled group: hypersensitivity reactions, pancreatitis, hepatic

injury, decreased renal function, diabetic ketoacidosis (DKA), ketone measurements reported as AE, genital infection, arthralgia, and volume depletion. For DKA, there was no patient in the empagliflozin (active) pooled group who was reported with DKA.

There were no relevant differences between placebo and empagliflozin pooled with regard to heart rate and growth assessments (weight, height, BMI, and growth velocity).

3.5. Uncertainties and limitations about unfavourable effects

For hypoglycaemic events, up to Week 26, there were remarkably higher overall rates for patients in the empagliflozin pooled group compared with placebo (23.1 vs 9.4%), but there were no relevant differences among treatment groups with regard to rates of symptomatic hypoglycaemia. There were no severe hypoglycaemia events.

There were no relevant safety differences between empagliflozin 10 and 25 mg (including hypoglycaemia), but the groups were small.

Only limited safety data up to 52 weeks is available in the paediatric population. Although no new safety concerns emerge from the data presented, long-term safety in the paediatric population (aged 10 years and above) is missing.

3.6. Effects Table

Table 19 Effects Table for Jardiance

Effect	Short description	Unit	Jard.	Plac.	Uncertainties / Strength of evidence	References
Favourable Effects						
HbA1c	Change from baseline	%	−0.17	0.68	ETD −0.84 % (95% CI -1.50 to −0.19 (-16.4 to -2.1]; p=0.012) No additive efficacy of the 25 mg dose	Trial 1218.91
Unfavourable Effects						
Adverse events		%	64.2	40		Trial 1218.91
Serious adverse events		%	3.8	3.8		
Hypoglycaemia		%	23.1	9.4	No cases of severe hypoglycaemia	
Diabetic ketoacidosis		%	0	2		
Genital infections		%	2	2		
Urinary tract infections		%	6%	2%		

Abbreviations: ETD: estimated treatment effect compared to placebo

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In children from 10 to ⩽17 years of age, empagliflozin (10 mg and 25 mg combined) was associated with a clinically relevant decrease in HbA1c compared to placebo. However, the Hba1c change in non-responders on 10 mg was lower in those uptitrated to empagliflozin 25 mg (+0.52% since re-

randomisation) compared to those who remained on 10 mg (-0.10% since re-randomisation). The absence of any additional HbA1c lowering effect of the 25 mg dose is an important issue. Studies in adults have also shown that the added value of the 25 mg dose is very small compared to the 10 mg dose. However, the higher mean baseline HbA1c value in the 25 mg group and one outlier may explain the disappointing results in the 25 mg group. As there were no relevant differences between empagliflozin 10 and 25 mg in clinical safety, increasing the dose from 10 to 25 mg may be useful in some patients who tolerate the 10 mg dose and have insufficient glycaemic control.

In paediatric patients, no unexpected safety concerns were identified for empagliflozin (pooled doses) with regard to AEs, drug-related AEs, AESIs, safety laboratory parameters, and other safety parameters assessed in the paediatric programme.

However, for hypoglycaemic events, there were higher overall rates for patients in the empagliflozin pooled group compared with placebo (23.1 vs 9.4%). There were no relevant differences among treatment groups with regard to rates of symptomatic hypoglycaemia. In addition, there were no severe hypoglycaemia events. However, there was an increased risk of hypoglycaemia in patients using insulin as a background (14.3 vs. 32.0) as well as in patients without insulin background (6.3 vs. 14.8). A higher risk of hypoglycaemia with insulin as comedication is known in adults and mentioned in SmPC. The data above demonstrate that empagliflozin in paediatric patients is associated with an increased risk of hypoglycaemia, independent of insulin treatment. In the SmPC it has been stated that there were higher overall rates of hypoglycaemic events for patients in the empagliflozin pooled group compared with placebo (23.1 vs 9.4%).

Only limited safety data up to 52 weeks is available in the paediatric population. Although no new safety concerns emerge from the data presented, the potential need for long-term safety data in this population is important. Long term safety data in the paediatric population needs to be followed. The MAH committed to following this issue closely in all upcoming PSURs.

3.7.2. Balance of benefits and risks

The overall benefit-risk ratio is considered positive.

3.8. Conclusions

The Extension of Indication to include treatment of children 10 years and above is approvable. The updated product information and RMP are agreed.

The overall benefit risk balance of Jardiance is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for JARDIANCE to include treatment of children aged 10 years and above with type 2 diabetes based on results from study DINAMO 1218-0091; this is 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. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes in the product information. Version 21.1 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0283/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.