EMA/464344/2024
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Procedure No. EMEA/H/C/003770/II/0078

Invented name: Synjardy

International non-proprietary name: Empagliflozin / Metformin

Note

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

The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP/PRAC members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	02 Mar 2024	02 Mar 2024	☐
☐	CHMP Rapporteur Assessment Report	26 Apr 2024	23 Apr 2024	☐
☐	PRAC Rapporteur Assessment Report	03 May 2024	30 Apr 2024	☐
☐	PRAC members comments	07 May 2024	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	08 May 2024	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	16 May 2024	16 May 2024	☐
☐	CHMP members comments	21 May 2024	21 May 2024	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 May 2024	23 May 2024	☐
☐	Request for Supplementary Information	30 May 2024	30 May 2024	☐
☐	Re-start of procedure	22 Jul 2024	22 Jul 2024	☐
☐	CHMP Rapporteur Assessment Report	20 Aug 2024	20 Aug 2024	☐
☐	CHMP members comments	09 Sep 2024	09 Sep 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	12 Sep 2024	12 Sep 2024	☐
☒	Opinion	19 Sep 2024	19 Sep 2024	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Declarations

☒The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report, including in the Product Information, if any.

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 13 February 2024 an application for a variation.

The following changes were proposed:

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 to include the treatment of children aged 10 years and above with type 2 diabetes for Synjardy, based on the final results from study 1218-0091 (DINAMO) - 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, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 16.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/271/2011 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

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.

2. Recommendations

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

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 to include the treatment of children aged 10 years and above with type 2 diabetes for Synjardy, based on the final results from study 1218-0091 (DINAMO) - 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, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 16.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

☒is recommended for approval.

Amendments to the marketing authorisation

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

3. Scientific discussion

3.1. Introduction

3.1.1. Problem statement

Claimed therapeutic indication

The current application aims to add the following indication:

Synjardy is indicated in adults **and children aged 10 years and above** for the treatment of ~~**adults with**~~ type 2 diabetes mellitus as an adjunct to diet and exercise:

- in patients insufficiently controlled on their maximally tolerated dose of metformin alone
- in combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with metformin and these medicinal products
- in patients already being treated with the combination of empagliflozin and metformin as separate tablets.

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

3.1.2. About the product

Synjardy combines two anti-hyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: empagliflozin, an inhibitor of sodium glucose co transporter 2 (SGLT2), and metformin hydrochloride, a member of the biguanide class.

Empagliflozin
Empagliflozin is a reversible, highly potent (IC_{50} of 1.3 nmol) and selective competitive inhibitor of SGLT2. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation.

Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes and hyperglycaemia leads to excess glucose excretion in the urine. In addition, initiation of empagliflozin increases excretion of sodium resulting in osmotic diuresis and reduced intravascular volume.

Metformin
Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms: reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis; in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization; and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

3.1.3. General comments on compliance with GCP

Clinical studies supporting this submission were conducted in compliance with Good Clinical Practice guidelines.

3.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

3.2.1. Pharmacology

No new information has been provided, which is considered acceptable.

3.2.1. Pharmacokinetics

No new information has been provided, which is considered acceptable.

3.2.2. Toxicology

No new information has been provided, which is considered acceptable.

3.2.3. Ecotoxicity/environmental risk assessment

Introduction

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 Synjardy (empagliflozin / metformin) 5 mg/850 mg, 5 mg/1000 mg, 12.5 mg/850 mg, 12.5 mg/1000 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).

Statement on the Environmental Risk Assessment (ERA)

This statement refers to the current variation application for Synjardy to include the treatment of Type 2 Diabetes of paediatric patients.

Empagliflozin and metformin as monotherapies and the fixed dose combination (FDC) of empagliflozin and metformin are on the market. The maximum daily dose for the individual active substances and the FDC of empagliflozin and metformin are the same, i.e. 25 mg empagliflozin and 2000 mg metformin.

Environmental Risk Assessments (ERA) for empagliflozin and for metformin were submitted with the initial MAA. Additionally, an updated ERA for empagliflozin was submitted after completion of an additional study. The risk assessments resulted in the conclusion that no significant impact on the environment is expected.

In the ERAs for both active substances, the estimation of the predicted environmental concentration (PEC) of empagliflozin and metformin 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 25/2000 mg. The recommended maximum daily dose of the newly proposed paediatric indication will be the same as for the already approved indications.

Since the newly proposed paediatric indication can be considered an "orphan-like" indication, with a prevalence of only 0.6 – 2.7 / 100,000[1], the environmental exposure to the drug substance is considered negligible, and in consequence, the market penetration factor (Fpen) is refined as follows:

Fpen = Preg = **0.000027**

The PECsurface water is then calculated:

$$PEC_{surface\ water} = \frac{Dose(ai) \cdot F_{pen}}{Wastwater \cdot Dilution}$$

- $PEC_{surface\ water}$: *Predicted local surface water concentration* [mg L^{-1}]
- Dose(ai) = 25; 1000 : *Maximum daily dose of active ingredient consumed per patient* [mg d^{-1} $patient^{-1}$]
- Wastewater = 200 : *Amount of wastewater per inhabitant per day (default)* [L inh^{-1} d^{-1}]
- Dilution = 10 : *Dilution factor (default)* [-]
- F_{pen} = 0.00000057 : *Fraction of the overall market penetration (refined)* [-]

Refined PECsurface water for empagliflozin: **0.00034 µg/L**

Refined PECsurface water for metformin: **0.03 µg/L**

The PECsurface water for empagliflozin is clearly below the threshold of 0.01 µg/L for a Phase II environmental effect analysis including ERA studies.

The PECsurface water for metformin triggers a Phase II environmental assessment. Therefore, the refined PECsurface water of 0.03 µg/L for the newly proposed paediatric indication and the PECsurface water of 10.0 µg/L of the already approved indication are summed-up and the resulting PEC/PNEC ratios are updated.

For the calculation of the PEC/PNEC ratios in the various environmental compartments the PNEC values as mentioned in the original Environmental Risk Assessment [U11-2693-01] are used (see Table 1 and Table 2).

Table 1 PEC and PNEC values for metformin

Compartment	$PEC_{Type\ 2\ Diabetes}$ [µg/L]	$PEC_{all\ indications}$ [µg/L]	PNEC [µg/L]
Surface water	10.0	10.03	1300
Microorganisms	10.0[1]	10.03[1]	14100
Groundwater	2.5[2]	2.51[2]	2200

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

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

Table 2 PEC/PNEC ratios for metformin

Compartment	PEC/PNEC ratio Type 2 Diabetes	PEC/PNEC ratio all indications	Trigger for Tier B
Surface water	0.008	0.008	1
Microorganisms	0.0007	0.0007	0.1
Groundwater	0.001	0.001	1

Conclusion

The calculation of the PECsurface water for empagliflozin using a refined Fpen considering the prevalence for the orphan-like paediatric indication resulted in a PECsurface water of 0.00034 µg/L for the European Union, which is clearly below the threshold of 0.01 µg/L for a Phase II environmental effect analysis including ERA studies.

The calculation of the total PECsurface water for metformin for all proposed indications of Synjardy® resulted in PEC/PNEC ratios for all three compartments, which are clearly below the trigger values of 1 and 0.1, respectively.

Therefore, the use of Synjardy for all proposed indications can be considered to result in insignificant environmental risk.

3.2.4. Discussion on non-clinical aspects

The current application concerns an extension of the indication of Synjardy 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.

With respect to the Environmental Risk Assessment (ERA) for Synjardy, it is agreed with the MAH that the ERA conclusions, based on the previous ERA of empagliflozin and metformin, remain unchanged, meaning that the use of Synjardy for all proposed indications can be considered not to result in a significant environmental risk.

An updated ERA summary table for empagliflozin was submitted as the information on persistence (metabolite M3 and M12, see Jardiance, EMEA/H/C/002677/II/0076) has been changed.

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)	**vP** (for transformation products M3 in sediment, TP M12 in water)

		$DT_{50,\ 12°C\ sediment}$ =**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			
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)	0.125	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

3.2.5. Conclusion on the non-clinical aspects

Except for an Environmental Risk Assessment (ERA) for empagliflozin and for metformin, no new non-clinical data have been submitted in this application, which is considered acceptable for the extension of indication for Synjardy.

Based on the updated data submitted in this application, the extended indication does not lead to a significant increase in environmental exposure further to the already approved use of empagliflozin and of metformin. Considering the above data, empagliflozin and metformin are not expected to pose a risk to the environment.

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

3.3. Clinical aspects

3.3.1. Introduction

Synjardy contains the active substances empagliflozin (5 mg and 12.5 mg) and metformin (850 mg and 1000 mg).

Empagliflozin is an orally administered, potent, and highly selective SGLT-2 inhibitor. Empagliflozin is a medicine used to treat type 2 diabetes, chronic (long-term) heart failure and chronic kidney disease. In type 2 diabetes, empagliflozin is used in adults and children aged 10 years and above whose condition is not controlled well enough. In chronic heart failure (a condition in which the heart does not pump blood around the body as well as it should), empagliflozin is used in adults to treat symptoms of the disease. Empagliflozin is also used in adults with chronic kidney disease. In paediatric patients aged >10 years and adults, the recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other medicinal products for the treatment of diabetes. In patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 ml/min/1.73 m^2 and need tighter glycaemic control, the dose can be increased to 25 mg once daily.

Metformin is a medicine used to treat type 2 diabetes, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. In adults, the recommended starting dose is 500 mg or 850 mg metformin 2 or 3 times daily given during or after meals. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. In adults, the maximum recommended dose is 3000 mg daily, taken as 3 divided doses. In paediatric patients aged >10 years, the recommended starting dose is 500 mg or 850 mg metformin once daily given during or after a meal. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. In paediatric patients aged >10 years, the maximum recommended dose is 2000 mg daily, taken as 2 or 3 divided doses.

3.3.2. Pharmacokinetics

Empagliflozin

The PK data for the paediatric indication of empagliflozin in patients aged >10 years was submitted and assessed within procedure EMEA/H/C/002677/II/0076 for Jardiance (EPAR: https://www.ema.europa.eu/en/documents/variation-report/jardiance-h-c-002677-ii-0076-epar-assessment-report-variation_en.pdf). In the current variation application for the extension of the indication for Synjardy, PK data was provided for clinical studies 1245.0087 (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) and 1218-0091 (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).

Metformin

No PK data were provided for metformin.

3.3.3. Discussion on clinical pharmacology

No new PK data was submitted for empagliflozin and metformin within the current application.

The PK data for the paediatric indication of empagliflozin in patients aged >10 years was submitted and assessed in Procedure EMEA/H/C/002677/II/0076 for Jardiance (EPAR: https://www.ema.europa.eu/en/documents/variation-report/jardiance-h-c-002677-ii-0076-epar-assessment-report-variation_en.pdf). Empagliflozin is currently approved in the EU for the treatment of type II diabetes. In paediatric patients aged >10 years, the recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other medicinal products for the treatment of diabetes. The dose can be increased to 25 mg once daily.

Metformin is currently approved in the EU for the treatment of type II diabetes. In paediatric patients aged >10 years, the recommended starting dose is 500 mg or 850 mg metformin once daily given during or after a meal. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. In paediatric patients aged >10 years, the maximum recommended dose is 2000 mg daily, taken as 2 or 3 divided doses.

The dosing in paediatric patients is similar to already marketed (maximum dose of 25 mg empagliflozin and 2000 mg of metformin) and should be similar to the dose of the already prescribed individual components.

3.3.4. Conclusions on clinical pharmacology

The dosing in paediatric patients is similar to already marketed (maximum dose of 25 mg empagliflozin and 2000 mg of metformin) and should be similar to the dose of the individual components.

3.4. Clinical efficacy

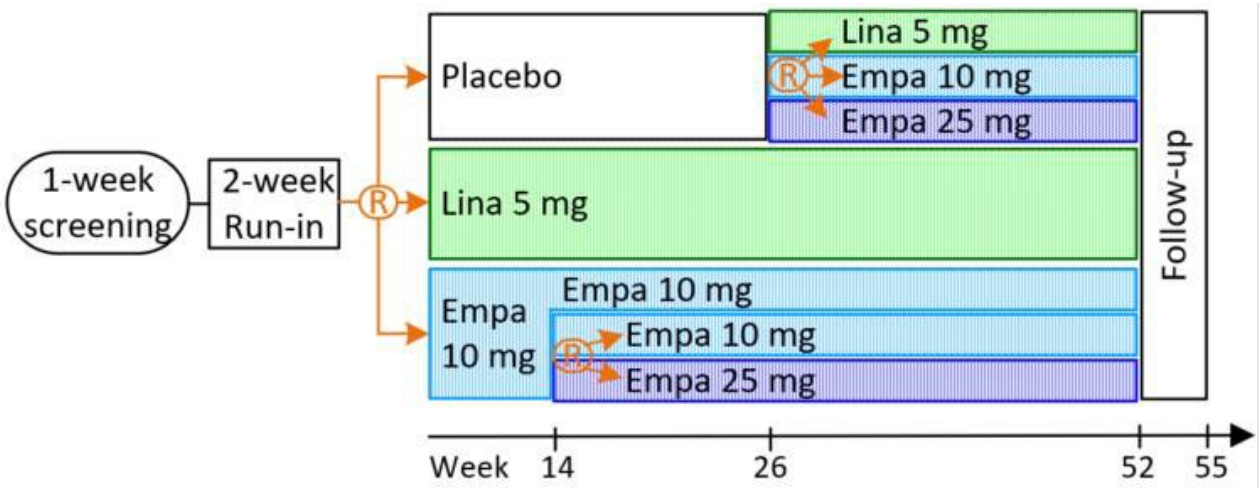
3.4.1. Main study

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).

Methods

This concerns a 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 HbA1c <7.0% at Week 12 (i.e. non-responders) were re-randomised at Week 14 to either continue with 10 mg empagliflozin or increase to 25 mg empagliflozin. The trial included a double-blind active treatment safety extension period up to 52 weeks: patients on placebo were re-randomised at Week 26 to receive either linagliptin or empagliflozin (10 mg or 25 mg) (Figure 1). The initial randomisation was stratified so that between 30% and 70% of randomised patients were <15 years of age and between 30% and 70% of randomised patients were female.

Figure 1: Overview of Trial Design



Study participants

Patients (10 to ≤17 years of age) with documented T2DM for at least 8 weeks at Visit 1A.

Main inclusion criteria:

- Male or female patients aged 10 to ≤17 years at the time of randomisation
- Documented diagnosis of T2DM for at least 8 weeks at Visit 1A
- Insufficient glycaemic control at Visit 1A: HbA1c ≥6.5% and ≤10.5%
- Patients treated with diet and exercise plus metformin (at least 1000 mg/day or up to a maximal tolerated dose) at a stable dose for 8 weeks prior to randomisation
  AND/OR
  diet and exercise plus stable insulin therapy (basal or multiple dose injection) for 8 weeks prior to randomisation. Stable insulin therapy was defined as a weekly average variation of the basal insulin dose ≤0.1 IU/kg over 8 weeks prior to randomisation
- Patients not tolerating metformin and treated with diet and exercise only

Main exclusion criteria

- Any history of acute metabolic decompensation such as diabetic ketoacidosis within 8 weeks prior to Visit 1A and up to randomisation (mild to moderate polyuria at the time of randomisation was acceptable)
- Diagnosis of monogenic diabetes (e.g. MODY)
- History of pancreatitis
- Diagnosis of metabolic bone disease
- Gastrointestinal disorders that might interfere with study drug absorption according to investigator assessment
- Secondary obesity as part of a syndrome (e.g. Prader-Willi syndrome)
- Any antidiabetic medication (with the exception of metformin and/or insulin background therapy for DINAMO) within 8 weeks prior to Visit 1A and until Visit 2

- Treatment with weight reduction medications (including anti-obesity drugs) within 3 months prior to Visit 1A and until Visit 2
- History of weight-loss surgery or current aggressive diet regimen (according to investigator assessment) at Visit 1A and until Visit 2
- Treatment with systemic corticosteroids for >1 week within 4 weeks prior to Visit 1A and up to Visit 2. Inhaled or topical use of corticosteroids (e.g. for asthma/chronic obstructive pulmonary disease) was acceptable
- Change in dose of thyroid hormones within 6 weeks prior to Visit 1A or planned change or initiation of such therapy before Visit 2
- Impaired renal function defined as eGFR <60 ml/min/1.73m² (according to Zappitelli formula)
- Indication of liver disease defined by serum level of either alanine transaminase (ALT), aspartate transaminase (AST) or alkaline phosphatase above 3-fold upper limit of normal (ULN)

Study or treatment discontinuation

Every effort was to be made to keep the randomised patients in the trial, if possible on treatment, or at least to collect important trial data. Patients who discontinued treatment prematurely were followed up until the end of the trial, unless they withdrew their consent for the trial participation. All assessments related to the primary and secondary endpoints (i.e. blood drawing for HbA1c and FPG, body weight, blood pressure and collection of adverse events and concomitant therapy) and safety laboratory tests had to be performed as if the patient had remained on trial treatment. For patients with a temporary trial drug discontinuation, every effort was to be made to re-introduce trial treatment unless the patient discontinued the trial treatment for safety reasons.

Treatments

Patients, investigators, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial remained blinded with regard to the randomised treatment assignments until after database lock.

Patients were randomised to receive either placebo, 5 mg linagliptin, or 10 mg empagliflozin. Patients receiving empagliflozin who did not achieve an HbA1c value <7% at Week 12, were re-randomised to receive either 10 mg or 25 mg empagliflozin. At Visit 5, patients on placebo were re-randomised to receive either 5 mg linagliptin or 10 mg empagliflozin or 25 mg empagliflozin.

Background therapy

Throughout the duration of the trial, patients were to continue to take their background therapy (metformin and/or insulin). The dose of background therapy at the time of screening was to be recorded in the eCRF. If medically appropriate, the dose and dosing frequency was to remain unchanged. For patients on insulin, the weekly average variation of the basal insulin dose was to remain ≤0.1 IU/kg.

For patients on insulin, investigators were advised to adjust the patient's total insulin dose based on need as assessed by frequent SBGM and close patient follow-up upon initiation of randomised trial medication. In all cases, the actual dose adjustment was dependent on individual glucose values. Thereafter and until the end of the trial, further adjustments to insulin therapy (both basal and, MDI insulin) may have been implemented as necessary to avoid hypoglycaemia and also hyperglycaemia to ensure that, in the investigator's opinion, the patient was achieving the best standard of care in accordance with local

guidelines. In addition, transfers to another type or brand of insulin as well as changes of the type of insulin pen were to be avoided.

Rescue medication
The use of rescue medication (i.e. insulin) was permitted from the first day of treatment (after randomisation) until the end of the trial.

With the exception of metformin and insulin used as background therapy, in any other situation than rescue condition, the use of any other antidiabetic agents was prohibited during the course of the trial.

Objectives

Outcomes/endpoints

Primary endpoint:

- Change in HbA1c (%) 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 HbA1c <6.5% at the end of 26 weeks
- Proportion of patients who achieve HbA1c <7.0% at the end of 26 weeks

Further endpoints:

- Change in HbA1c (%) 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 HbA1c <6.5% at the end of 52 weeks
- Proportion of patients who achieve HbA1c <7.0% at the end of 52 weeks
- Proportion of patients who achieve HbA1c 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 HbA1c (%) from Week 12 to the end of 26 weeks in patients randomised to empagliflozin 10 mg and not achieving glycaemic target at Week 12.

Safety criteria for evaluation

Safety was assessed descriptively after 26 and 52 weeks based on adverse events (AEs), adverse events of special interest (AESIs), and specific AEs. AESIs were prespecified in the clinical trial protocol as hypersensitivity reactions, skin lesions, pancreatitis, pancreatic cancer, hepatic injury, decreased renal function, diabetic ketoacidosis (DKA), and events involving lower limb amputation (LLA).

The analysis of specific AEs comprised hypoglycaemia, urinary tract infections, genital infections, acute pyelonephritis or urosepsis, bone fracture, arthralgia, pemphigoid in bullous conditions, volume depletion, and ketone measurements reported as AE. In addition, clinically relevant findings or changes in laboratory assessments, vital signs, and heart rate were assessed.

Sample size

Based on previous experience with empagliflozin and linagliptin in adults with T2DM, it was estimated that the mean change in HbA1c from baseline would be -0.55% for an active group treatment group (linagliptin or empagliflozin) compared with placebo, with a standard deviation of 0.9%.

The primary analysis of the primary endpoint intended to show superiority of pooled empagliflozin (10 mg and 25 mg) and of 5 mg linagliptin, each compared with placebo and tested simultaneously using the Hochberg procedure at the study-wise α of 0.05. With a covariate-adjusted standard deviation of 0.9 and assuming that the HbA1c values follow a normal distribution, a sample size of 50 patients per initial randomised treatment group (i.e. 150 patients in total) was needed to provide a power of 85% for the comparisons versus placebo. The lower bound of the expected power (considering the Hochberg correction for multiplicity) was 78% power with an α of 0.025, the same sample size of 50 per treatment group, and the same standard deviation of 0.9.

The sample size of 50 patients per initial randomised treatment group presents a balance of clinical, regulatory, ethical, feasibility, and statistical considerations. The objective was to minimise exposure of children, given that the available paediatric population is also limited in number, while maintaining acceptable statistical properties.

It was planned to recruit 150 patients from approximately 110 trial sites in this trial.

Randomisation

Randomisation was stratified by age category (<15 years; ≥15 to <18 years); at least 30% but no more than 70% of randomised patients were to be <15 years of age. Additionally, between 30% and 70% of randomised patients had to be female.

Screening of patients for this trial was competitive, i.e. screening for the trial stopped at all centres when the target number of randomised patients was achieved. Investigators were notified when screening was complete and were not allowed to recruit additional patients thereafter. Patients who had completed screening procedures prior to the notification of the termination of recruitment were allowed to be randomised in the trial, if they met all eligibility criteria. Re-screening and/or re-testing (of assessments) was permitted.

Blinding (masking)

During the open-label placebo run-in, patients took 3 tablets once daily, i.e. placebo-matching linagliptin, placebo-matching 10 mg empagliflozin, and placebo-matching 25 mg empagliflozin tablets. During the randomised treatment period (double-blind, double dummy), patients took also 3 tablets once daily. Patients randomised to placebo took 3 placebo tablets and patients randomised to active medication took 1 tablet with active medication and 2 placebo tablets.

Statistical methods

The sample size for this trial is powered to detect as primary endpoint a change of 0.55% HbA1c (MCID 0.50), with a power of 0.78, a SD of 0.9 and a two-sided alpha of 0.05, which results in approximately 50 patients per arm (including loss to follow-up etc). A range of appropriate secondary endpoints are included as well, which will be multi-test corrected with Hochberg. A randomisation is performed, which should include between 30-70% female patients and, and 30-70% patients below 15 yo. All trial arms included 3 tablets, as two different medications and placebo are tested. Furthermore a range of additional analyses are outlined in the appendix. This includes (among others) a bayesian borrowing analysis, due to the mentioned SD of 0.9 apparently not being a robust value, and a blinded analysis indicating a SD of 1.6. This analysis is meant to further support the claim. This analysis was not prespecified, and is not sufficiently outlined in the supporting documents. The result of these analyses also do not impact the overall outcome, as the arm was successful despite the increased SD. Other methods include a MMRM, which is suitable for this type of data, and descriptive statistics.

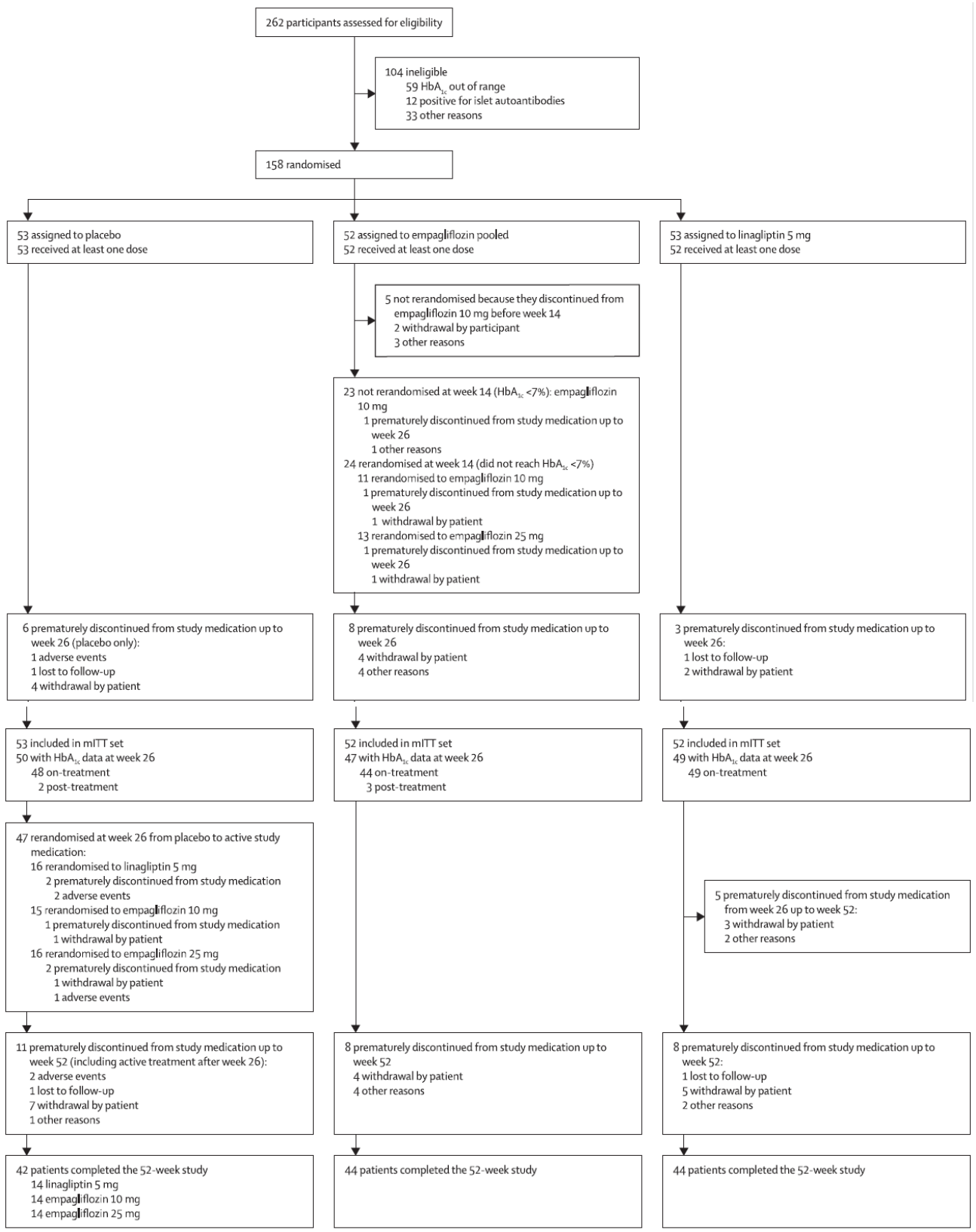
Results

Despite the current variation concerns empagliflozin and 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.

Participant flow

The participant flow of study 1218.91 is depicted in Figure 2. About 40% of the screened patients were not randomised, most commonly because the inclusion criterion 'insufficient glycaemic control (HbA1c $\geq$ 6.5% and $\leq$10.5%)' was not met (56.7% of patients) or the exclusion criterion 'positive for islet cell antigen auto-antibodies and glutamic acid decarboxylase auto-antibodies' was met (11.5% of patients). Re-screening was possible up to 5 times with at least 8 weeks between screening visits.

Figure 2: Participant Flow



Recruitment

Trial 1218.91 was carried out at 78 clinical sites in 13 countries in Asia, Europe, North and South America (Table 1).

Table 1: Overview of screened and randomised patients by region

Geographical region	Countries	Patients screened N	Patients randomised N
Total	13 countries	262	158
North America	Canada, United States	162	108
South America	Argentina, Brazil, Colombia, Mexico	57	27
Europe	Germany, Israel, Russian Federation, United Kingdom	32	18
Asia	China, Korea, Thailand	11	5

Conduct of the study

Baseline data

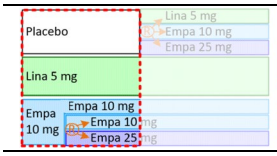
Baseline was defined as the last observed measurement prior to administration of any initially randomised trial medication at Day 1. For patients randomised but not treated, the measurement on or prior to the date of randomisation was used instead of prior to date of trial drug intake.

The results for demographics, baseline characteristics, medical history, and concomitant medications were generally balanced across the 3 treatment groups, according to the Investigator. Details are provided in Table 1 and Table 3.

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%).

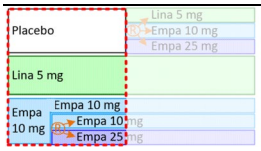
Patients with insufficient glycaemic control of HbA1c ≥6.5% and ≤10.5% could participate in this trial. About half of the patients had baseline HbA1c values of <8%; for the remaining patients, approximately similar proportions had either HbA1c values of 8.0% to 9.0% or of >9%. The mean baseline FPG was 158.70 mg/dL (SD 55.56). The mean weight was 99.92 kg (SD 26.78), and the maximum weight was 171.0 kg. The majority of patients had SBP <140 mmHg and DBP <90 mmHg. The mean fasting C-peptide values at baseline were 0.9932 nmol/L. The mean eGFR was 129.79 mL/min/1.73 m2. 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).

Table 2: Demographic data at baseline



	Placebo		Lina 5		Empa pooled		Total	
Treated patients (N, %)	53	100.0	52	100.0	52	100.0	157	100.0
Sex (N, %)								
Male	19	35.8	22	42.3	19	36.5	60	38.2
Female	34	64.2	30	57.7	33	63.5	97	61.8
Race (N, %)								
American Indian/Alaska Native	1	1.9	3	5.8	4	7.7	8	5.1
Asian	3	5.7	4	7.7	2	3.8	9	5.7
Black/African American	17	32.1	13	25.0	19	36.5	49	31.2
Native Hawaiian or other Pacific Islander	1	1.9	2	3.8	0		3	1.9
White	29	54.7	26	50.0	23	44.2	78	49.7
Other including mixed or missing race	2	3.8	4	7.7	4	7.7	10	6.4
Ethnicity (N, %)								
Not Hispanic or Latino	32	60.4	30	57.7	35	67.3	97	61.8
Hispanic or Latino	21	39.6	22	42.3	17	32.7	60	38.2
Region (N, %)								
Asia	1	1.9	3	5.8	1	1.9	5	3.2
Europe	7	13.2	5	9.6	6	11.5	18	11.5
North America	34	64.2	37	71.2	36	69.2	107	68.2
South America	11	20.8	7	13.5	9	17.3	27	17.2
Age [years] at informed consent (mean, SD)	14.6	1.8	14.6	1.9	14.4	1.9	14.5	1.9
Age [years] at randomisation (N, %)								
<15	26	49.1	25	48.1	25	48.1	76	48.4
≥15 to <18	27	50.9	27	51.9	27	51.9	81	51.6
BMI [kg/m^2] (mean, SD)	36.07	10.07	36.50	7.55	35.54	7.17	36.04	8.33
Time since diagnosis of T2DM in categories (N, %)								
<1 year	18	34.0	16	30.8	17	32.7	51	32.5
1 year to 3 years	24	45.3	21	40.4	21	40.4	66	42.0
>3 years	11	20.8	15	28.8	14	26.9	40	25.5
Tanner stage (N, %)								
1	0		0		0		0	
2 to 4	21	39.6	19	36.5	24	46.2	64	40.8
5	32	60.4	33	63.5	28	53.8	93	59.2

Table 3: Baseline efficacy variables



	Placebo		Lina 5		Empa pooled		Total	
Treated patients (N, %)	53	100.0	52	100.0	52	100.0	157	100.0
HbA_{1c} [%] (mean, SD)	8.05	1.23	8.05	1.11	8.00	1.29	8.03	1.20
HbA_{1c} [%] (N, %)								

<8.0	29	54.7	26	50.0	28	53.8	83	52.9
8.0 to 9.0	12	22.6	16	30.8	12	23.1	40	25.5
>9.0	12	22.6	10	19.2	12	23.1	34	21.7
FPG [mg/dL] (mean, SD)	158.62	53.80	162.81	56.01	154.43	57.78	158.70	55.56
Weight [kg] (mean, SD)	98.38	29.55	102.76	26.40	98.66	24.35	99.92	26.78
Blood pressure [mmHg] (N, %)								
SBP ≥140 or DBP ≥90	3	5.7	6	11.5	1	1.9	10	6.4
SBP <140 and DBP <90	50	94.3	46	88.5	51	98.1	147	93.6
Fasting C-peptide [nmol/L] (mean, SD)	0.8967	0.4311	1.1245	0.6269	0.9598	0.5302	0.9932	0.5400
eGFR[1] [mL/min/1.73 m²] (mean, SD)	124.28	22.96	135.11	36.42	130.09	26.78	129.79	29.39
UACR [mg/g crea] (N, %)								
<30 (normal)	40	75.5	36	69.2	40	76.9	116	73.9
30 to 300 (microalbuminuria)	9	17.0	14	26.9	10	19.2	33	21.0
>300 (macroalbuminuria)	3	5.7	2	3.8	1	1.9	6	3.8

1 According to Zappitelli et al.

Use of metformin at baseline

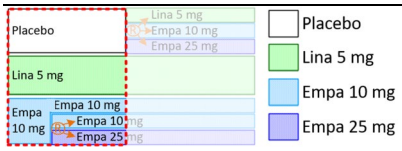
As defined in the inclusion criteria, the trial included patients who were treated with diet and exercise plus a stable dose of metformin and/or insulin or who were not tolerating metformin. About half of the patients (85 patients, 54.1%) took 1 background antidiabetic treatment and 63 patients (40.1%) took 2 background antidiabetic medications (

Table **4**). There were 80 patients (51.0%) with only metformin as background antidiabetic therapy, 5 patients (3.2%) with only insulin treatment, 63 patients (40.1%) with metformin and insulin treatment, and 9 patients (5.7%) with no background antidiabetic medication. The mean total daily dose of metformin at baseline was 1661.5 mg and the mean total daily dose of insulin was 54.3 IU/day.

For the patients on metformin (with or without insulin) the mean (SD) daily dose at baseline in the empagliflozin pooled group was 1561.5 (482.7) mg and in placebo group 1718.1 (583.5) mg. The mean (SD) total daily dose of metformin at Week 52 was 1610.5 (524.8) mg in the empagliflozin pooled group.

In the majority of patients metformin dose remained unchanged during the study: 42 (87.5%) in the empagliflozin pooled group and 42 (89.4%) in the placebo group from baseline to visit Week 26 and 38 (79.2%) in the empagliflozin pooled group up to Week 52.

Table 4: Background antidiabetic treatment at baseline



	Placebo		Lina 5		Empa pooled		Total	
Treated patients (N, %)	53	100.0	52	100.0	52	100.0	157	100.0
Number of background antidiabetic medications (N, %)								
0	4	7.5	4	7.7	1	1.9	9	5.7
1	30	56.6	26	50.0	29	55.8	85	54.1
2	19	35.8	22	42.3	22	42.3	63	40.1
Background antidiabetic treatment (N, %)								
Metformin only	28	52.8	26	50.0	26	50.0	80	51.0
Insulin only	2	3.8	0		3	5.8	5	3.2
Metformin and insulin	19	35.8	22	42.3	22	42.3	63	40.1
None (diet and exercise only, metformin not tolerated)	4	7.5	4	7.7	1	1.9	9	5.7

Numbers analysed

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

	Placebo		Lina 5		Empa pooled		Total	
	N	%	N	%	N	%	N	%
Randomised set (RS)	53	100.0	53	100.0	52	100.0	158	100.0
Treated set (TS; % of RS)	53	100.0	52	98.1	52	100.0	157	99.4
Modified intention-to-treat set (mITT; % of TS)	53	100.0	52	100.0	52	100.0	157	100.0
Per-protocol set (PPS; % of mITT)	44	83.0	49	94.2	45	86.5	138	87.9

Outcomes and estimation

Compliance

Up to week 26, 8 patients (15.4%) in the empagliflozin pooled population prematurely discontinued the trial drug, compared with 6 patients (11.3%) on placebo. This remained stable up to 52 weeks for empagliflozin patients and increased to 11 patients (20.8%) on placebo. The most common reasons for premature discontinuation of trial drug up to Week 26 were withdrawal by patient (10 patients, 6.4%) and other reasons like discontinuation, exclusion criterion met, and non-compliance (in total 4 patients, 2.5%).

Non-compliance with trial drug intake was reported for 3 patients (5.8%) in the empagliflozin pooled population and 7 (13.2%) in the patients on placebo.

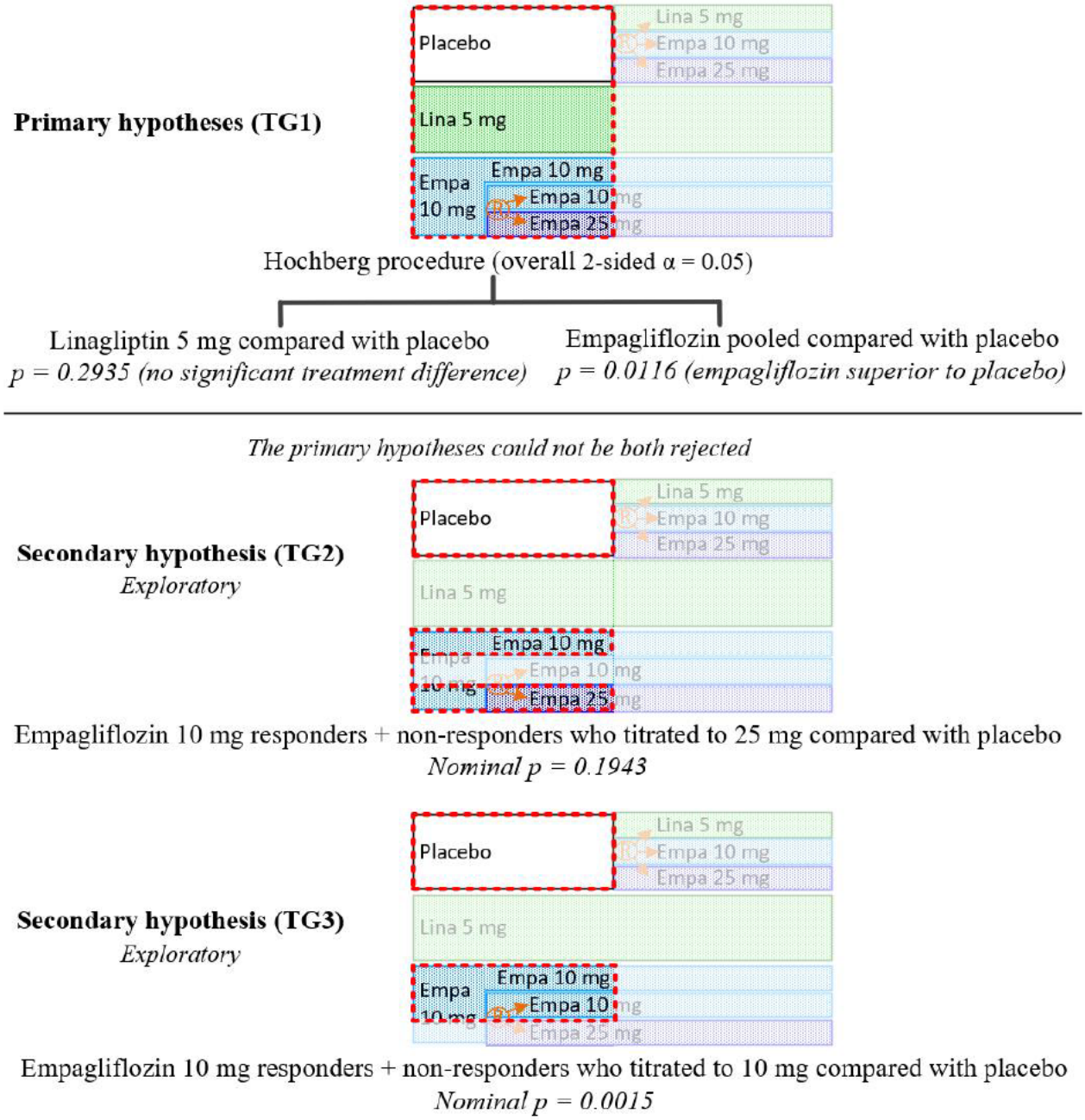
Primary endpoint

The primary endpoint was the change in HbA1c [%] from baseline to the end of 26 weeks. Based on TG1 (box with dashed red line in Figure 3), 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 HbA1c from baseline after 26 weeks (Table 5).

Based on TG1 and according to the Hochberg procedure, the null hypothesis that there is no difference between the effect of placebo and linagliptin 5 mg was not rejected ($p \geq 0.05$), whereas the null hypothesis that there is no difference between the effect of placebo and empagliflozin pooled was rejected ($p < 0.025$; Figure 3).

Since the primary hypotheses (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.

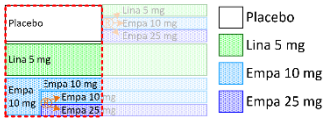
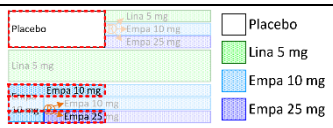
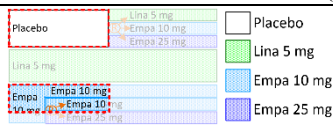
Figure 3: Hierarchical testing results



Based on TG2 (Table 5, box with dashed red line), 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 HbA1c of −0.52% (95% CI: −1.31% to 0.27%) at Week 26, although the effect had a nominal p-value of 0.1943.

Based on TG3 (Table 5, box with dashed red line), 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 HbA1c 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).

Table 5: HbA1c [%] change from baseline at Week 26, ANCOVA – mITT (OC-AD)

Treatment	N analysed	Baseline Mean	Baseline SD	Change from baseline Adjusted mean	Change from baseline 95% CI		Comparison vs placebo Adjusted mean	Comparison vs placebo 95% CI		Comparison vs placebo 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)

On request, an additional (subgroup) analysis was performed on the primary endpoint, for patients on metformin (with or without insulin), see Table 6.

Table 6: HbA1c [%] change from baseline at Week 26, ANCOVA – mITT (OC-AD) (only patients with metformin)

Treatment	N analysed	Baseline Mean	Baseline SD	Change from baseline Adjusted mean	Change from baseline 95% CI		Comparison vs placebo Adjusted mean	Comparison vs placebo 95% CI		Comparison vs placebo p-value
Primary hypotheses based on TG1, multiple imputation with wash-out approach										
Placebo	47	8.12	1.22	0.59	0.11	1.06				
Lina 5	48	7.99	1.09	0.37	−0.11	0.85	−0.22	−0.89	0.46	0.5261
Empa pooled	48	8.05	1.32	−0.18	−0.67	0.32	−0.76	−1.45	−0.08	0.0295

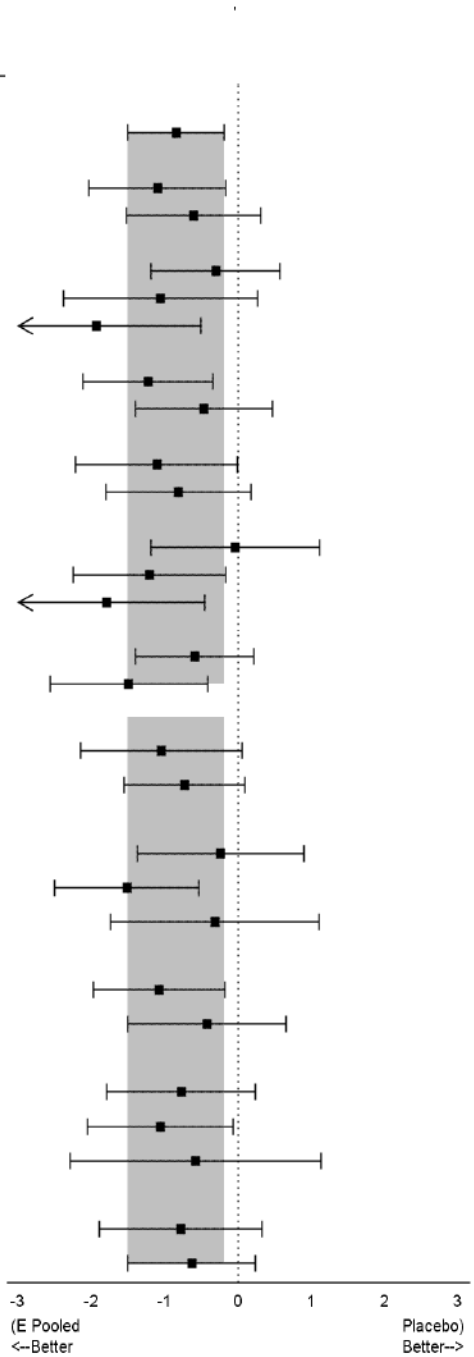
Subgroup analyses

For empagliflozin pooled vs placebo, a trend towards the higher the baseline HbA1c or FPG the more treatment effect in HbA1c 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; this effect was mainly

contributed by a larger mean increase in HbA1c from baseline in the placebo group of 1.15% (Figure 4). The primary analysis results were consistent across the rest of the subgroups.

Figure 4: Empagliflozin – subgroup analysis 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



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).

Secondary and further endpoints

All secondary endpoints were considered exploratory.

Change in FPG, body weight, SBP and DBP from baseline to the end of 26 weeks, and from baseline to the end of 12 and 52 weeks

FPG

The adjusted mean change from baseline at Week 26 in FPG compared with placebo for empagliflozin pooled was −35.18 mg/dL (95% CI: −58.61 to −11.74) (Table 7). The change in FPG from baseline to the end of 52 weeks was a further endpoint. The mean (SD) change from baseline at Week 52 for empagliflozin pooled was −4.94 (66.57) mg/dL.

In the subpopulation of patients with metformin background therapy the adjusted mean change from baseline at Week 26 was −38.28 mg/dL (95% CI: −60.47 to −16.10). The change in FPG from baseline to the end of 52 weeks was −6.81 (57.84) mg/dL.

Body weight

The mean (SD) change in body weight was for empagliflozin pooled −0.75 kg (95% CI: −2.68 to 1.19) compared with placebo (Table 7). In all treatment groups, no obvious changes in body weight over time were observed according to the Investigator (Figure 5).

In the subpopulation of patients with metformin background therapy the adjusted mean change in body weight (OC-AD) at Week 26 for empagliflozin pooled was −0.89 kg (95% CI: −2.90 to 1.13) compared with placebo. *Systolic and diastolic blood pressure (SDP) (DBP)*

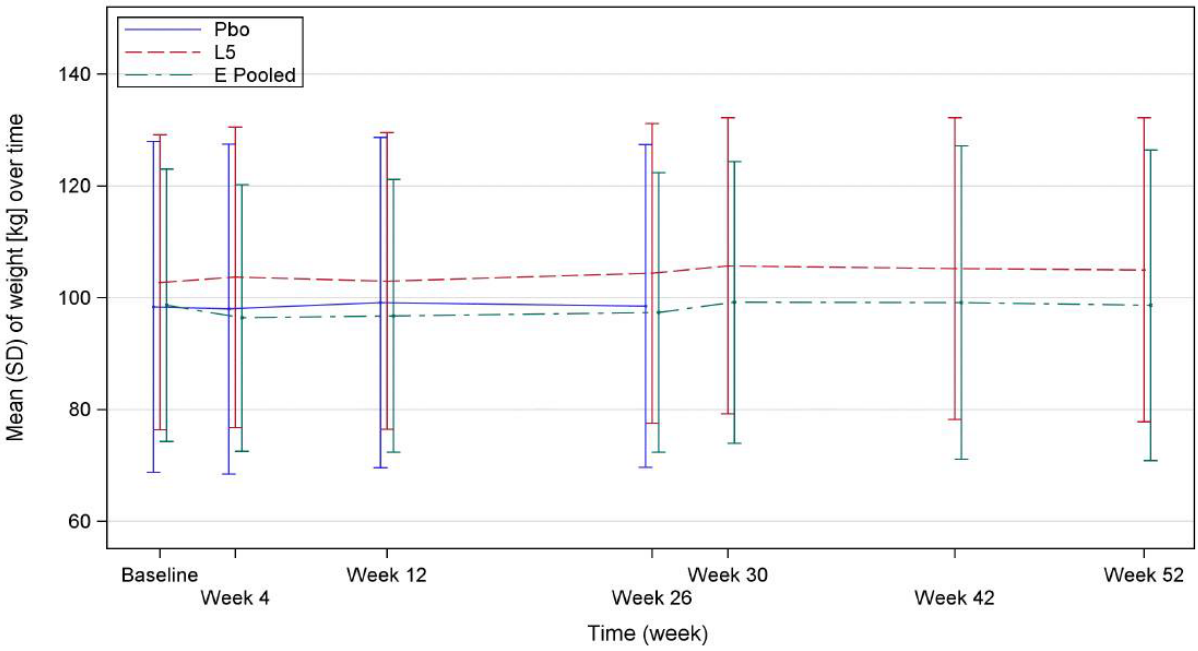
Compared with placebo, the adjusted mean change from baseline at Week 26 for empagliflozin pooled in SBP was −1.42 mmHg (95% CI: −4.72 to 1.88), and in DBP was 0.02 mmHg (95% CI: −2.52 to 2.56) (Table 7), for the subpopulation of patients with metformin background therapy this was, −1.49 mmHg (95% CI: −4.94 to 1.96) for SBP, and 0.46 mmHg (95% CI: −2.29 to 3.20) for DBP. In all treatment groups, no obvious changes in SDP and DBP over time were observed according to the Investigator (Figure 6, Figure 7).

Table 7: Secondary endpoints based on FPG, body weight, SBP and DBP: change from baseline at Week 26 – mITT (TG1)

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.)

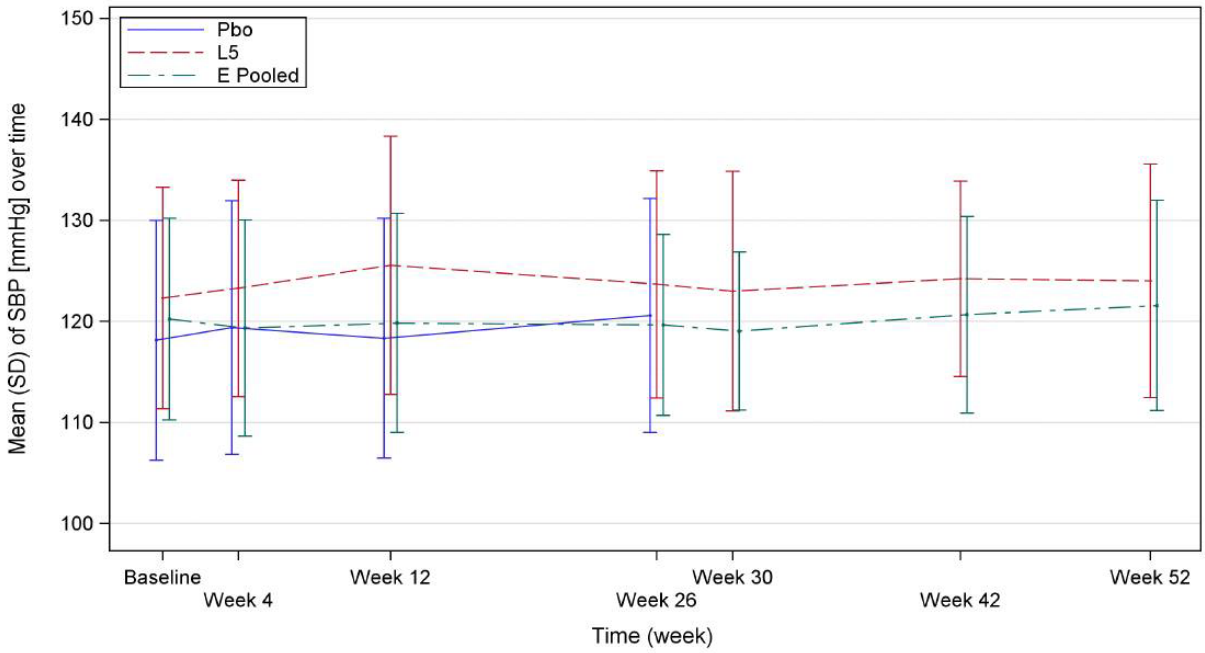
Figure 5: Descriptive statistics of body weight [kg] over time up to Week 52 – mITT (TG1, TG5) (OC-AD)



Number of patients							
Pbo	53	50	52	50	0	0	0
L5	52	49	50	49	47	47	47
E Pooled	52	49	48	48	44	44	47

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

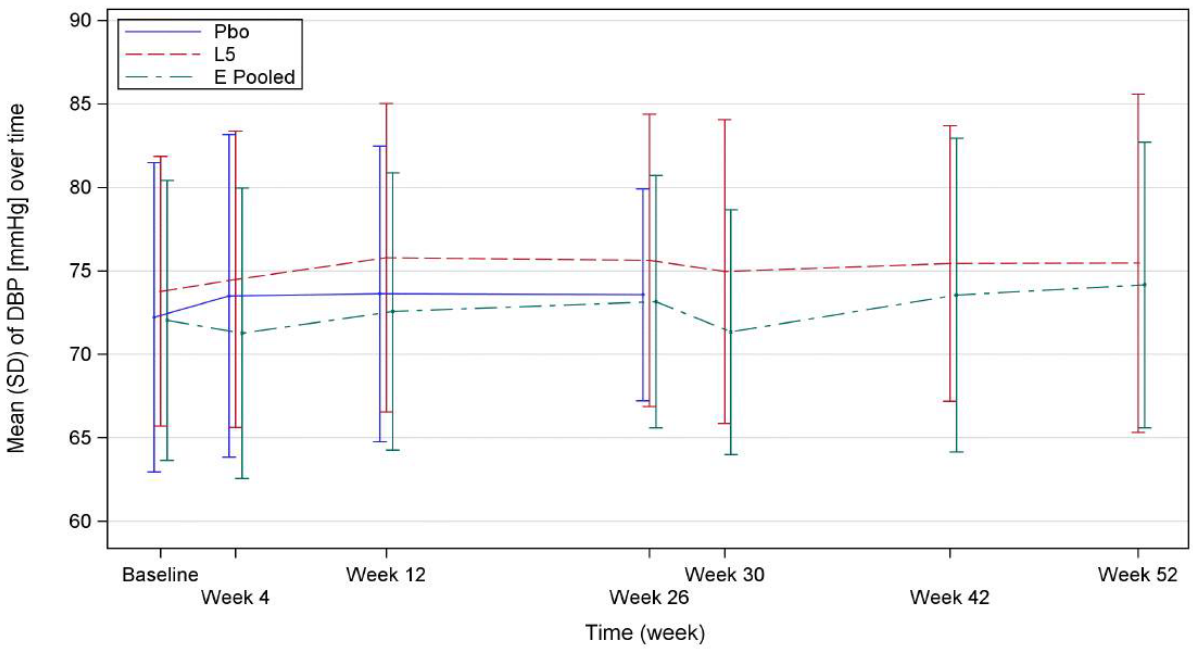
Figure 6: Descriptive statistics of SBP [mmHg] over time up to Week 52 – mITT (TG1, TG5) (OC-AD)



Number of patients							
Pbo	53	50	52	50	0	0	0
L5	52	49	50	49	47	47	47
E Pooled	52	49	48	48	44	44	46

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

Figure 7: Descriptive statistics of DBP [mmHg] over time up to Week 52 – mITT (TG1, TG5) (OC-AD)



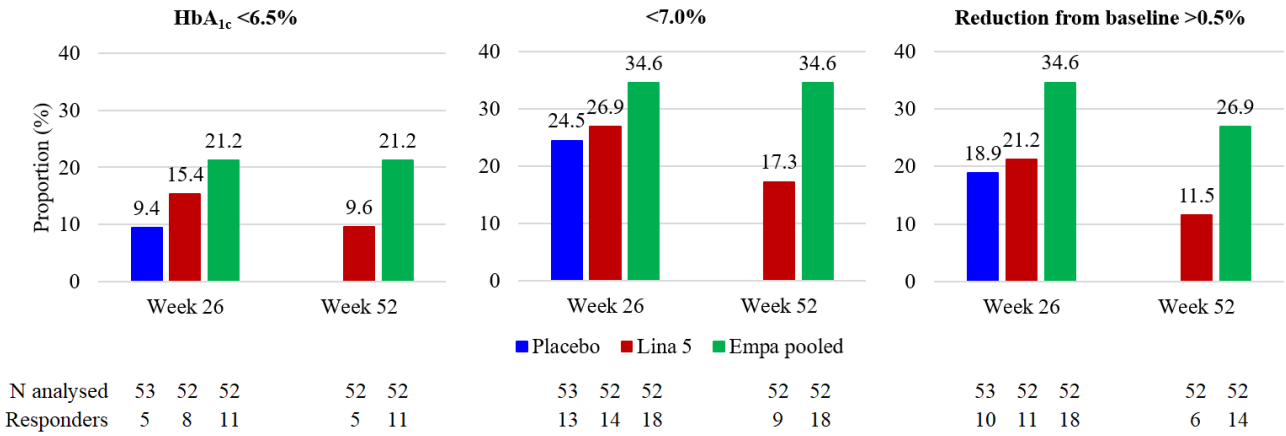
Number of patients							
Pbo	53	50	52	50	0	0	0
L5	52	49	50	49	47	47	47
E Pooled	52	49	48	48	44	44	46

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

Proportion of patients who achieve HbA1c <6.5% or HbA1c <7.0% at the end of 26 weeks

The rate difference to placebo for the proportion of patients for empagliflozin pooled achieving HbA1c <6.5% at Week 26 was 11.7% (95% CI: −2.4 to 26.3) and for achieving HbA1c <7.0% at Week 26 was 10.1% (95% CI: −7.7 to 28.1) (Table 7). At Week 52, the proportion of patients achieving HbA1c <6.5% or HbA1c <7.0% remained stable for empagliflozin pooled (Figure 8).

Figure 8: Proportion of patients who achieved a response based on HbA1c – mITT (TG1, TG5) (NCF)



For only patients with metformin background therapy, the rate difference of patients achieving HbA1c <6.5% at Week 26 of empagliflozin pooled versus placebo was 10.2% (95% CI: −5.4 to 26.0) and for achieving HbA1c <7.0% at Week 26 was 9.9% (95% CI: −9.6 to 28.3). At Week 52, the proportion of patients achieving HbA1c <6.5% (11 patients (22.9%)) or HbA1c <7.0% (17 patients (35.4%)) remained stable for empagliflozin pooled.

Glycaemic rescue therapy (new antidiabetic treatment or an >0.1IU/kg increase of basal insulin)

Up to Week 26 (based on TG1), 6 patients (11.3%) in the placebo group, and 5 patients (9.6%) in the empagliflozin pooled group initiated glycaemic rescue therapy. Up to Week 52 (based on TG5), 6 patients (11.5%) in the empagliflozin pooled group initiated glycaemic rescue therapy. For only patients on metformin background therapy this was, 5 patients (10.6%) in the placebo group, and 4 patients (8.3%) in the empagliflozin pooled group (Week 26) and up to Week 52, 4 patients (8.3 %).*Change in fasting serum C-peptide [nmol/L] from baseline to the end of 26 and 52 weeks*

The median (Q1, Q3) change from baseline at Week 26 for placebo was −0.0248 (−0.2459, 0.1155) nmol/L and for empagliflozin pooled −0.0858 (−0.1815, 0.0330) nmol/L. The median (Q1, Q3) change from baseline at Week 52 for empagliflozin pooled was −0.0347 (−0.2921, 0.1782) nmol/L.

Urine albumin creatinine ratio (UACR) [mg/g crea] from baseline to the end of 26 and 52 weeks

The median (Q1, Q3) change from baseline at Week 26 for placebo was 2.33 (−0.60, 6.50) mg/g and for empagliflozin pooled 1.40 (−9.23, 4.48) mg/g, and at Week 52 −0.21 (−4.94, 7.43) mg/g for empagliflozin pooled. For any treatment group, no obvious change in UACR over time were observed.

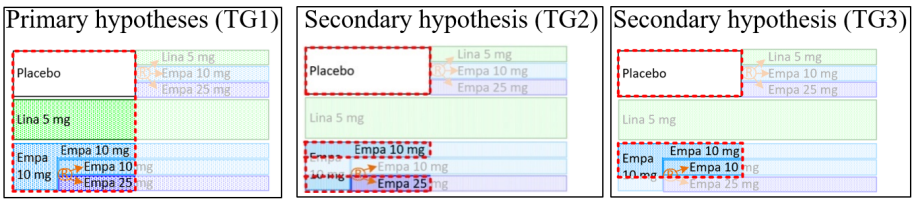
Change in eGFR [mL/min/1.73m²] from baseline to the end of 26 and 52 weeks

The mean (SD) change from baseline at Week 26 for placebo was 3.39 (12.81) mL/min/1.73m and for empagliflozin pooled −2.22 (17.74) mL/min/1.73m², and the mean (SD) change from baseline at Week 52 was −3.27 (19.36) mL/min/1.73m² for empagliflozin pooled. For any treatment group, no obvious change in eGFR over time were observed.

Ancillary analyses

Summary of main study

The following tables summarise 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>
<tr><td colspan="4">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)</td></tr>
<tr><td>Study identifier</td><td colspan="3">1218.91 (DINAMO)</td></tr>
<tr><td>Design</td><td colspan="3">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).</td></tr>
<tr><td></td><td>Duration of main phase
Duration of Run-in phase
Duration of Extension phase</td><td colspan="2">26 weeks
2 weeks placebo
26 weeks</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority of linagliptin vs placebo and empagliflozin vs placebo</td></tr>
<tr><td rowspan="3">Treatment groups</td><td>Linagliptin</td><td colspan="2">Linagliptin 5 mg once daily, up to 52 weeks, 53 patients initially randomised</td></tr>
<tr><td>Empagliflozin</td><td colspan="2">Empagliflozin once daily pooled (10 mg + 25 mg), up to 52 weeks, 52 patients initially randomised</td></tr>
<tr><td>Placebo</td><td colspan="2">Placebo once daily, up to 26 weeks, 53 patients initially randomised</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint</td><td colspan="2">Change in HbA_{1c} (%) from baseline to the end of 26 weeks</td></tr>
<tr><td>Database lock</td><td colspan="3">10 Aug 2022</td></tr>
<tr><td colspan="4">Results and Analysis</td></tr>
<tr><td>Analysis description</td><td colspan="3">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">Primary endpoint, mITT, after 26 weeks of treatment
 
</td></tr>
</table>

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 hypothesis (TG2; exploratory)	Comparison groups	Empagliflozin 10 mg + titrated to 25 mg vs placebo
		Adjusted mean	−0.52
		95% CI	−1.31, 0.27
		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.		

3.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The current variation subject to this assessment aims to extend the already approved indications (all in adults) to:

"**the treatment of children aged 10 years and above** with type 2 diabetes mellitus as an adjunct to diet and exercise:

- when treatment with both empagliflozin and metformin is appropriate
- inadequately controlled with metformin alone or in combination with insulin (see section 5.1)
- in patients already being treated with the combination of empagliflozin and metformin as separate tablets."

Study design

The design and conduct of trial 1218.91 (DINAMO) have also been considered in the extension of indication for empagliflozin to children aged 10 years and over (EMEA/H/C/002677/II/0076). In brief, trial 1218.91 (DINAMO) was a Phase III randomised, double-blind, placebo-controlled parallel group trial with 3 treatment arms (placebo, 5 mg linagliptin, 10 mg empagliflozin) lasting 26 weeks in children from 10 to ≤17 years of age.

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

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. However, it should be noted, that the fixed combination medicinal products (FCMP) of empagliflozin 5 mg/ 12.5mg and metformin 850mg/ 1000mg has not been used in this trial.

Inclusion and exclusion criteria

One of the key inclusion criteria was treatment with metformin and/ or insulin, or not tolerating metformin and treated without antidiabetic medication. Almost all included empagliflozin patients (n=48, 92.3%) were on background metformin treatment. Consequently, almost none of the patients were not on background metformin treatment. Overall, the inclusion and exclusion criteria are considered acceptable.

Patient' characteristics

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.

The sample size calculation, including all parameters, are mostly standard, and therefore acceptable.

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.

In total, 92.3% of the empagliflozin patients were concomitantly treated with metformin, with (42.3%) or without (50.0%) insulin at baseline. Of the placebo treated patients, 88.6% of patients were treated with metformin, with (35.8%) or without (52.8%) insulin. The mean total daily dose of metformin (with or without insulin) remained stable during the study.

Primary outcome: HbA1c change

In the context of the current variation, the HbA1c change from baseline to 26 weeks in patients who are on metformin background therapy are considered most relevant. Compared with placebo, patients on empagliflozin pooled had a mean HbA1C reduction of 1.07% (95% CI -0.97; -0.18) without background use of insulin and -0.42% (95% CI -1.50, 0.66) with insulin. These results are in line with the HbA1C reduction of 0.84% in the empagliflozin pooled population.

The previous results are consistent with the change in HbA1c in adults from baseline to 24 weeks; -0,57% (95% CI -0,72; -0,42) for adult patients on 10 mg empagliflozin and -0,64% (95%CI -0,79; -0,48) for adult patients on 25 mg.

The other endpoint related to change in HbA1c are not for patients on the combination of empagliflozin and metformin and are therefore considered less relevant for the current variation.

Secondary and other outcomes

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 in all empagliflozin treated patients. These results were not stratified according to background metformin use and are therefore considered less relevant for the current variation.

Generalisability from study results to current variation

Trial 1218.91 (DINAMO) was intended to assess efficacy of empagliflozin (and linagliptin) compared with placebo. As mentioned by the MAH, >90% of patients on empagliflozin included in the study concomitantly used metformin, either with or without insulin. As the data for patients only on metformin are comparable to the overall population, the data from the DINOMA trail can be used.

3.4.3. Conclusions on the clinical efficacy

In children from 10 to ⩽17 years of age with background metformin treatment, empagliflozin (10 mg and 25 mg combined) was associated with a clinically relevant decrease in HbA1c compared to placebo. However, as all other endpoints were not stratified on background metformin therapy, these cannot be assessed in the context of the current variation.

3.5. Clinical safety

The trial 1245.87 was a single dose PK/PD trial. In this trial, all 3 single doses of empagliflozin were well tolerated. The safety results of this trial were consistent with those observed in previous empagliflozin trials with adults. No new safety signals were observed

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.

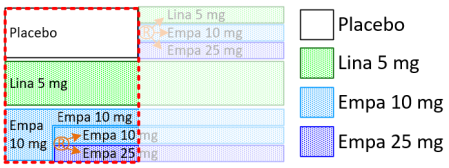
Exposure

The median exposure to trial medication up to Week 26 was 182 days (about 6 months) in both the placebo and empagliflozin pooled treatment groups, with around 90% of patients treated for at least 16 weeks and around 60% of patients treated for at least 26 weeks. The median exposure to trial medication up to Week 52 was 357 days (about 12 months) in the empagliflozin active pooled group, with 53.0% of patients treated for at least 46 weeks.

Adverse events

The main analysis of safety focused on TG1 up to Week 26, for a randomised, placebo-controlled comparison. According to the Investigator, The rate of any AE in the empagliflozin pooled group was slightly higher than on placebo (placebo: 34 patients, 64.2%; empagliflozin pooled: 40 patients, 76.9%), while the rates of severe AEs, AEs leading to discontinuation, drug-related AEs, and SAEs were generally comparable with the rates on placebo (Table 8).

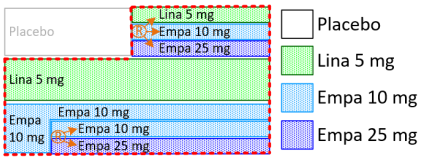
Table 8: Overall summary of adverse events up to Week 26 – TS (TG1)

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.

The rates of AEs, severe AEs, AEs leading to discontinuation, drug-related AEs, and SAEs up to Week 52 were similar to the rates reported for the empagliflozin pooled group up to Week 26.

Table 9: Overall summary of adverse events up to Week 52 – TS active (TG6)

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

On the preferred term (PT) level, up to Week 26, the most frequently reported AEs for patients 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 most frequently AEs reported in patients on placebo were headache (7 patients, 13.2%) and hypoglycaemia, vitamin D deficiency, and diarrhoea (each reported for 5 patients, 9.4%).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 Weeks 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 were of mild or moderate intensity in all treatment groups. Severe AEs were reported for 2 patients (3.8%) on placebo, and 1 patient (1.9%) in the empagliflozin pooled group. Up to Week 52, severe AEs were reported for 3 patients (3.6%) in the empagliflozin pooled group.

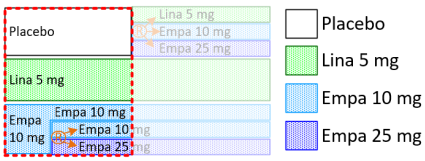
Adverse events leading to treatment discontinuation

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, 1 patient (1.2%) in the empagliflozin active pooled group had an AE leading to discontinuation (PT: tubulointerstitial nephritis).

AESIs and specific AEs

AESIs were prespecified in the CTP as hypersensitivity reactions, skin lesions, pancreatitis, pancreatic cancer, hepatic injury, decreased renal function, DKA, and events involving lower limb amputation (LLA). Specific AEs comprised hypoglycaemia, urinary tract infections (UTIs), genital infections, acute pyelonephritis or urosepsis, bone fracture, arthralgia, pemphigoid in bullous conditions, volume depletion, and ketone measurements reported as AE.

Table 10: AESIs and specific AEs up to Week 26 – TS (TG1)

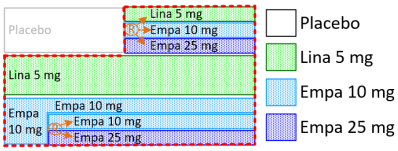
Category of AEs 	Placebo			Empa pooled		
	N	%	Rate/ 100 py	N	%	Rate/ 100 py
Number of patients	53	100.0		52	100.0	
Hypersensitivity reactions (narrow SMQ)	1	1.9	4.1	4	7.7	17.6
Skin lesions (narrow SMQ)	0			0		
Pemphigoid in bullous conditions (HLT-primary path)	0			0		
Pancreatitis (narrow SMQ, PT)	1	1.9	4.0	0		
Pancreatic cancer (narrow BIcMQ)	0			0		
Hepatic injury (narrow sub-SMQ)	1	1.9	4.0	2	3.8	8.6
Decreased renal function (narrow SMQ)	1	1.9	4.0	0		
Diabetic ketoacidosis (DKA; narrow BIcMQ)	1	1.9	4.0	0		
DKA (investigator assessment)	1	1.9	4.0	0		
Ketone measurements reported as AE (narrow BIcMQ)	2	3.8	8.2	2	3.8	8.6
AEs leading to lower limb amputation (LLA; investigator assessment)	0			0		
Hypoglycaemia AE	5	9.4	21.7	12	23.1	63.3
PG <54 mg/dL[1]	4	7.5		10	19.2	

Urinary tract infection (UTI; narrow sub-BIcMQ)	1	1.9	4.1	3	5.8	12.9
UTI (investigator assessment)	1	1.9	4.1	4	7.7	17.6
Genital infection (narrow sub-BIcMQ)	1	1.9	4.0	1	1.9	4.2
Genital infection (investigator assessment)	2	3.8	8.1	3	5.8	12.9
Acute pyelonephritis (narrow sub-BIcMQ) or urosepsis (PT)	0			0		
Acute pyelonephritis or urosepsis (investigator assessment)	0			0		
Bone fracture (narrow BIcMQ)	0			0		
Arthralgia (HLGT-primary path)	1	1.9	4.1	1	1.9	4.3
Volume depletion (narrow BIcMQ)	1	1.9	4.0	0		

SMQ = standardised MedDRA query; BIcMQ = Boehringer Ingelheim customised MedDRA query; HLT = high level term; HLGT = high level group term; PT = preferred term; PG = plasma glucose

1 There were no events of severe hypoglycaemia requiring assistance.

Table 11: AESIs and specific AEs up to Week 52 – TS active (TG6)

Category of AEs	Empa active		
	N	%	Rate/ 100 py
Number of patients	83	100.0	
Hypersensitivity reactions (narrow SMQ)	5	6.0	8.5
Skin lesions (narrow SMQ)	0		
Pemphigoid in bullous conditions (HLT-primary path)	0		
Pancreatitis (narrow SMQ, PT)	0		
Pancreatic cancer (narrow BIcMQ)	0		
Hepatic injury (narrow sub-SMQ)	3	3.6	5.0
Decreased renal function (narrow SMQ)	0		
DKA (narrow BIcMQ)	0		
DKA (investigator assessment)	0		
Ketone measurements reported as AE (narrow BIcMQ)	8	9.6	13.6
AEs leading to lower limb amputation (LLA; investigator assessment)	0		
Hypoglycaemia AE	16	19.3	32.2
PG <54 mg/dL [1]	15	18.1	
Urinary tract infection (UTI; narrow sub-BIcMQ)	6	7.2	10.1

UTI (investigator assessment)	8	9.6	13.8
Genital infection (narrow sub-BIcMQ)	1	1.2	1.6
Genital infection (investigator assessment)	3	3.6	5.0
Acute pyelonephritis (narrow sub-BIcMQ) or urosepsis (PT)	0		
Acute pyelonephritis or urosepsis (investigator assessment)	0		
Bone fracture (narrow BIcMQ)	0		
Arthralgia (HLGT-primary path)	2	2.4	3.3
Volume depletion (narrow BIcMQ)	0		

SMQ = standardised MedDRA query; BIcMQ = Boehringer Ingelheim customised MedDRA query; HLT = high level term; HLGT = high level group term; PT = preferred term; PG = plasma glucose

1 There were no events of severe hypoglycaemia requiring assistance.

Hypersensitivity reactions

Up to Week 26, hypersensitivity reactions were reported for 1 patient (1.9%) in the placebo group and 4 patients (7.7%) in the empagliflozin pooled group. Only 1 PT (rash) was reported in >1 patient in either group (3 patients [5.8%] in the empagliflozin pooled group) (Table 10). None of these events was serious. Up to Week 52, they were reported for 5 patients (6.0%) in the empagliflozin active pooled group (Table 11). None of the events was serious, none led to discontinuation of trial medication, and in all cases the patients recovered.

Skin lesions

No event was reported (Table 10, Table 11).

Pemphigoid in bullous conditions

No event was reported (Table 10, Table 11).

Pancreatitis

Pancreatitis was reported as an AESI for 1 patient (1.9%) in the placebo group in the period

up to Week 26 (Table 10) with an onset on Day 24. The event was severe and serious (life-threatening, and requiring hospitalisation), and led to discontinuation. No event of pancreatitis was reported for empagliflozin-treated patients (Table 10, Table 11).

Pancreatic cancer

No event was reported (Table 10, Table 11).

Hepatic injury

Up to Week 26, the rates of hepatic injury were comparable for placebo and the empagliflozin pooled group (placebo: 1 patient, 1.9%; empagliflozin pooled: 2 patients, 3.8%). On the PT level, hepatic injury AEs were increased ALT, increased AST, increased GGT, increased transaminases, and hepatic steatosis, each reported by 1 patient in each group. None of the hepatic injury events reported as AESIs led to discontinuation of trial medication, none were SAEs, and in all except 2 cases the outcome was recovered.

Up to Week 52, 2 patients (3.8%) in the empagliflozin active pooled group were reported with transaminase elevation (ALT and/or AST ≥3x ULN). Up to Week 26 and up to Week 52, no patients in the

placebo or empagliflozin pooled groups had events that met the criteria for adjudication by the CEC for hepatic injury.

Decreased renal function
Up to Week 26, there was 1 patient (1.9%) in the placebo group with an AESI of decreased renal function and no patient in the empagliflozin pooled group. Up to Week 52, there was no patient in the empagliflozin active pooled group with decreased renal function.

In the analysis of safety laboratory parameters for renal function, no cases of serum creatinine ≥2x the baseline value and above the normal range were reported for empagliflozin-treated patients (Table 10, Table 11). Change in eGFR was discussed above in the efficacy section.

Diabetic ketoacidosis (DKA)
Up to Week 26 there was 1 patient (1.9%) on placebo with an AESI of DKA (narrow BIcMQ and according to the investigator assessment) and no patient in the empagliflozin pooled group (Table 10). Up to Week 52, there was no case of DKA (narrow BIcMQ or according to investigator assessment) for patients in the empagliflozin active pooled group (Table 11).

Ketone measurement reported as AE
Up to Week 26, ketone measurements reported as an AE occurred for 2 (3.8%) patients on placebo and 2 (3.8%) patients in the empagliflozin pooled group (Table 10). In all cases, the PT was blood ketone body increased. Up to Week 52, ketone measurements reported as an AE occurred in 8 (9.6%) patients in the empagliflozin active pooled group (Table 11). The PTs were increased blood ketone body (7 patients), acetonaemia (1 patient), and ketosis (1 patient). There were no severe events.

AEs leading to lower limb amputation (LLA)
No event was reported (Table 10, Table 11).

Hypoglycaemia
Up to Week 26, hypoglycaemia was reported for 5 patients (9.4%) on placebo and 12 patients (23.1%) in the empagliflozin pooled group; 4 patients on placebo and 10 patients on empagliflozin with such events had at least 1 event with plasma glucose (PG) values <54 mg/dL. No patient had an event that required assistance. Up to Week 52, hypoglycaemia was reported for 16 patients on empagliflozin (19.3%) (Table 11). No patient had any severe event that required assistance.

Urinary tract infection (UTI)
Up to Week 26, UTIs were reported for 1 (1.9%) patient in the placebo group and 3 (5.8%) patients in the empagliflozin pooled group (based on the narrow sub-BIcMQ). According to the investigator assessment, there was 1 additional patient with a UTI in the empagliflozin pooled group (giving a total of 4 patients, 7.7%) (Table 10). None of the events was serious or led to treatment discontinuation. All patients with UTIs had a single event, and none of the events were severe. The time to onset was <90 days for all except 2 patients (both in the empagliflozin pooled group). Two patients (1 in the placebo group and 1 in the empagliflozin pooled group) had lower UTIs, 1 (empagliflozin pooled group) had an upper UTI, and 2 (empagliflozin pooled group) had asymptomatic bacteriuria.

Up to Week 52, UTIs were reported for 6 (7.2%) patients in the empagliflozin active pooled group (based on the narrow sub-BIcMQ). According to the investigator assessment, there were 2 additional patients with a UTI in the empagliflozin active pooled group (total 8 patients, 9.6%). No serious events or events leading to treatment discontinuation were reported up to Week 52. All patients with UTIs had a single event, and none of the events were severe. The time to onset was after the first 90 days of treatment for 5 patients (6.0%).

Genital infection
Up to Week 52, genital infection was reported for 1 (1.2%) patient in the empagliflozin active pooled

group (based on the narrow sub-BIcMQ), and according to the investigator assessment, genital infection was reported for 2 patients (3.8%) in the placebo group and for 3 patients (5.8%) in the empagliflozin pooled group (Table 10). None of the events was severe or led to treatment discontinuation. Up to Week 52, genital infection was reported for 1 (1.2%) patient in the empagliflozin active pooled group (based on the narrow sub-BIcMQ). No serious events or events leading to treatment discontinuation were reported up to Week 52 (Table 11).

Acute pyelonephritis or urosepsis
No event was reported (Table 10, Table 11).

Bone fracture
No event was reported (Table 10, Table 11).

Arthralgia
Up to Week 26, arthralgia (HLGT-primary path) was reported for 1 patient each (1.9%) in the placebo and empagliflozin pooled groups (Table 10). Up to Week 52, arthralgia (HLGT-primary path) was reported for 2 patients (2.4%) in the empagliflozin active pooled group (Table 11).

Volume depletion
Up to Week 26, volume depletion (narrow BIcMQ) was reported for 1 patient (1.9%) on placebo (PT: hypovolaemic shock) and no patient in the empagliflozin pooled group (Table 10). Up to Week 52, volume depletion (narrow BIcMQ) was reported for no patient in the empagliflozin active pooled group (Table 11).

Serious adverse event/deaths/other significant events

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. 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.

Vital signs

No obvious changes over time in SBP or DBP were observed for either treatment group in this trial (see efficacy).

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

Growth assessments

Growth was assessed based on weight (see clinical efficacy), height, BMI, and growth velocity. Height increased slightly in both groups. Mean (SD) changes from baseline to Week 26 were as follows: placebo: 1.0 (1.5) cm; empagliflozin pooled: 1.1 (1.5) cm. BMI decreased slightly from baseline to Week 26 for patients on placebo (mean (SD) change: -0.29 kg/m2, (1.82)) and on empagliflozin (mean change: -0.74 kg/m2 (1.40)). Growth velocity at Week 26 was comparable between treatment groups: placebo: mean 1.65 cm/year, SD 3.04; empagliflozin pooled: 1.92 cm/year, SD 2.60. At Week 52, the mean change in height for the empagliflozin pooled group was 1.8 cm, SD 2.2. Mean change in BMI was -0.77 kg/m2, SD 2.03. Mean growth velocity was 1.72 cm/year, SD 2.14.

Sexual maturation

Most patients had an unchanged score at Week 26 compared with baseline, no patient had a lower score, and a small number of patients had a higher score. In the placebo group, 6 patients increased from a score of 3 or 4 at baseline to 5 at Week 26. In the empagliflozin pooled group, 5 patients increased from a score of 3 to 4, and 6 patients increased from a score of 4 to 5. A similar pattern of change in Tanner staging score was seen in the empagliflozin active pooled group from baseline to Week 52.

Safety in special populations

Subgroups were not specifically analysed for safety in the paediatric trials.

Safety related to drug-drug interactions and other interactions

Drug interactions were not specifically studied in the paediatric trials.

3.5.1. Discussion on clinical safety

Safety findings from trial 1218.91 (DINAMO) were also considered in the extension of indication for empagliflozin to children aged 10 years and over (EMEA/H/C/002677/II/0076). In brief, 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. 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.

For hypoglycaemic events, up to Week 26, there were higher overall rates for patients in the empagliflozin pooled group compared with placebo. However, no relevant difference among treatment groups concerning rates of symptomatic hypoglycaemia were reported. There were no severe hypoglycaemia events. Hypoglycaemia is a known AE of and already included in the SmPC of Synjardy. Therefore, the rates of hypoglycaemia were acceptable.

More cases of hypersensitivity were reported in patients in the empagliflozin pooled group than in placebo patients. The hypersensitivity reactions included rash, dermatitis and eczema, were mild and did not lead to drug discontinuation. Hypersensitivity reactions are not included as such in the SmPC, but e.g. rash is included in section 4.8. Therefore, this is acceptable and no adjustments in the SmPC are considered needed.

Safety results were not stratified according to background metformin therapy, which would be relevant considering that the present variation concerns the FCMP empagliflozin/ metformin. However, >90% of patients in the empagliflozin pooled population in 1218.91 (DINAMO) were on background metformin therapy. Thus, it seems reasonable to assume that safety findings (in absolute terms) will not differ substantially for the patients on background metformin compared with the total empagliflozin pooled population.

Long-term safety data (>52 weeks) is missing from this study, but this is covered in the PSUR Single Assessment which includes both Jardiance and Synjardy.

3.5.2. Conclusions on clinical safety

Safety findings from trial 1218.91 (DINAMO) were also considered in the extension of indication for empagliflozin to children aged 10 years and over (EMEA/H/C/002677/II/0076). Safety results were not stratified according to background metformin therapy, but >90% of patients in the empagliflozin pooled population in 1218.91 (DINAMO) were on background metformin therapy. It seems reasonable to assume that safety findings (in absolute terms) will not differ substantially.

3.5.3. 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.

4. Risk management plan

At the start of the procedure, the MAH submitted an updated RMP version with this application (RMP v16.0, date of final sign off: 11 Dec 2023).

4.1. Overall conclusion on the RMP

A consolidated version of the RMP was submitted by the MAH and agreed (RMP v16.1).

5. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet (PL) is updated accordingly.

In addition, the list of local representatives in the PL is being revised.

Please refer to Attachment 1.

5.1. 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 considered acceptable.

6. Benefit-Risk Balance

Synjardy combines two anti-hyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: empagliflozin, an inhibitor of sodium glucose co transporter 2 (SGLT2), and metformin hydrochloride, a member of the biguanide class.

Based on the results of the paediatric clinical programme, the MAH sought an indication for empagliflozin for the treatment of paediatric patients with T2DM.

The proposed indication in paediatric patients is:

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

- in patients insufficiently controlled on their maximally tolerated dose of metformin alone
- in combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with metformin and these medicinal products
- in patients already being treated with the combination of empagliflozin and metformin as separate tablets.

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

6.1. 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.

6.1.1. Disease or condition

As for the adults population, 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.

6.1.2. 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, SGLT2 inhibitors (empagliflozin and dapagliflozin) have already been approved for use in paediatric patients aged 10 years and above.

6.1.3. Main clinical studies

PK/PD trial

Trial 1245.87 was a phase 1 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 3 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 HbA1c <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.

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.

6.2. Favourable effects

In the context of the current application, the primary efficacy analysis in the patients on background metformin treatment is considered most relevant. Compared with placebo, patients on empagliflozin with background metformin therapy had a mean HbA1C reduction of 1.07% (95% CI -0.97, -0.18) without insulin and -0.42% (95% CI -1.50, 0.66) with insulin use. These results are in line with the HbA1C reduction of 0.84% in the empagliflozin pooled population.

The proposed indication relates to an add-on indication to metformin and possible other medicinal products for patients insufficiently controlled with metformin possibly on top of other medicinal products and a substitution indication as defined in the EMA guideline "Guideline on clinical development of fixed combination medicinal products". Study results from trial 1218.91 (DINAMO) are considered relevant mainly for the add-on indication.

Efficacy results were not stratified according to background metformin therapy, which would be relevant considering that the present variation concerns the fixed dose combination of empagliflozin/ metformin. However, >90% of patients in the empagliflozin pooled population in 1218.91 (DINAMO) were on background metformin therapy and metformin use was largely stable during the study. Therefore, sufficient information is presented on the efficacy of empagliflozin added to metformin therapy.

Considering acceptance of the add-on indication demonstrating additional efficacy of empagliflozin on top of metformin, the substitution indication is acceptable. Further, both of empagliflozin and metformin are approved for the use in paediatric patients with T2DM aged 10 years and over and are concomitantly being used in clinical practice for this population and recommended according to international guidelines.

6.3. Uncertainties and limitations about favourable effects

Uncertainties have previously been discussed in the EMEA/H/C/002677/II/0076 procedure including the effects in the 25 mg dose.

6.4. Unfavourable effects

The risks of empagliflozin 10 and 25 mg in paediatric patients with T2DM aged 10 and over has been previously assessed (EMEA/H/C/002677/II/0076). In brief, 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. 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. Two patients had SAEs that were considered to be life-threatening: 1 patient on placebo and 1 patient on empagliflozin (suicidal ideation). No patient had a fatal AE.

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.

For hypoglycaemic events, up to Week 26, there were higher overall rates for patients in the empagliflozin pooled group compared with placebo. However, no relevant difference among treatment groups concerning rates of symptomatic hypoglycaemia were reported. There were no severe hypoglycaemia events. Hypoglycaemia was previously discussed in EMEA/H/C/002677/II/0076. It is a known AE of empagliflozin and already included in the SmPC of Synjardy. Therefore, the rates of hypoglycaemia were acceptable.

More cases of hypersensitivity were reported in patients in the empagliflozin pooled group than in placebo patients. The hypersensitivity reactions included rash, dermatitis and eczema, were mild and did not lead to drug discontinuation. Hypersensitivity reactions are not included as such in the SmPC, but e.g. rash is included in section 4.8. Therefore, this is acceptable and no adjustments in the SmPC are considered needed.

Safety results were not stratified according to background metformin therapy, which would be relevant considering that the present variation concerns the fixed dose combination of empagliflozin/ metformin. However, >90% of patients in the empagliflozin pooled population in 1218.91 (DINAMO) were on background metformin therapy and metformin use was largely stable during the study. It seems reasonable to assume that safety findings (in absolute terms) did not differ substantially for the patients on background metformin compared with the total empagliflozin pooled population.

6.5. Uncertainties and limitations about unfavourable effects

Safety data in children is limited.

6.6. Effects Table

Effect	Short description	Unit	Empagl.	Plac.	Uncertainties / Strength of evidence
Favourable effects					
HbA1c	Change from baseline	%	−0.17	0.68	**SoE:** (ETD −0.84 % (95% CI -1.50 to −0.19 (p=0.016)). Subgroup data on top of metformin are consistent with the overall data (-0.76% (95%CI -1.45%, -0.08%)). **Unc:** No additive efficacy of the 25 mg dose
Unfavourable effects					
Adverse events		%	64.2	40	
Serious adverse		%	3.8	3.8	

Effect	Short description	Unit	Empagl.	Plac.	Uncertainties / Strength of evidence
events					
Hypoglycaemia		%	23.1	9.4	No cases of severe hypoglycaemia
Diabetic ketoacidosis		%	0	2	

Abbreviations: ETD: estimated treatment effect compared to placebo
Based on trial 1218.91 (DINAMO)

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

In children from 10 to ≤17 years of age, empagliflozin (10 mg and 25 mg combined) with background of metformin treatment was associated with a clinically relevant decrease in HbA1c compared to placebo.

Safety findings from trial 1218.91 (DINAMO) have also been considered in the extension of indication for empagliflozin to children aged 10 years and over (EMEA/H/C/002677/II/0076). Safety results were not stratified according to background metformin therapy, which would be relevant considering that the present variation concerns the FCMP empagliflozin/ metformin. However, >90% of patients in the empagliflozin pooled population in 1218.91 (DINAMO) were on background metformin therapy. Thus, it seems reasonable to assume that safety findings (in absolute terms) will not differ substantially for the patients on background metformin compared with the total empagliflozin pooled population.

6.7.2. Balance of benefits and risks

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

- in patients insufficiently controlled on their maximally tolerated dose of metformin alone
- in combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with metformin and these medicinal products
- in patients already being treated with the combination of empagliflozin and metformin as separate tablets.

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

The benefit-risk analysis in children aged 10 years and above for the treatment of type 2 diabetes mellitus is positive.

6.8. Conclusions

The overall B/R in children aged 10 years and above for the treatment of type 2 diabetes mellitus

of Synjardy is positive.