EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 March 2014
EMA/CHMP/137741/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jardiance

International non-proprietary name: empagliflozin

Procedure No. EMEA/H/C/002677/0000

Note

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

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Product information

Name of the medicinal product:	Jardiance
Applicant:	Boehringer Ingelheim International GmbH Binger Strasse 173 55216 Ingelheim GERMANY
Active substance:	Empagliflozin
International Nonproprietary Name/Common Name:	Empagliflozin
Pharmaco-therapeutic group (ATC Code):	Other blood glucose lowering drugs, excl. insulins (A10BX12)
Therapeutic indication:	Treatment of type 2 diabetes mellitus to improve glycaemic control in adults as: <u>Monotherapy</u> When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance. <u>Add-on combination therapy</u> In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).
Pharmaceutical form:	Film-coated tablet
Strengths:	10 mg and 25 mg

Route of administration:	Oral use
Packaging:	blister (PVC/Alu)
Package sizes:	7, 10, 14, 28, 30, 60, 70 90 and 100 tablets,

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Boehringer Ingelheim International GmbH submitted on 5 March 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ronjoli (empagliflozin), through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 December 2011. During the procedure the applicant changed the name of the medicinal product to Jardiance.

The applicant applied for the following indication.

"Ronjoli is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate.

Add-on combination therapy

In combination with other glucose –lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see section 5.1 for available data on different combinations)."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that empagliflozin was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0309/2012 on the agreement of a paediatric investigation plan (PIP)

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation

(EC) No 847/2000, the applicant 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.

New active Substance status

The applicant requested the active substance empagliflozin contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Pieter de Graeff Co-Rapporteur: Bart Van der Schueren

- The application was received by the EMA on 5 March 2013.
- The procedure started on 27 March 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 June 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2013.
- During the meeting on 25 July 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 July 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 October 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to

the List of Questions to all CHMP members on 26 November 2013.

- During the CHMP meeting on 19 December 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 February 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 14 March 2014.
- During the meeting on 17-20 March 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Jardiance.

2. Scientific discussion

2.1. Introduction

The most common type of diabetes is type 2 diabetes, which is characterised by insulin resistance, impaired insulin secretion, and increased glucose production. Type 2 diabetes is also associated with microvascular complications and elevated cardiovascular risk. Treatment of type 2 diabetes usually involves lifestyle interventions such as diet and exercise, as well as the administration of antidiabetic drugs. Although initially effective, currently available oral antidiabetic agents often fail to maintain long-term glycaemic control or are associated with side effects, often including weight gain, which may limit their use. Hence, there is a need for new therapeutic options to provide sustained improvements in glycaemic control and to contribute to reducing cardiovascular risk factors such as overweight and hypertension in patients with type 2 diabetes.

The kidney has a role in the regulation of blood glucose levels and can therefore serve as a target for new antidiabetic drugs. The sodium-dependent glucose co-transporter 2 (SGLT 2) is expressed in the renal proximal tubules and accounts for approximately 90% of renal glucose reabsorption. Inhibition of SGLT 2 decreases the renal reabsorption of glucose, thereby promoting glucose excretion in the urine with a consequent reduction in blood glucose levels. Due to their mainly insulin-independent mechanism of action, SGLT 2 inhibitors may have a low risk of hypoglycaemia. Further effects of SGLT 2 inhibition may include weight loss due to the calorie loss associated with increased glucose excretion and a reduction in blood pressure that is possibly due to a mild diuretic effect.

Empagliflozin is a novel, orally administered, potent, and selective SGLT 2 inhibitor.

2.2. Quality aspects

2.2.1. Introduction

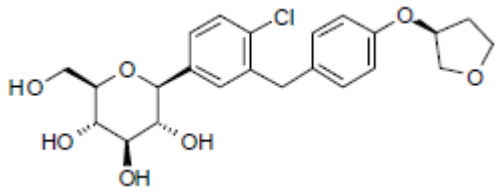
The finished product is presented as a film-coated tablet containing either 10 or 25 mg of empagliflozin as active substance.

Other ingredients are lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide (E171), talc, macrogol 400 and iron oxide yellow (E172).

The product is available in perforated PVC/aluminium unit dose blisters.

2.2.2. Active Substance

The chemical name of empagliflozin is (1*S*)-1,5-anhydro-1-(4-chloro-3-{4-[(3*S*)-tetrahydrofuran-3-yloxy]benzyl}phenyl)-D-glucitol, also known as D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3*S*)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-(1*S*), and has the following structure:



The structure of empagliflozin was unambiguously confirmed by ^{1}H and ^{13}C NMR, UV spectroscopy, FT-IR spectroscopy, mass spectrometry and elemental analysis.

Empagliflozin is a white to yellowish non-hygroscopic crystalline solid, very slightly soluble in water (pH 1-7.4), slightly soluble in acetonitrile and ethanol, sparingly soluble in methanol, and practically insoluble in toluene.

Empagliflozin is chiral and possesses 6 stereogenic centres. Enantiomeric purity is controlled routinely by suitable analytical methods. A single polymorphic form has been observed for empagliflozin which is non-solvated and non-hydrated.

The active substance is a chemical substance not previously authorised as a medicinal product in the European Union. Furthermore, it is neither a salt, complex, derivative, isomer (or mixture of isomers) of a previously authorised substance. Empagliflozin thus meets the definition of a New Active Substance according to the Notice to Applicants (NtA), Vol 2A, Chapter 1, Annex 3 and a Marketing Authorisation Application in accordance with Article 8(3) of Directive 2001/83/EC pertaining to a New Active Substance is justified.

Manufacture

The manufacture of the active substance was satisfactorily described including a flow chart. Empagliflozin is synthesized from well-defined starting materials with acceptable specifications. Enough of the manufacturing process is described and the physicochemical properties of the

active substance are well controlled by the process. Potential and actual impurities were well discussed with regards to their origin and fate and characterised. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are considered adequate.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), impurities (HPLC), diaseteromer (chiral HPLC), assay (HPLC), residual solvents (GC), water content (KF), residue on ignition (Ph. Eur.), and particle size (laser diffraction). Optical purity is controlled by a test for specific optical rotation. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. Impurity limits will be re-evaluated when sufficient commercial scale experience has been gained to fully assess the capability of the active substance manufacturing process.

Batch analysis data on 11 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch. Batch analysis data on a further 35 pilot scale batches carried out using previous incarnations of the synthetic process and used for toxicology and clinical studies are also provided, with all batches conforming to specifications in place at the time.

Stability

Stability data on three commercial scale batches of empagliflozin manufactured using the proposed commercial process stored in the intended commercial packaging for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Stability was also tested under stressed conditions in the solid state (1 commercial scale batch) and in solution (1 development batch). Solid state photostability testing following the ICH guideline Q1B was performed on 1 commercial scale batch. Solid state material was also exposed to high temperature (80 ^{o}C) and to open storage conditions (40 ^{o}C / 75% RH). Empagliflozin was tested in solution at low (2.5), intrinsic, and high (13) pH, each under heat stress conditions (80 ^{o}C), in the presence of strong (H_2O_2), or mild (AIBN) oxidants, and under UV irradiation. The following parameters were tested: appearance, impurities (HPLC), diaseteromer (chiral HPLC), assay (HPLC), water content (KF) and particle size (laser diffraction). The analytical methods used were the same as for release.

No changes to any test parameters were observed under long term or accelerated conditions. Empagliflozin is neither photosensitive, nor affected by high temperature or humidity in the solid state. In solution, empagliflozin is prone to degradation at low and high pH and in the presence of a strong oxidant. It is also unstable to a mild oxidant at high pH and slightly sensitive to light.

None of the chiral centres showed any propensity to epimerisation during the stability studies. The results demonstrate that the analytical methods are stability indicating.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container. Primary stability studies on the 3 commercial batches will continue up until the proposed re-test period.

2.2.3. Finished Medicinal Product

Pharmaceutical development

The objective of formulation development was to develop an immediate-release oral dosage form of empagliflozin with reliable release and bioavailability. The active substance is a crystalline solid, routinely manufactured as a single polymorphic form. It is very slightly soluble in aqueous media between pH 1-7.5 but has low intestinal permeability (BCS class III). Particle size was not found to be critical for dissolution, but since coarser API dissolves slightly more slowly, the drug substance is milled and particle size is tightly controlled.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards except for the Opadry yellow film-coating which is manufactured by an established supplier and tested according to established methods. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. Their compatibility with the active substance was demonstrated during the development process. The compositions of the 2 tablet strengths are not proportional.

A wet granulation process was used throughout development, during which several trial formulations were developed. The final formulation, used in the phase III clinical trial, contains the same excipients as those used in earlier development, the levels of which were optimised to improve *in vivo* performance. Bioequivalence between the final and earlier clinical formulations was demonstrated *in vivo*.

The principles of Quality by Design were applied to the pharmaceutical development. A quality target product profile (QTPP) was established and is defined as a once daily orally administered immediate release film-coated tablet available in 2 strengths (10 and 25 mg) with adequate purity, chemical, physical and mechanical stability, an appearance suitable to ensure patient compliance, and a 3 year shelf-life which is stored in a product-compatible package with adequate protection from environmental conditions so as to ensure adequate and reliable *in vivo* performance.

Critical quality attributes (CQAs) were suitably defined. The different steps of the tableting process were evaluated through the use of risk assessment to identify potential critical material attributes and critical process parameters based on the prior experience from formulation development. Those with a potential to impact on the CQAs were investigated experimentally. CMAs are controlled by IPCs at relevant points in the manufacturing process.

The primary packaging is PVC/aluminium perforated unit dose blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents *via* Human and Veterinary Medicinal Products.

Manufacture of the product

The manufacturing process consists of 4 main steps including granulation, blending, compression and film-coating. The process is considered to be a standard manufacturing process. Critical material attributes are assured by IPCs at relevant points in the process.

Major steps of the manufacturing process have been validated by 3 commercial scale batches for both strengths of tablet. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for the production of Jardiance film-coated tablets.

Product specification

The finished product release specifications comprise appropriate tests for this kind of dosage form including description (visual test), identification (HPLC and UV), degradants (HPLC), assay (HPLC), dissolution (Ph. Eur.), uniformity of dosage unit (HPLC) and microbiological quality (Ph. Eur., skip lot testing as per ICH Q6A). The absence of tests for organic solvents, inorganic impurities, disintegration and water content has been adequately justified by the applicant. The discriminatory power of the dissolution method has been demonstrated.

Batch analysis results for 13 commercial scale batches confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of 3 commercial scale batches of finished product stored under long term conditions (25 ºC / 60% RH) for up to 36 months and under accelerated conditions (40 ºC / 75% RH) for up to 6 months according to the ICH guidelines were provided. The batches of Jardiance are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for description, degradants, assay, dissolution and microbiological quality. No relevant change or trend to any of the measured parameters was observed under either condition. The analytical procedures used are stability indicating.

In addition, stressed stability studies were carried out on 1 commercial scale batch. The finished product was exposed for 6 months to heat (60 ^{o}C, closed amber bottle) and various open storage

conditions (25 °C / 60% RH, 30 °C / 75% RH, 40 °C / 75% RH). It was also exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No relevant change or trend to any of the measured parameters was observed on exposure to light or heat. Only a minor increase in water content and decrease in hardness is observed under open storage conditions but these do not impact the tablet performance.

Stability studies on 2 commercial scale batches of bulk drug product stored under warehouse conditions reveal no significant changes in any of the test parameters.

Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design spaces were claimed.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

> Review the limits for impurities when sufficient commercial scale experience has been gained to fully assess the capability of the active substance manufacturing process. If necessary, the specification of the active substance should be tightened *via* the appropriate regulatory procedure.

2.3. Non-clinical aspects

2.3.1. Pharmacology

In vitro studies using transfected HEK and CHO cells showed that empagliflozin is a selective and potent inhibitor of the human, rat and mouse glucose transporter SGLT2 (IC_{50}: 1.3 nM, 1.7 nM and 1.7 nM respectively). Receptor kinetics show that the affinity (Kd) of empagliflozin for SGLT2 is reduced in the presence of glucose, indicating competitive binding to the receptor. Affinity to other human SGLT's were 5000-fold, >3500-fold, >350-fold and >600-fold lower for SGLT1, SGLT4, SGLT5 and SGLT6 respectively. Of these, only SGLT1 and SGLT2 are expressed to a relevant degree in the kidney. Likewise, empagliflozin up to 10 µM did not have an effect on glucose transport via a glucose transporter expressed in most cells, GLUT1. It should be noted that there is no *in vitro* data available for the dog. This can be accepted, since efficacy is shown *in vivo*.

Three glucuronide metabolites of empagliflozin have low affinity for SGLT2, and these therefore do not contribute to the pharmacological effect of empagliflozin. In a safety pharmacology study, the applicant mentions an "active" metabolite. In the pharmacokinetic section it appears that this metabolite is a major component in rats, however, it is shown that this metabolite is not present at relevant levels in human plasma (up to 0.12%). Therefore this metabolite has not been investigated separately.

A panel of 98 human, rat, mouse, and rabbit enzymes and receptors were not affected by exposure to empagliflozin up to 10 µM. Selectivity of empagliflozin was further confirmed in another panel showing no relevant activity in 106 assays that span a broad area of the human proteome consisting of 49 receptor binding assays, 21 ion channel binding assays, 29 enzyme and uptake assays, 7 in vitro metabolism assays, one cellular and nuclear receptor functional assay and another study in which empagliflozin was tested in 50 kinase assays.

Primary pharmacodynamic studies

The primary pharmacodynamics effect of empagliflozin on inhibition of glucose re-uptake in the kidneys, was demonstrated in mice, rats and dogs. All species showed increased urine glucose concentrations after treatment. In dogs the ED_{50} was determined at 0.9 mg/kg empagliflozin. Urine volume was also increased, especially in dogs treated with 10 mg/kg empagliflozin. This is an expected effect, since SGLT2 is a co-transporter of glucose, sodium and water molecules. Increased urine glucose excretion leads to lowered blood glucose concentration, as shown in diabetic $^{db/db}$mice and ZDF rats. A reduction of up to 46% was seen after a single dose of 3 mg/kg, with an estimated ED_{50} of 0.6 mg/kg for both species. The effect lasted for at least 7 hours in rats. Doses as low as 1 mg/kg in mice and rats had a significant effect on lowering of blood glucose levels after an oral glucose tolerance test (OGTT). Further, the effect on glycemic control was evaluated in ZDF rats after 5 weeks treatment of up to 3 mg/kg empagliflozin. Prandial and fasting blood glucose lowering lasted up to 16 hours post-dose. The diabetic ZDF rat has an increased HbA1c, which was reduced by treatment with empagliflozin.

Secondary pharmacodynamic studies

In secondary pharmacology evaluations, treatment with 10 mg/kg/day empagliflozin for 28 days, has an effect on body weight loss in obese rats. This is likely due to a small decrease in food consumption, together with the pharmacological effect of inhibition of glucose re-uptake in the kidneys. Of note, in the repeated dose toxicology studies, healthy rats generally had increased food consumption. This is probably due to a compensatory reaction in relation to a reduction in blood glucose, which is not seen in obese rats. Urine glucose excretion was increased and serum glucose decreased from 3 mg/kg, the lowest dose tested, whereas urine Na^+, Cl^- and osmolality were increased at the mid and high dose (10 and 30 mg/kg), when measured in the first 4 hours after treatment. Serum electrolytes also seem to be effected, especially potassium and chloride (increased in urine), as well as serum free fatty acids (increased in serum). Regarding the increase in serum free fatty acids, this could be the result of compensation for energy source, due to the drop in glucose levels.

Safety pharmacology programme

In a battery of safety pharmacology studies, empagliflozin was evaluated for effects on central nervous system, respiratory system, gastro-intestinal system, and cardiovascular system. Empagliflozin had no effect on the central nervous system of mice and rats, when administered up to 30 mg/kg and up to 2000 mg/kg respectively. Also, no effect on the respiratory system of rats was seen, when administered up to 2000 mg/kg. There was no effect of intraduodenal administration of empagliflozin on gastric secretion in a gastric ulcer rat-model, and no effect of treatment was seen on intestinal motility in rats. The high dose of 30 mg/kg did have an effect on gastric emptying, which was increased by 33%. No toxicokinetic data is available from this study, but from the repeated dose studies, it can be extrapolated that a dose of 30 mg/kg corresponds to a AUC of approximately 10 M.h. This is in excess of the AUC of 4740 nM.h for humans at the recommended dose, and therefore the effect is likely not relevant. There was no effect on hERG tail current by empagliflozin up to 10.0 µM. Two *in vivo* studies were performed in conscious dogs up to 100 mg/kg to evaluate the effect of empagliflozin in cardiovascular parameters. There was no effect on any parameter that could be related to treatment. Cardiovascular parameters were also measured in a number of repeated dose toxicity studies, which revealed no effects due to treatment with empagliflozin. The doses used in the safety pharmacology studies result in exposures that are in excess of the clinical exposure at the recommended dose.

Pharmacodynamic drug interactions

Several combination studies were performed, to evaluate if empagliflozin can have an additive effect on the blood glucose lowering effect of some existing substances of different classes, on the market for treatment of type II diabetes. Combination treatment with metformin, a sulphonylurea (glipizide), a DPP-4 inhibitor (linagliptin), a GLP-1 analog (exendin-4), an α-glucosidase inhibitor (voglibose), a PPARγ agonist (pioglitazone) and with insulin resulted in greater improvement in glucose tolerance in ZDF rats compared to each individual monotherapy.

2.3.2. Pharmacokinetics

Empagliflozin was absorbed well after oral dosing in mouse, rat and dog. Oral bioavailability following administration of empagliflozin was moderate to high in mouse and dog (>81%) and low in rat (25-33%). After iv administration of empagliflozin, plasma clearance differed between the species examined, varying from low in dog (1.7-1.8 ml/min/kg) and rat (12-15 ml/min/kg) to moderate in mouse (33-40 ml/min/kg). The volume of distribution was 0.5-1.2 L/kg in all species, which indicates reasonable distribution into tissues. The half-live values were long in general, but it is hard to draw conclusions since half-lives were not only variable between species but also within species. Following repeated doses, the exposure to empagliflozin increased dose-proportional in mice, rats and dogs, except for female rats in the 2 years study where a less than proportionally increase with dose was observed and in the 52-week study in dogs where a slightly greater than dose-proportional increase was observed between the mid and high dose levels. There were no consistent trends suggesting an effect of repeated dosing on C_{max} or AUC, indicating that there was little or no accumulation of empagliflozin. Empagliflozin C_{max} and AUC values were consistently greater in females compared to males in mice, rats and dogs, with a few exceptions.

Binding to plasma proteins is high in all species examined for empagliflozin (87-92%). In human plasma, protein binding was 82-84%, and this binding was predominantly to albumin. Protein binding of empagliflozin was independent on the concentration in the range investigated, which indicates no saturation of binding sites. The concentration range (0.01-40 µg/mL) covers the plasma levels at indicated clinical application (C_{max} in humans is 0.3 µg/mL). Partitioning of empagliflozin into red blood cells was limited and independent of the concentration in any of the species investigated. Distribution of drug-related radioactivity into tissue was limited. Highest tissue concentrations were observed 1 hour after administration and were measured in gastrointestinal tract contents, urine, and bile. Empagliflozin-related radioactivity was not distributed into the central nervous system at any time point analysed. Besides the contents of the gastrointestinal tract and urine, drug-related radioactivity was still observed after 24 hours in the kidney, suggesting some accumulation of empagliflozin-related material may occur when using daily. Distribution into the renal cortex was similar in rats and mice and showed no gender specificity. Binding to melanin was not observed. Empagliflozin crosses the placenta barrier in rats, although at low levels. Placental transfer in humans may be expected based on the results. This has been included in the SmPC.

In vitro data suggest that metabolism of empagliflozin is low in humans and that CYP enzymes do not contribute significantly to empagliflozin metabolism. However, compared to humans, *in vitro* metabolism was higher in the animals examined, especially in rats. Three glucuronide conjugates are present in human plasma, though each glucuronide represents less than <10% of the parent AUC when tested at the supratherapeutic dose of 50 mg. In the pre-clinical species, oxidation of empagliflozin is the primary metabolism pathway. UGT1A3, 1A8, 1A9 and 2B7 are identified to be involved in the glucuronidation of empagliflozin. The enzymes involved in the (oxidative) metabolism of empagliflozin in animals have not been identified. In mechanistic studies concerning the finding of renal tumours in male mice the formation of an instable metabolite was identified, which led to the formation of the cytotoxic compound 4-hydroxy-crotonaldehyde (4OH-CTA). The Applicant provided the metabolite patterns in plasma of mouse, rat, dog and humans as percentage of radioactivity and as concentration (in nM) in the sample

per individual sampling time point. This hampered an interspecies comparison of the metabolite pattern in the pre-clinical species with that in humans in a quantitative/proportional manner. Qualitatively, based on the metabolite profile provided for the non-clinical species and humans, it can be concluded that oxidation is the major metabolic pathway in the non-clinical species while direct glucuronidation is the major metabolic pathway in humans. The provided data indicate that all metabolites observed in humans are also observed in the pre-clinical species, except for a fourth glucuronide present in human plasma only at trace levels. Furthermore, the data suggest that after repeated dosing metabolites accumulate in the pre-clinical species as indicated by the $AUC_{m/p}$ ratios even up to ~9400%. This accumulation is not observed in humans. Covalent binding studies in liver microsomes suggest that empagliflozin has a low potential for reactive intermediate formation via phase I metabolism in humans.

Generally, across the non-clinical species, faecal and/or biliary excretion are the most important elimination routes. In rats, biliary excretion is found to be a major route of excretion. However, empagliflozin and its related radioactivity may also be directly secreted into the intestine via drug transporters such as BCRP. In humans, both renal (~54%) and faecal (~41%) excretion are important elimination routes in contrast to most observations in the non-clinical species. Empagliflozin may be excreted via milk with milk:plasma ratios up to 5.0 as is observed in rats.

Empagliflozin is not an *in vitro* inducer of CYP at clinically relevant organ and intestinal concentrations. Therefore, no *in vivo* CYP induction and correspondingly drug-drug interactions in humans is expected.

Empagliflozin is not an inhibitor of CYPs 1A2, 2B6, 2C8, 2C19, 2D6 and 3A4 at clinically intestinal and systemic concentrations. Empagliflozin is not expected to be a CYP2C9 inhibitor *in vivo*. In addition, empagliflozin or its glucuronides are not considered irreversible CYP inhibitors. Thus, drug-drug interactions involving the investigated CYPs are considered unlikely. At maximum organ concentrations, empagliflozin is not an inhibitor of UGT1A1. UGTs involved in the glucuronidation of empagliflozin, i.e. UGT1A3, 1A8, 1A9 and 2B7 were not investigated by the Applicant. According to the EMA drug-drug interaction guideline, it is recommended to study the UGTs involved in the glucuronidation. The Applicant stated that UGT2B7 is involved in the formation of M/626/1 and UGT1A3, 1A8, 1A9 and 2B7 in the formation of M626/3. At therapeutic concentrations UGT2B7 is not involved in the formation of M626/1 and M626/3. However, M626/1 was formed in patients at clinically relevant dosing, indicating that either UGT2B7 or an unknown UGT is involved in patients in the formation of this metabolite.

Empagliflozin is an inhibitor of the efflux transporters BCRP and MRP2, and of the hepatic uptake transporters OATP1B1, OATP1B3 and OATP2B1 and of the renal uptake transporter OAT3. The contribution of oatp1a1/Oatp1a1 toward the overall transport of empagliflozin into kidney slices from rat and mouse is very small compared to oat3/Oat3 and sglt(s)/Sglt(s). At systemic and local organ concentrations achieved after the maximum therapeutic dose, no drug-drug interactions involving inhibition of these transporters are expected *in vivo*. Glucuronidation is the major metabolism pathway in humans. Therefore, inhibition of UGTs by concomitantly drug administration could potentially lead to drug-drug interactions. Empagliflozin is a substrate for the efflux transporters P-gp and BCRP. No clinically relevant increase of the plasma concentrations of empagliflozin is expected by P-gp and BCRP inhibition by concomitant administration of P-gp and BCRP inhibitors, since the absolute bioavailability of orally administered empagliflozin is high and linear kinetics are observed. However, increased plasma

concentrations due to the inhibition of the excretion by P-gp and BCRP cannot be ruled out. Empagliflozin is a substrate of two uptake transporters expressed in the liver, OATP1B1 and OATP1B3, and of one kidney transporter, OAT3, at local organ concentrations. Inhibition of these transporters by concomitantly administered drugs may have an effect on the drug disposition and elimination of empagliflozin.

2.3.3. Toxicology

Single dose toxicity

Acute toxicity of empagliflozin was tested in mice and rats by oral and intraperitoneal administration up to 2000 mg/kg and appeared to be low with mortality only seen in mice above 300 mg/kg by the intraperitoneal route.

Repeat dose toxicity

In a 13-week repeated dose toxicity in **mice**, the kidneys and liver were identified as target organs. Increased kidney weights and cystic tubular hyperplasia were seen in both sexes at all dose levels, but tubular single cell necrosis, tubular hypertrophy, tubular karyomegaly and exacerbation of the proliferative marker Ki-67 were treatment-related findings in males only. In the mouse carcinogenicity study, cystic tubular hyperplasia is associated with tubular cysts, lower urinary tract dilatation and increased mortality in males. Increased liver weights seen in both sexes were due to an exacerbation of midzonal hydropic change. The cause of the hydropic changes was not discussed by the Applicant. It could point to electrolyte imbalances, but clinical chemistry data only contained data for calcium and not sodium or potassium. Slight decreases in plasma calcium and inorganic phosphorus were not considered adverse. Swollen abdomen (in the carcinogenicity study) and abnormal feces suggest empagliflozin administration may interfere with normal digestion. Based on the histopathological findings in males the NOAEL in this study should be considered to be less than 500 mg/kg/day, corresponding to a C_{max} of <32.4 µM and an AUC of <130 µM.h.

These findings were confirmed in a second mechanistic 13-week toxicity study in mice with interim sacrifices and further analysis of the kidneys. Administration of empagliflozin changed transcript levels of genes related to renal development and function, cell cycle regulation, cell proliferation, cell to cell signalling, cell adhesion and cytoskeleton in high dose male mouse specifically when compared to vehicle groups.

Repeat dose oral toxicity evaluations in **rat** included studies of 2, 4, 13, and 26 week duration [05R214, 06R073, 07R036, 08R019]. In the 4 week study, the doses were 30, 100, and 1000 mg/kg/day, and in the 13, and 26 week studies, the doses were 30, 100, and 700 mg/kg/day. In all studies there was a largely consistent pattern of observations including increases in food consumption, decreases in body weight gain, decreases in plasma glucose, glucosuria and polyuria, all of which are related to the primary mode of pharmacological action. Decreased serum chloride and sodium were attributed to polyuria, however, pharmacological inhibition of SGLT2 would be expected to decrease sodium reabsorption in the kidney. At higher doses and/or longer term exposures additional observations included increases in blood urea nitrogen (BUN), plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides, and ketonurea. These effects are consistent with secondary responses to high dose pharmacology

and are consistent with an adaptive metabolic shift towards gluconeogenesis and fatty acid metabolism. All clinical chemistry changes returned to control values during recovery periods.

Exacerbation of spontaneously occurring renal tubular mineralization, characterized as tubular, papillary and pelvic mineralization, was observed in the 13- and 26-week studies. In the 13-week study, the finding was observed in the 100 and 700 mg/kg/day groups and, although dose related in severity, it was considered non-adverse. After 4 weeks of treatment-free recovery, the mineralization was still increased in incidence and severity. In the 26-week study, non-adverse exacerbated renal tubular mineralization was observed at doses >30 mg/kg/day, and persisted through the 3-month recovery period. In the rat carcinogenicity study similar findings were made at all dose levels (≥100 mg/kg) and in addition vacuolation of renal cortical tubular cells was seen. The Applicant hypothesises that renal mineralisation is a consequence of a rat-specific mechanism related to intestinal SGLT1 inhibition, glucose malabsorption, decrease of intestinal pH, increase of calcium absorption, increased urinary excretion of calcium and pelvic and corticomedullary nephrocalcinosis. Based on the apparent change in calcium and phosphorus homeostasis, mineral deposits are likely calcium phosphate. In the 13 and 26-weeks studies, no bone abnormalities were observed and in the parathyroid only a low incidence of hypertrophy was seen, which was similar in control and high dose animals. Yet, in the rat carcinogenicity study some bone abnormalities were observed (increased prominence of basophilic-staining residual cartilage in the cortical bone of the proximal diaphysis of the femur and increase in trabecular bone in the sternum). Urinary calcium and markers of renal damage were not assessed in the long-term studies, but were evaluated in a subsequent 7 day mechanistic toxicity study in rats. Based on these data and public data for other SGLT2 inhibitors, it was concluded that a calcium-driven mechanism for the renal tubular mineralisation is likely involved. Increased glomerular reabsorption of phosphorus is suggested to contribute as well, although the precise mechanism for the latter has not been shown.

Other rat organs having non-adverse responses to empagliflozin treatment include pancreas, thyroid, liver, and adrenals and were typically only observed in the 26 week study and/or the carcinogenicity study. Pancreatic changes in rats featured occasionally observed vacuolation of the basilar portion of cells which were depleted of zymogen, an effect considered secondary to the increased food consumption and decreased body weight.

In thyroid glands, minimal follicular cell hypertrophy was observed at a low incidence only in males and the Applicant suggests this reflects increased activity. The cause of this increased activity was not discussed. This effect on the thyroid seems not to be relevant for human, since it was minimal in severity and not observed in mice or dogs.

In the rat carcinogenicity study erosion/ulceration of the stomach was noted. The cause of the stomach erosions in the rat remains obscure, but thus far it seems to be limited to the rat carcinogenicity study.

In both 13 and 26-weeks studies in rats there was a slight increase in liver weight in females in the high dose group. In the 26-weeks study in all dose groups microvescicular hepatocytic vacuolation was observed. These changes may reflect an adaptive response to the lower glucose availability. In both studies increases of AST and ALT were observed. However, the magnitude of these increases was small and in view of the absence of a histopathological correlate not considered of toxicological relevance. In the rat carcinogenicity study, increased vacuolation of

sinusoidal cells was seen in the absence of other pathological phenomena. Yet, in the 26-weeks study, in the liver, mild multifocal random foci of hepatocellular necrosis were noted at a low incidence (three animals) in 700 mg/kg/day females and a very low incidence (one animal) in 100 mg/kg/day females and hepatocellular eosinophilic globules were observed in treated males at a low incidence and minimal severity in the 30- (two animals) and 100- (one animal) mg/kg/day dose groups. These changes were classified as being of uncertain nature.

In the adrenals, two test article-related microscopic changes were observed. Vacuolation of the *zona glomerulosa* was observed in males and females from all dose groups ranging in severity from minimal to moderate. Considering that empagliflozin will reduce sodium reabsorption by SGLT2 (and SGLT1 (in the rat)) inhibition, the observed effects in the *zona glomerulosa* may reflect an adaptive response to reduced sodium levels triggering increased aldosterone synthesis. The second microscopic change, hypertrophy of the *zona fasciculata*, was observed in males and females at all dose levels. The etiology of these effects were not further discussed by the Applicant, but may reflect an adaptive response to reduced glucose levels triggering increased glucocorticoid (cortisol) synthesis.

In the rat carcinogenicity study, vessel mineralization was observed in the heart, tongue, kidney, eye, axillary and mesenteric lymph nodes, mandibular salivary gland and pancreas. In addition, tissue mineralization was seen in seminal vesicle, glandular stomach muscularis and aorta. Mineralisation predominantly seen in males and for some tissues (aorta, tongue, kidney, glandular stomach muscularis) was already increased at the low dose. Vascular mineralization graded minimal to moderate varied from small subintimal foci to more extensive mineralization affecting the entire tunica media of some larger vessels. Although serum calcium and phosphorus levels were not measured in the carcinogenicity study, in the pathology report it is hypothesized that it is likely that empagliflozin-related hyperphosphatemia (referring to the 6-months repeat dose toxicity study in rats) contributed to findings of systemic vascular and soft tissue mineralization. To explain the vascular and soft tissue mineralisation the Applicant points to the rat specific intestinal SGLT1 inhibition and subsequent increased calcium absorption. As long as electrolyte levels in patients are not affected, notably calcium and phosphate, it may be expected that there is no risk for humans. However, when the calcium levels and/or phosphate levels increase in patients, e.g. when kidney function significantly decreases, soft tissue and vascular mineralisation could be an issue for humans as well.

Most changes observed during the dosing phases of the 13- and 26-week studies in rats resolved during the 4-week and 3-month recovery periods but exacerbation of renal tubular mineralization persisted in both studies as did the body weight gain decrement exhibited by high-dose females. As a carcinogenicity study does not contain a reversibility phase, it is not known whether vessel and tissue mineralisation was reversible.

Repeat dose oral toxicity evaluations in **dog** included studies of 2-, 4-, 13-, 26-, and 52-week duration. In all studies except the 2-week dose range finding study, the doses were 10, 30, and 100 mg/kg/day. Similar to studies in the rat, there was a largely consistent pattern of observations including soft stool/diarrhea, decreased body weight gain, decreased plasma glucose, glucosuria and polyuria. Unlike the rat, however, secondary responses to glucose loss indicative of shifts in metabolism were not typically observed. Only in the 52-week study were changes in serum electrolytes apparent, which included increases in serum potassium and decreases in serum sodium and chloride all of which are related to diarrhea and polyuria.

Increases in bone specific serum alkaline phosphatase (ALP) were observed but these were within published limits, there were no changes in serum osteocalcin, and there were no histopathology findings in bone.

Histologically, the kidney was the single consistent target organ of toxicity of empagliflozin. Interstitial nephritis and tubular nephropathy were observed in the 4-, 13-, and 52-week dog studies almost exclusively in the high dose animals. In the pathology report of the 52-week study the lesions were described as ranging from minimal to mild in severity and characterized by the presence of interstitial infiltrates of mononuclear leukocytes with variable amounts of collagen within the cortex and/or corticomedullary junction. Infiltrates expanded the interstitium to separate tubules or obscured tubular architecture. These areas may have foci of increased interstitial collagen fibers (fibrosis). Tubules associated with the nephritis had a relative increase in cytoplasmic basophilia, an increased nuclear to cytoplasmic ratio, decreased luminal diameter, or variable luminal dilation with epithelial flattening. These tubules sometimes showed degenerative changes. These animals also demonstrated a minimal to moderate cortical tubule nephropathy (5 males and 2 females of the 100 mg/kg/day dose group), which was characterized by scattered tubules throughout the cortex with dilated lumens and lined with basophilic epithelial cells. This change may accompany and may overlap drug-related foci of chronic interstitial nephritis. The report states that this lesion was not observed after a 13-week recovery period in the 52-week study, but minimal mixed or mononuclear infiltrates were present in the cortex in both high dose recovery females. Moreover, interstitial nephritis was not fully recoverable in one dog of the 4-week study given a 8-week recovery period and was observed in one male of the 13-week study after a 13-week recovery. Renal cortical discoloration was observed in 0/6, 5/6, 6/6 and 6/6 animals in control, low, mid and high dose animals, respectively. In view of a lack of histopathological lesions or any other evidence pointing to an actual effect of empagliflozin on renal blood flow, it was concluded that the latter observations are likely not clinically relevant.

In the liver of a single 100 mg/kg/day male in the 26-week study, centrilobular degeneration characterized by microvesicular vacuolation of centrilobular hepatocytes was observed that may have been associated with loss of hepatocytes. Also, in a 30 and a 100 mg/kg/day female dog hepatocellular vacuolation was seen. In the pathology report the finding in the male is judged of being of uncertain nature, but the findings in the females are not discussed. In view of the small number of animals, these liver findings could be a signal of a treatment-related effect. In the 52-week study, one low dose animal showed panlobular, hepatocellular vacuolation and was characterized by one or more, round, punctate, clear macrovesicular vacuoles within hepatocytes of numerous hepatic lobules.

In the 52-week study there was an increase in severity from minimal to moderate of adrenal zona glomerulosa vacuolation. Possibly these changes reflect endocrine reactions to the long-term change in electrolyte balance.

In the same study one high dose animal showed testicular atrophy, a finding considered as being of uncertain nature. In the 4-weeks study reduction of testis and epididymis weight was observed in the high dose animals at the end of the recovery period. In the high dose males of the 2-weeks and the 26 weeks study small prostrate was observed, whereas in the high dose animals from the 13 weeks study and the mid and high dose animals from the 4 weeks study glandular atrophy of the prostrate was seen. Considering the high dose levels in these animals,

these effects where possibly related to weight loss and/or emaciation of the animals. It was considered non adverse as it was readily reversible during treatment-free recovery periods. Also in view of the high exposure multiples at these dose levels these findings are probably not clinically relevant for patients.

In the repeated dose toxicity studies in rats and dogs, empagliflozin-induced effects were generally mild at the low dose levels. At these dose levels (rats 100 mg/kg/day, dogs 10 mg/kg/day) exposure multiples were 10 and 18, respectively. Serious toxicity was generally limited to the high dose levels where exposure multiples were sufficiently in excess of human therapeutic exposure: rats 35, dogs 141-241. Yet in the carcinogenicity studies chronic effects were apparent including renal pathology in rats and male mice and vascular and soft tissue mineralization in rats that already appeared at the lowest dose level. For these chronic effects safety margins were <17 in rats and <4.4 in mice.

Genotoxicity

The genotoxic potential of empagliflozin was investigated in a bacterial reverse mutagenicity assay, an *in vitro* mammalian mutagenicity assay in L5178Y $tk^{+/-}$ Mouse Lymphoma cells and two *in vivo* rat bone marrow micronucleus tests with a three day exposure period. All of these tests were negative. Based on these data it is concluded that empagliflozin is without genotoxic potential.

Carcinogenicity

The carcinogenic potential of empagliflozin was studied in CD-1 mice at doses of 100, 300 or 1000 mg/kg/day and in Wistar (Han) rats at doses of 100, 300, or 700 mg/kg/day. At the highest dose, systemic exposure attained a 45x and 62x multiple of human therapeutic exposure in male and female mice, respectively, and in rats exposure multiples of 42x and 72x were achieved in the high dose males and females, respectively. Survival was decreased in male mice given 1000 mg/kg/day resulting in early termination of that group at week 97. Survival was unaffected by treatment in other groups of mice and all groups of rats.

There were no tumors observed in female mice. In the high dose males (1000 mg/kg/day), 5 renal tumors (3 adenomas and 2 carcinomas) were observed. Atypical hyperplasia was only observed in the high dose males. A wider spectrum of changes, including tubular hypertrophy, karyomegaly and cystic hyperplasia was seen in the lower dose groups in a dose-related manner. When these changes are seen as a continuum ranging from adaptive responses to the pharmacological action of empagliflozin to neoplastic changes leading to tumour formation, it is difficult draw the line where neoplastic transformation starts. The Applicant provided additional mechanistic studies to resolve the mode of action for renal tumors in CD-1 mice.

The weight of evidence on the absence of genotoxicity, gender and apparent mouse strain specificity, and the dose response and temporal relationships of chronic sustained degenerative/regenerative changes with renal neoplasms is consistent with a non-genotoxic mode-of-action. Both literature evidence and study data support a necessary but not sufficient mode-of-action role of predisposing pro-proliferative factors supported by background cystogenic changes in the CD-1 mouse strain (key event 1) and non-gender specific renal stress associated with the expected pharmacology (key event 2). These events turn out to be procystogenic but are not sufficient to cause tumors, which is evident from the lack of tumors in CD1 female mice

and rats. Chronic empagliflozin treatment in male mice results in additional and accelerated compound-related renal injury (key event 3) on top of key events 1 and 2, facilitated by exposure to cytotoxic 4-OH CTA generated from the unstable male-mouse predominant renal metabolite M466/2. Key event 4 is supported by study data showing more pronounced cystic tubular changes in CD-1 male mice with age and chronic empagliflozin treatment, and literature evidence suggesting impaired reserve capacity/injury susceptibility in aging rodents. Key event 5 is supported by study data showing the high co-occurrence of atypical hyperplasia and renal neoplasms in high dose male mice with chronic degenerative/regenerative renal tubular changes, and literature evidence suggesting an influencing or promoting role for renal tubular injury/tumors with the co-occurrence of similar cystogenic changes in rodents.

While the single renal tubular adenoma in a male mouse given 300 mg/kg/day cannot be definitively dissociated from empagliflozin treatment, there were several reasons why this tumor is not considered empagliflozin-related. The occurrence of this single neoplasm was not statistically significant and the incidence (1 of 50 animals; 2%) was within the historical control range (0.0-2.9%) for renal tubular adenomas of the test facility and supplier (from studies performed between 2002 and 2006). Furthermore, the kidneys of this animal either lacked degenerative and proliferative findings (cysts, karyomegaly and tubular atrophy) or harbored a severity similar to controls (CPN and tubular hypertrophy) when compared to that which was associated with empagliflozin-related renal tubular neoplasms in males given 1000 mg/kg/day. Although cystic hyperplasia was observed in this animal, the grade was slight and there was no karyomegaly or tubular atrophy, which was generally associated with the renal tumors observed in the 1000 mg/kg/day male dose group. In the 13-week mouse study, degenerative changes (karyomegaly, single cell necrosis and cystic hyperplasia) detected in the 500 mg/kg/day dose group were not accompanied by increased tubule cell proliferation as evidenced by a lack of increased Ki-67 staining at this dose level. This indicates that a threshold dose of >500 mg/kg/day is required to produce a level of tubular degeneration that results in a proliferative regenerative response. Furthermore, the preneoplastic precursor lesion of renal tubular adenomas, atypical hyperplasia, was not detected in males in the 300 mg/kg/day dose group. For these reasons the single renal tubular adenoma in the 300 mg/kg/day was not considered empagliflozin-related.

Thus the 300 mg/kg dose can be considered the NOAEL for empagliflozin-induced tumor formation, which provides as safety margin based on systemic exposure of 11.

In male rats given 700 mg/kg/day, a statistically significant increased incidence (18%) of benign vascular tumors (hemangiomas) in the mesenteric lymph node was observed. The lack of genotoxic activity of empagliflozin, the well-established high background incidence of hemangioma of the mesenteric lymph node in Wistar (Han) rats, the specific susceptibility of the male rat to these tumors, the extreme rarity of hemangiomas arising in lymph nodes in humans, the presence of lymph node findings (sinus histiocytosis, pigmented macrophages, mast cells and/or sinus erythrocytes) in the rat carcinogenicity study consistent with known or proposed epigenetic mechanisms for the vascular tumors (vascular obstruction, chronic antigenic stimulation and increased hemolysis, hemosiderosis and iron overload), and the absence of vascular neoplasms in any other species following empagliflozin administration suggest a low relevance of this finding to human safety. The exposure multiple to the dose of 300 mg/kg/day at which the finding was not considered empagliflozin-related is 26x relative to the steady state

exposure in clinical trials at 25 mg/day. Taken together the increased incidence of hemangioma of the mesenteric lymph node in male rats of the 700 mg/kg/day dose group is a finding that is considered of low relevance to human safety and is not considered to materially influence the benefit/risk assessment of empagliflozin.

Also in males, a statistically increased incidence of benign interstitial (Leydig) cell tumors of the testes of 14% and 12% was observed in males given 300 or 700 mg/kg/day, respectively. It is currently uncertain which mechanism leads to these tumours. Yet, in view of the minimal increase in incidence and the acceptable safety margin of 18 at the low dose level these tumours are likely of little relevance for humans.

Reproduction Toxicity

Male and female fertility and early embryonic development were not affected in rats up to 700 mg/kg/day.

Empagliflozin did not show teratogenic potential in the embryofetal developmental studies in rats or rabbits up to 700 mg/kg. Effects on foetuses were limited to a few foetuses with bent limbs in rats and post-implantation loss attributable to complete litter loss in one rabbit, both occurring at the highest maternally toxic dose level.

In the pre- and postnatal toxicity study in rats empagliflozin caused a minimal transient decrease in body weight gain that did not result in any lasting deficits in development, learning or memory. starting at a dose level of 30 mg/kg. At the NOAEL of 10 mg/kg/day, the systemic exposure of the dams was comparable to human exposure at the anticipated therapeutic dose (safety margin is 1). Although empagliflozin is transferred via the placenta, the levels are considered very low. Exposure via the milk is considered a possibility. However, in the pre- and postnatal developmental toxicology study in rats, plasma levels of empagliflozin measured on postnatal day 18 in pups born to dams treated with up to 100 mg/kg/day from GD 6 through lactation day 20 were all below limits of quantitation. The Applicant states that there was no change in the composition of the milk. However, only protein, lactose and glucose were measured. Glucose could not be detected in any sample, including the samples from control animals. The transient effects on body weight probably were a consequence of the pharmacological action of empagliflozin. The statistically significant deficit in learning and memory observed in male pups born to dams of the 100 mg/kg/day group was only observed at PND21. At PND62 no deficit was apparent. This indicates no irreversible functional loss in learning and memory had occurred.

Local Tolerance

Local tolerance of empagliflozin was assessed in a dermal sensitization test in mice and dermal and ocular irritation tests in rabbits and was found to be negative in all tests.

Other toxicity studies

The weight of evidence demonstrates that empagliflozin is not immunotoxic in the species used in the preclinical studies and therefore is not considered to have an immunotoxic potential in humans under the conditions of therapeutic use.

Based on the calculations provided by the Applicant, the human to animal safety margin at the proposed impurity specifications would be 6, 42 and 17, respectively. When a similar calculation is made, but based on qualification in the 4-week, 13-week and 13-week studies in dogs, instead of rats, the safety margins would be 2, 14 and 6. Thus for both species, the proposed impurity specifications provide safety margins in excess of unity.

The specified impurities were tested for genotoxic properties in bacterial reverse mutation assay and *in vitro* micronucleus assay in CHO cells. All tests provided negative results.

Concerning the lack of structural alerts of any potential impurities, the Applicant provided an *in silico* assessment report, which revealed no structural alerts for genotoxicity.

Combination toxicology studies were undertaken by the Applicant to support clinical trials for fixed dose combinations of empagliflozin and metformin or linagliptin. Such fixed dose combinations are not the subject of this MAA. However, once marketed, combination therapy of diabetes patients with empagliflozin and other antidiabetic medication might be considered. Therefore these studies were briefly reviewed based on summary information provided by the Applicant.

The combination of empagliflozin with metformin did not affect the pharmacokinetics of empagliflozin. No new toxicities were revealed. However, when combined with metformin, the NOAEL in rats was reduced as compared to empagliflozin administration alone, reflecting a greater sensitivity to empagliflozin toxicity in the presence of metformin. Although not discussed by the Applicant, one possibility for this greater sensitivity might be a greater reduction of blood glucose levels in the presence of metformin.

When linagliptin and empagliflozin were combined at high dose levels a drug-drug interaction was observed as the co-administration of linagliptin increased the exposure to empagliflozin whereas empagliflozin decreased the systemic exposure to linagliptin when dosed concomitantly. Again no new toxicities were revealed, however, liver effects appeared to be more prominent in the presence of linagliptin.

2.3.4. Ecotoxicity/environmental risk assessment

Based on the outcome of the OECD 107 log Kow determination, empagliflozin is not expected to be PBT or vPvB.

PEC_{sw} is 0.125 µg/L, which exceeds the action limit of 0.01 µg/L. A Phase II assessment is warranted.

Based on the results of the PEC/PNEC calculations in the phase II Tier A environmental risk assessment, no unacceptable adverse effects for the surfacewater, groundwater and STP compartment are expected from empagliflozin.

However, the dossier is incomplete. Based on the total residue approach, significant shifting to sediment is observed in the OECD 308 study. Therefore, the environmental risks of empagliflozin to the sediment compartment should be assessed. The applicant is requested to calculate a PECsediment, perform a toxicity study on a sediment dwelling organism (*Hyalella sp., Lumbriculus sp.* or *Chironomus sp.*), and compare the PEC and PNEC for the sediment compartment.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of empagliflozin to the environment.

Table 1. Summary of main study results

Substance (INN/Invented Name): Empagliflozin					
CAS-number (if available): 864070-44-0					
PBT screening		Result			**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD107	Log K_{ow} = 1.73			Not potentially PBT, nor vPvB
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	Log K_{ow} = 1.73			not B
Persistence	DT50 or ready biodegradability	Not readily biodegradable			Potentially P
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 $_{surfacewater}$, 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	

2.3.5. Discussion on non-clinical aspects

The most prominent target organ in toxicity studies in mice, rats and dogs is the kidney, although the observed effects differ to some extent between the species. In the mouse at all dose levels renal tubular dilatation occurs, which is considered a consequence of the pharmacology of empagliflozin. At higher dose levels this leads to cyst formation and the high dose animals show tubular adenomas and carcinomas in the carcinogenicity study. A mode of action for empagliflozin-associated male mouse renal tumors involving diminished oxidative stress handling capacity and predisposition to cystogenesis in the male CD-1 mouse,

pharmacology related renal stress, additional compound related renal metabolic stress involving a male mouse-predominant renal metabolite, accelerated depletion of renal stress reserve and conversion to constitutive proliferative phenotype is proposed. A systematic approach for analyzing the relevance of a cancer mode of action for humans was employed and the weight of evidence on the absence of genotoxicity, gender and apparent mouse strain specificity, and the dose response and temporal relationships of chronic sustained degenerative/regenerative changes with renal neoplasms is consistent with a non-genotoxic mode-of-action of which the relevance for humans is currently unknown. The 300 mg/kg dose can be considered the NOAEL for empagliflozin-induced tumor formation, which provides as safety margin based on systemic exposure of 11. Pharmacology related renal stress occurring at all dose levels is not species specific and could be relevant for humans as well. It is therefore important that renal function, especially where related to renal tubular integrity, is followed up clinically.

In the rat tubular mineralisation occurs at all dose levels and vascular and soft tissue mineralisation and increased trabecular bone formation in the sternum and increased prominence of residual cartilage in the femur were observed. Disturbance of calcium homeostasis is suggested to be the main contributory factor leading to mineral deposition and bone changes.

Various hepatic changes were seen in the non-clinical studies. No clear pattern was observed. In mice and rats increased liver weight was observed. In mice hydropic changes (13-week study) and hepatocytic cytoplasmic vacuolation (carcinogenicity study) were seen. In rats, microvescicular hepatocytic vacuolation was observed and incidentally, mild multifocal random foci of hepatocellular necrosis and hepatocellular eosinophilic globules were seen in the repeated dose toxicity studies, but in the carcinogenicity study vacuolation of sinusoidal cells was seen. Mild increases in ALT and AST were seen in rats and dogs. In dogs, hypertrophy of Kuppfer cells was observed. In addition, centrilobular degeneration characterised by microvescicular vacuolation of centrilobular hepatocytes was seen in a single animal and in another animal panlobular hepatocellular macrovescicular vacuolation was observed. Finally in the combination toxicology study with empagliflozin and linagliptin, liver effects appear more prominent. As no further in depth toxicological investigations have been undertaken to determine the precise nature of the vacuolation or the cause of AST/ALT elevations and sporadic incidence of necrosis, it is premature to conclude that there would be no risk for adverse liver events in patients. It is therefore agreed that liver safety is followed up in long-term clinical studies and included as an important potential risk in the RMP. Yet, it can be accepted that currently no further non-clinical mechanistic studies are undertaken.

2.3.6. Conclusion on the non-clinical aspects

Pharmacology studies *in vitro* and in animal models have shown that empagliflozin is a selective SGLT2 inhibitor reducing blood glucose levels by diminishing reabsorption of glucose in the renal tubuli.

The provided pharmacokinetic studies indicate that the chosen species were adequate for the toxicology studies. Besides a few omissions, the pharmacokinetics have been sufficiently studied.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. The table below lists the main phase II and phase III studies submitted as part of this Marketing Authorisation Application.

Table 2: Overview of Phase 2 and 3 Studies

Trial characteristics	Trial number	Geographical regions	Duration analysed
Pivotal double-blind phase III trials	1245.19	Europe, Asia, North America	24 weeks
	1245.20	Europe, Asia, North America	24 weeks
	1245.23$_{(met)}$	Europe, Asia, North America, Latin America	24 weeks
	1245.23$_{(met+SU)}$	Europe, Asia, North America, Latin America	24 weeks
Double-blind phase III extension trials	1245.31	Europe, Asia, North America, Latin America	52 weeks[1]
Additional phase IIb/III double-blind individual trials	1245.28	Europe, Asia, North America, Latin America, Africa/Middle East	52 weeks[2]
	1245.33[3]	Europe, Asia, North America,	78 weeks
	1245.48	Europe, North America, Africa/Middle East	12 weeks
	1245.36	Europe, Asia, North America, Africa/Middle East	52 weeks
	1245.25	Europe, Asia, North America, Latin America, Africa/Middle East	12 weeks[4]
Open label phase IIb extension trial	1245.24	Europe, Asia, North America, Latin America	90 weeks[5]

[1] Including the 24-week treatment duration in the preceding trials; 52-week efficacy data from a prespecified interim analysis are included in this submission. The overall planned duration (initial trials + extensions) is 76 weeks

[2] Minimum duration at time of interim analysis; overall planned duration is 208 weeks

[3] Trial 1245.33 was conducted in patients with basal insulin as background therapy. This trial was originally designated as a phase IIb trial. Since it had confirmatory testing introduced via a protocol amendment, it is considered to be equivalent to a confirmatory phase III trial for the assessment of the efficacy and safety of empagliflozin

[3] Minimum duration at time of interim analysis; overall anticipated duration is between 6 and 8 years

[5] Data from a combined analysis with the preceding double-blind preceding trials 1245.9 and 1245.10 are presented

2.4.2. Pharmacokinetics

During drug development three formulations were used:

The formulation **TF-I** was developed in the dose strengths of 0.5 mg, 5 mg, 25 mg and 100 mg. Formulation **TF-II** was developed for Phase II clinical studies based on TF-I as this formulation provided the desired systemic exposure and stability. The qualitative composition of TF-II is the same as for TF-I but differ in the quantitative composition. The final formulation 25 mg **FF** contained in the tablet core the same excipients as TF-II with an optimized quantitative composition. The 10 mg formulation has a composition different from the 25 mg tablets.

Specific and high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) methods for the quantification of empagliflozin and its metabolite were developed and validated for human urine and plasma to support the clinical empagliflozin development program. Initially, the assays were developed for empagliflozin and its metabolite and they were later modified for the determination of empagliflozin only.

Population Pharmacokinetic/pharmacodynamic Modelling

The applicant performed a Population pharmacokinetic and pharmacokinetic-pharmacodynamic modelling of empagliflozin in patients with type 2 diabetes mellitus.

Pharmacokinetic Results

The demographic covariates (BMI, age, gender, and race) as well as TPRO had a significant, but small impact on empagliflozin's CL/F and AUC,ss, respectively. The typical AUC,ss values were generally within ±25% of a reference patient and thus were considered as not clinically relevant. Furthermore, the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. The typical AUC,ss increased by 18.5% (95% CI: 13.0, 24.8), 49.2% (95% CI: 39.2, 60.6), 88.1% (95% CI: 69.9, 107) in patients with an eGFR of 60, 30, and 15 mL/min/1.73 m2, respectively, compared to a reference patient with a eGFR of 100 mL/min/1.73 m2. Other covariates tested included smoking status and liver enzymes (LDH, AST, ALT, and AP) did not have a significant effect on the PK of empagliflozin. These results are further elaborated and commented upon with the respective headers in this report.

Absorption

The Applicant did not provide an absolute bioavailability study in which a comparison of the exposure to empagliflozin is compared between an intravenous dose and an oral dose.

However, in the mass-balance study 54% of the radioactivity administered orally was found in the urine and about 7% in the faeces as metabolites. It can therefore be assumed that at least 60% of the dose is absorbed with oral solution.

The provided data indicates that the final 25 mg formulation can be considered bioequivalent with the trial formulation TF-II which is used in the pivotal pharmacokinetic studies. However, in some phase I studies also the trial formulation TF-I was used. As the quantitative composition of this formulation differ substantially from the final formulation (FF) as well as from the other trial formulation FT-II, comparison of the results with this first formulation is difficult to make as no comparative bioavailability study was submitted. As stated by Applicant empagliflozin can be considered as a BCS Class III drug, a biowaiver for this formulation can be granted as this formulation was only used in three non-pivotal studies. The submitted studies demonstrate that food significantly affect the bioavailability of empagliflozin. The extent of exposure (AUC) is decreased by 16% and the peak levels C_{max} by more than 37%. The differences are considered not clinical relevant.

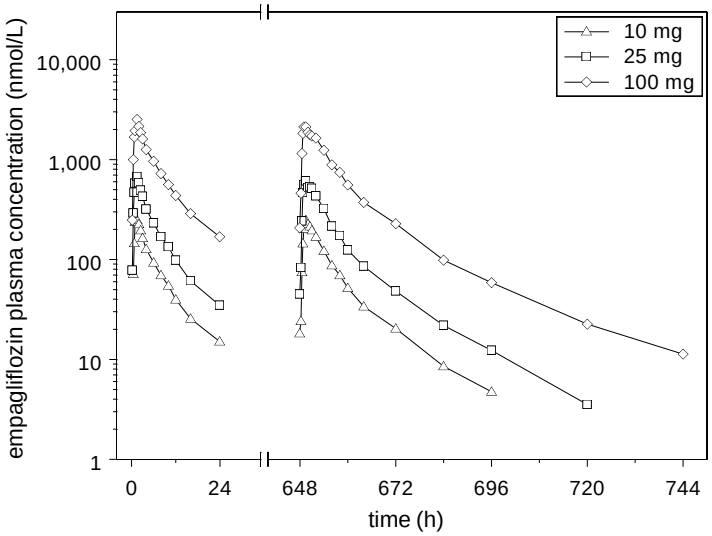
In study 1245.79, the 10 mg formulation was shown to be bioequivalent with the 25 mg formulation under fasting conditions. The 90% confidence intervals for the extent and rate of absorption were, after dose correction, within the acceptance ranges of 0.80 - 1.25.

Distribution

Empagliflozin is rapidly absorbed following oral administration with a mean t_{max} of 0.938 h in plasma. After reaching peak levels, plasma concentrations declined in a biphasic fashion with a rapid distribution phase and a slower elimination phase. The apparent steady-state volume of distribution was 73.8 L. The apparent terminal elimination half-life of empagliflozin was 12.4 hours, and the apparent oral clearance was 10.6 L/h.

The protein binding in human plasma is about 86% and the distribution to red blood cell 37% of the plasma concentration.

In the figure below a typical concentration-time curve of empagliflozin upon oral administration of 10, 25 mg, and 100 mg are given.



Elimination

Excretion

Of the total radioactivity orally administered 54% was recovered in the urine and 41% in the faeces.

In urine 28.6% of the dose is excreted unchanged in the urine. In faeces, unchanged empagliflozin was found to represent 82.9% of faecal radioactivity (34.1% of radioactive dose). The remaining faecal radioactivity was accounted for primarily by three metabolites, all of which were also observed in plasma.

Metabolism

In humans, unchanged empagliflozin is the most abundant drug-related component in plasma (75.5 - 77.4% of total radioactivity). A total of six metabolites of empagliflozin were detected in plasma. However, none are considered as major metabolites as the proportion of each metabolite was less than 10% of total drug-related exposure. Empagliflozin biotransformation primarily involved glucuronidation, and to a lesser extent oxidation. As such, the most abundant metabolites of empagliflozin were three glucuronide conjugates (3.3 - 7.4% of plasma radioactivity).

In urine only small amounts of this metabolite could be detected after oral administration of empagliflozin. As the metabolites do not contribute to the clinical efficacy and safety, the lack of further information on the pharmacokinetics of these metabolites is acceptable.

No information on possible genetic polymorphism was discussed by the Applicant as the metabolites formed by enzymes with are subjected to polymorphism (e.g. UGT1A1) are only formed in small quantities.

Empagliflozin exposure increased in a more or less dose proportional way over the dose range 0.5 mg to 800 mg following single oral administration to healthy volunteers. C_{max} was near dose proportional from 0.5 to 800 mg. Paired comparisons of dose groups indicated that increases in C_{max} were dose proportional from 0.5 to 400 mg and slightly less than dose proportional from 400 to 800 mg.

The pharmacokinetic characteristics of empagliflozin were similar after multiple dosing at steady-state compared to single dose suggesting that empagliflozin demonstrates linear pharmacokinetics.

As the proposed dose is only 25 mg, the deviation from linearity in the higher range is considered of no clinical relevance.

As no unexpected accumulation occur after multiple doing of empagliflozin, time dependent changes in the pharmacokinetics are unlikely to occur.

Pharmacokinetics in the target population

The exposure of empagliflozin in T2DM patients do not differ in a clinical significant way from healthy subjects. By comparing the pharmacokinetic variables after single dose in healthy subjects from with those of T2DM patients a slightly higher exposure was found in T2DM patients (see Table below). These exposure differences are marginal and as empagliflozin also shows

linear pharmacokinetics in both healthy volunteers and patients with T2DM, the observed minor differences in empagliflozin exposure are not expected to confine the applicability of healthy volunteer trial results to the patient population.

Parameter	2.5 mg		10 mg		25 mg		100 mg	
	HV[a] (n=6)	Patients[a] (n=9)	HV[a] (n=6)	Patients[a] (n=9)	HV[a] (n=6)	Patients[a] (n=9)	HV[a] (n=5)	Patients[a] (n=9)
$AUC_{0-\infty}$[b] (nmol.h/L)	396 (11.0)	476 (18.8)	1730 (21.8)	1910 (15.1)	3830 (21.5)	4900 (24.3)	16500 (14.5)	23600 (19.6)
C_{max} (nmol/L)	53.2 (11.7)	62.4 (19.8)	226 (20.4)	245 (21.0)	505 (25.9)	606 (24.2)	2500 (26.7)	2750 (25.5)
t_{max}[c] (h)	1.75 (0.983-2.98)	1.50 (0.667-1.50)	1.50 (0.983-2.03)	1.50 (0.983-2.00)	2.05 (1.00-3.02)	1.50 (0.983-4.00)	1.00 (0.750-3.00)	3.00 (9.83-4.00)
$t_{1/2}$ (h)	8.57 (6.86)	11.4 (20.2)	13.1 (30.9)	11.9 (11.5)	10.2 (20.9)	10.8 (18.3)	10.6 (23.5)	13.6 (27.5)

[a] HV study (trial 1245.1 [U08-1237]); Patients (trial 1245.2 [U09-1271])
[b] Patients: $AUC_{0-\infty}$ calculated after the first dose
[c] median (range)

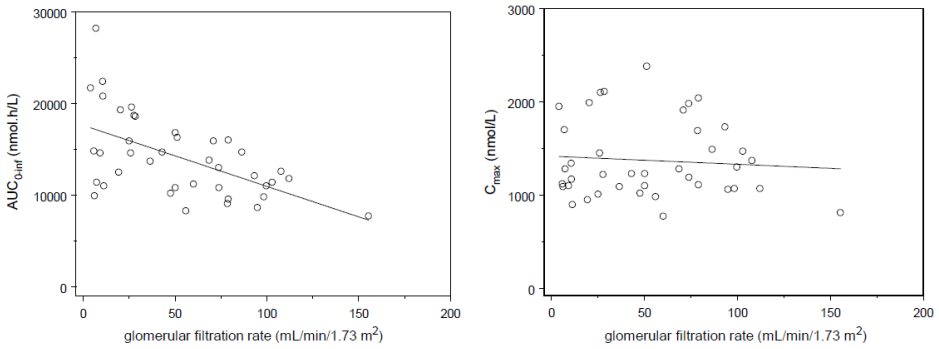
Special populations

The extent of exposure (AUC) is affected by renal insufficiency. In mild and moderate impairment the exposure is increased by 20% and in patients with severe impairment by 66%. Also the half-life is increased in severe renal impaired patients in comparison with normal renal functions.

This increase in exposure is mainly caused by a decrease in renal clearance of empagliflozin in these patients. As the active site of action of empagliflozin is the renal tubuli, the efficacy will be probably decreased in these patients as the glucose in urine is these patients is also decreased significantly.

This higher exposure and lower glucose excretion in patients with mild and moderate renal impairment may be considered of no clinical relevance. This is based on the data of the Phase III study 1245.36 from which the Applicant claims that patients with moderate renal impairment did show a positive B/R ratio.

The relationship between renal impairment and the exposure is shown in the figure below.



Liver impairment affects the exposure of empagliflozin significantly. The overall exposure (AUC) increased by 75% in severe liver impaired patients in comparison with healthy subjects. This is not due to renal insufficiency, which may be also manifest in patients with liver impairment, as

the amount excreted in urine is increased slightly also. No dose adjustment is considered necessary in these patients.

The exposure to empagliflozin in Japanese and Chinese subjects is significant higher after multiple dosing of 25 mg orally than in Caucasian subjects. This may be due to differences in the weight as exposure to empagliflozin appeared to decreases with weight.

The slight increase in exposure in patients over 65 years may be explained by a lesser renal function in these group of patients as renal impairment clearly affects the exposure to empagliflozin. It is therefore acceptable not to adjust the dose on the basis of age but more on the renal function.

Weight and gender does not have clinically significant effect on the exposure of empagliflozin.

Pharmacokinetic interaction studies

Potential drug-drug interactions of empagliflozin have been investigated in a number of phase I trials. The test substances were selected based on the properties of empagliflozin or as important and frequently prescribed co-medications in the target population.

Empagliflozin pharmacokinetics were similar with and without co-administration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, hydrochlorothiazide, and torasemide. Overall exposure (AUC) of empagliflozin increased 1.6-fold following co-administration with gemfibrozil, 1.35-fold with rifampicin, and 1.5-fold with probenecid. The observed increases in the overall exposure of empagliflozin were not considered to be clinically significant.

No dosage adjustment of empagliflozin is recommended when it is administered concomitantly with gemfibrozil, rifampicin, or probenecid. Therefore interaction on the level of the transporters OATP1B1, OATP1B3, OATP2B1 and OAT3 are considered not clinical relevant.

Empagliflozin had no clinically meaningful effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torasemide, and oral contraceptives when co-administered with any of these drugs.

2.4.3. Pharmacodynamics

The pharmacodynamics profile of empagliflozin has been characterised based on the results of ten clinical pharmacology studies, including one QT study.

Mechanism of action

The kidney has a role in the regulation of blood glucose levels. Therefore the kidney can serve as a target for antidiabetic therapy. The sodium-dependent glucose co-transporter-2 (SGLT-2) is localized in the renal proximal tubules, accounting for approximately 90% of renal glucose reabsorption. It reabsorbs most of the ~ 180 g glucose filtered under normal conditions through the glomeruli per day. SGLT-2 inhibition decreases renal glucose reabsorption, promotes glycosuria and results in reduced levels of blood glucose. Empagliflozin selectively inhibits SGLT-2 in the kidney, resulting in direct, insulin-independent, elimination of glucose by the kidney.

Primary and Secondary pharmacology

Primary pharmacology

The urinary glucose excretion (UGE) is the main parameter assessed in the investigation of the pharmacodynamic profile of empagliflozin. The choice of urinary glucose excretion (UGE) as the main parameter in the investigation of the pharmacodynamics of empagliflozin is acceptable and crucial in view of its claimed mechanism of action. UGE has been assessed in three trials in healthy volunteers and in five trials in subjects with T2DM.

From the three trials in healthy subjects it is concluded that oral administration of empagliflozin resulted in a dose-dependent increase in UGE. In healthy volunteers, UGE was higher with all doses (0.5 mg to 800 mg) compared with placebo (see figure). Following a single oral administration of empagliflozin, up to 91 g of glucose was excreted in urine. Empagliflozin inhibited reabsorption of <40% of filtered glucose with single daily doses up to 10 mg and approximately 40–60% of filtered glucose at higher doses, with the effect reaching a plateau at around the 100 mg dose. At doses less than 50 mg, the majority of glucose was excreted in the first 24 h, but at doses of 100 mg and above, glucose excretion continued for up to 48–72 h. The time to reach the maximum rate of UGE was 7 h in most subjects and was similar in all dose groups.

It is concluded that empagliflozin can induce sustained, dose-dependent glycosuria in healthy subjects.

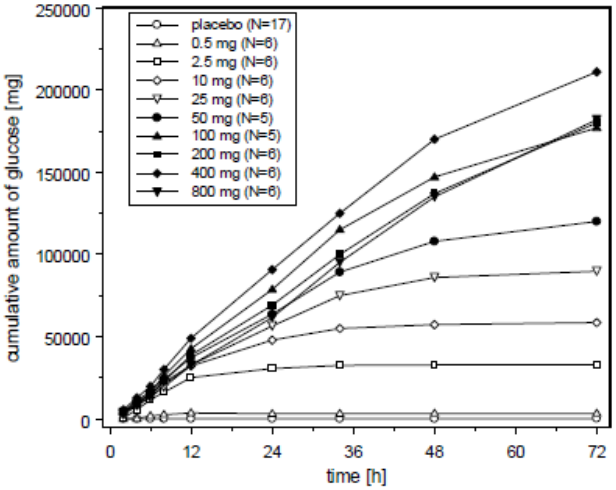


Figure PD01 Mean cumulative amounts of glucose excreted in urine following administration of single oral doses of 0.5 mg to 800 mg empagliflozin in healthy volunteers

In Caucasian, Japanese and Chinese patients with type 2 diabetes administration of empagliflozin results in a dose-dependent increase in urinary glucose excretion. UGE increases immediately following the first dose of empagliflozin, is observed over the entire 24-h dosing interval and is maintained at the end of a 4-week treatment period. It averages at about 78 g/day with 25 mg empagliflozin once daily. A plateau appears to be reached at the 10 mg dose of empagliflozin once daily. It should be noted that the rates of UGE in the empagliflozin 10 mg and 25 mg groups were similar. Increased UGE with empagliflozin treatment does not result in marked increases of urine volume.

In healthy volunteers empagliflozin does not have any effect on plasma glucose levels despite of increased glycosuria. However in patients with T2DM empagliflozin reduces plasma glucose in a more or less dose dependent fashion. However the differences between 10 and 25 mg are not significant.

With empagliflozin, cumulative amounts of glucose in urine decrease with renal impairment. However due to limited data the impact of lowered glomerular filtration rate on plasma glucose in T2DM as well as the safety aspects are further assessed in clinical studies.

In patient with hepatic impairment UGE was not affected; it was similar in subjects with liver impairment and subjects with normal hepatic function.

No effect of empagliflozin on serum insulin was observed during 8-day treatment of patients with T2DM with empagliflozin. Insulin AUEC and E_{max} were similar with and without empagliflozin treatment at all dose levels. However, after 24 weeks of treatment with empagliflozin (10 and 25 mg doses) reductions from baseline compared with placebo are observed for fasting plasma insulin. Following treatment with empagliflozin reductions in plasma levels of 1,5-AG are observed in T2DM reflecting the effect on glucose levels. Fructosamine levels decreased. However, the observed changes were not significantly different from placebo. There were no consistent trends in changes observed in glucagon levels with empagliflozin treatment.

Secondary pharmacology

Effects of empagliflozin on QT interval were investigated in Trial 1245.6. A total of 30 male and female subjects were randomised to receive 25 mg empagliflozin (therapeutic dose), 200 mg empagliflozin (supratherapeutic dose), 400 mg moxifloxacin (positive control), or 2 times placebo. Single oral doses of 25 mg (therapeutic) and 200 mg empagliflozin (supra-therapeutic) in healthy subjects are not associated with prolongation of the QT interval. The primary endpoint was mean change from baseline (MCfB) in the population heart rate-corrected QT interval (QTcN) between 1–4 h after dosing. The placebo-corrected adjusted mean change from baseline in QTcN within the time interval 1 – 4 h after dosing was 0.59 ms (90% CI: -0.69, 1.87) for 25 mg empagliflozin and -0.22 ms (90% CI: -1.39, 0.94) for 200 mg empagliflozin. The difference in the mean QTcN change from baseline between 2 h and 4 h after administration of moxifloxacin vs. placebo was 12.42 ms with a lower 90% CI of 10.7 ms clearly above zero. Also the analysis of the primary endpoint by gender and analyses of secondary endpoints indicated the absence of a clinically relevant increase from baseline in the mean QTcN interval. It is concluded that empagliflozin has no effect on QT-interval.

Genetic differences in PD response

In healthy subjects and in Caucasian, Japanese and Chinese patients with type 2 diabetes administration of empagliflozin results in a dose-dependent increase in urinary glucose excretion (UGE). UGE increases immediately following the first dose of empagliflozin, is observed over the entire 24-h dosing interval and is maintained at the end of a 4-week treatment period. It averages at about 78 g/day with 25 mg empagliflozin once daily. A plateau appears to be reached at the 10 mg dose of empagliflozin once daily. There are no differences between Japanese, Chinese and Caucasian subjects.

In healthy Caucasian and Japanese subjects empagliflozin does not influence plasma glucose. In Japanese and Chinese patients with type 2 diabetes as well as in Caucasian patients administration of empagliflozin reduces plasma glucose.

There are no arguments to conclude genetic differences between Caucasian, Japanese and Chinese subjects concerning serum insulin, 1,5-Anhydroglucitol, fructosamine or glucagon during administration of empagliflozin.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

In general, the pharmacokinetics of empagliflozin are well established and the pharmacokinetic variables with respect to absorption, distribution, excretion and metabolism do not give rise to unforeseen problems with this product.

The increased systemic exposure of empagliflozin in patients with moderate or severe renal impairment, the decreased empagliflozin and glucose excretion in urine in these patients is discussed further within the clinical context (see below).

The significant increase in exposure in patients with severe hepatic impairment may influence the Benefit/Risk of these patients in a negative sense. The impact of liver impairment on plasma glucose in T2DM as well as the safety aspects are further assessed in phase III studies (see below). Patients with T2DM did show similar exposure as healthy volunteers.

Pharmacodynamics

The pharmacodynamics of the compound have been assessed in healthy volunteers, in Caucasian, Japanese and Chinese subjects with T2DM and also in T2DM patients with renal and hepatic impairment. This is considered an adequate approach.

In healthy subjects and in Caucasian, Japanese and Chinese patients with type 2 diabetes administration of empagliflozin results in a dose-dependent increase in urinary glucose excretion (UGE). UGE increases immediately following the first dose of empagliflozin, is observed over the entire 24-h dosing interval and is maintained at the end of a 4-week treatment period. It averages at about 78 g/day with 25 mg empagliflozin once daily. A plateau appears to be reached at the 10 mg dose of empagliflozin once daily. No significant differences were found between 10 mg and 25 mg. In the clinical studies the 10 mg as well as the 25 mg dose have been studied. This is justified for an optimal dose selection.

In healthy volunteers empagliflozin does not have any effect on plasma glucose levels despite increased glycosuria. However in patients with T2DM empagliflozin reduces plasma glucose in a more or less dose dependent fashion.

In renal impairment with empagliflozin, cumulative amounts of glucose in urine decrease, which can be expected base on the mechanism of action. However due to limited data the impact of lowered glomerular filtration rate on plasma glucose in T2DM as well as the safety aspects should be further assessed in clinical studies.

In patients with liver impairment on the basis of pharmacokinetic results no dosage adjustment of empagliflozin can be recommended. The impact of liver impairment on plasma glucose in T2DM as well as the safety aspects are further assessed in phase III studies (see below).

A thorough QT study indicates that single oral doses of 25 mg (therapeutic) and 200 mg empagliflozin (supra-therapeutic) in healthy subjects are not associated with prolongation of the QT interval.

It is concluded that the data concerning pharmacodynamics of empagliflozin indicate efficacy of the compound in the treatment of T2DM.

2.4.5. Conclusions on clinical pharmacology

PK and PD of empagliflozin are adequately characterised and show the characteristics of a SGLT2 inhibitor. Dose-response data support the use of 10 and 25 mg in the phase III studies.

2.5. Clinical efficacy

2.5.1. Dose response studies

Dose selection for the phase III program was mostly based on the randomised, double-blind, placebo-controlled phase IIb trials 1245.9 and 1245.10. In trial 1245.9 empagliflozin (up to 25 mg once daily) was administered as monotherapy and in trial 1245.10, empagliflozin (up to 50 mg once daily) was administered as add-on therapy to a background regimen of metformin. All doses were well tolerated and showed a good safety profile. The primary endpoint HbA1c in trials 1245.9 and 1245.10 was the change from baseline in HbA1c after 12 weeks. In study 1245.9, an open-label metformin group was included (2x1000 mg, or maximum tolerated dose). In study 1245.10, an open-label sitagliptin group was included (100 mg).

In trial 1245.9, in which empagliflozin was administered as monotherapy, the differences between empagliflozin and placebo in the adjusted mean changes from baseline in HbA1c after 12 weeks increased with increasing dose of empagliflozin and were: -0.52% (5 mg), -0.57% (10 mg), and -0.72% (25 mg). The effect on the HbA1c level was highest in the metformin group (-0.85%).

In trial 1245.10, in which empagliflozin was administered as add-on therapy to background medication with metformin, the differences between empagliflozin and placebo in the adjusted mean changes from baseline in HbA1c after 12 weeks were -0.24% (1 mg), -0.39% (5 mg), -0.71% (10 mg), -0.70% (25 mg), and -0.64% (50 mg).

2.5.2. Main studies

Methods

A total of 11250 randomised and treated patients are included in the evaluation of efficacy presented. Of these, 3021 patients were randomised to empagliflozin 10 mg

and 3994 patients were randomised to empagliflozin 25 mg. Another 3081 patients were randomised to receive placebo and 1154 patients were randomised to an active comparator. At Day 120 an additional (add-on to insulin) study was submitted. Study 1245.49 enrolled 563 subjects of whom 186 received empagliflozin 10 mg and 189 empagliflozin 25 mg. See Table 3 for an overview of the trials.

Table 3 Overview of trials included in the evaluation of efficacy (only patients in randomized treatment groups) – FAS

		Number of patients, N (%)				
Trial characteristics	Trial number	Placebo	Empa 10 mg	Empa 25 mg	Active comparator	Total
Pivotal double-blind phase III trials	1245.20	228 (25.4)	224 (24.9)	224 (24.9)	223 (24.8)[1]	899 (100.0)
	1245.23$_{(met)}$	207 (32.5)	217 (34.1)	213 (33.4)	0	637 (100.0)
	1245.23$_{(met+SU)}$	225 (33.8)	225 (33.8)	216 (32.4)	0	666 (100.0)
	1245.19	165 (33.1)	165 (33.1)	168 (33.7)	0	498 (100.0)
Double-blind phase III extension trials	1245.31[2]	825 (30.6)	831 (30.8)	821 (30.4)	223 (8.3)[1]	2700 (100.0)
Additional double-blind individual trials	1245.28	0	0	765 (49.5)	780 (50.5)[3]	1545 (100.0)
	1245.33	170 (34.4)	169 (34.2)	155 (31.4)	0	494 (100.0)
	1245.48	271 (32.9)	276 (33.5)	276 (33.5)	0	823 (100.0)
	1245.36	319 (43.2)	98 (13.3)[4]	321 (43.5)	0	738 (100.0)
	1245.25	1496 (33.3)	1495 (33.3)	1504 (33.5)	0	4495 (100.0)
Open label phase II extension trial[5]	1245.24	0	152 (33.4)	152 (33.4)	151 (33.2)[6]	455 (100.0)
Overall total		3081 (27.4)	3021 (26.9)	3994 (35.5)	1154 (10.3)	11250 (100.0)

The full analysis set (FAS) usually included all randomised patients who received at least one dose of trial medication and had a baseline HbA_{1c} measurement (and in trial 1245.48, also a baseline mean 24-hour SBP measurement).
In trial 1245.48, the FAS included all randomised patients who received at least one dose of trial medication and had a baseline HbA1c measurement as well as a.

[1] Sitagliptin 100 mg

[2] Extensions of the pivotal placebo-controlled trials (1245.19, 1245.20, 1245.23$_{(met)}$, 1245.23$_{(met+SU)}$). The totals presented here comprise the totals of the patients randomised and included in the FAS of the preceding pivotal trials irrespective of whether they continued into the extension.

[3] Glimepiride 1 mg to 4 mg

[4] In trial 1245.36, patients with moderate or severe renal impairment were randomised to placebo or empagliflozin 25 mg (but not to empagliflozin 10 mg), while patients with mild renal impairment were randomised to placebo, empagliflozin 10 mg, or empagliflozin 25 mg.

[5] Totals for extension trial 1245.24 comprise totals of patients with or without metformin background therapy who were randomised to empagliflozin 10 mg, empagliflozin 25 mg, or active comparator and included in the FAS of the preceding randomised trials 1245.9 and 1245.10 irrespective of whether they continued into the extension trial.

[6] Sitagliptin (71 patients) or metformin (80 patients)

The pivotal data on efficacy and safety of empagliflozin in patients with type 2 diabetes mellitus are derived from 4 randomised, double-blind, placebo-controlled, parallel-group, phase III trials of empagliflozin (10 mg or 25 mg once daily) with a treatment duration of 24 weeks (1245.20, 1245.23(met), 1245.23(met+SU), and 1245.19). In total, 2957 patients were treated in these trials. The trials were identical in their main design features and trial procedures, but differed in

the required antidiabetic background medication. Trial 1245.20 investigated empagliflozin as monotherapy and also included an active control group (sitagliptin).

Supportive longer-term data are derived from the double-blind, controlled extensions of the 4 pivotal trials (1245.31). In these on-going trials, patients continued on the randomised trial treatment and the background medication they had taken in the initial trials.

Further supportive data come from the 5 randomised, double-blind, controlled trials 1245.36, 1245.48, 1245.25, 1245.28 (all phase III), and 1245.33 (phase IIb), all conducted in patients with type 2 diabetes. Trial 1245.36 was performed in patients with various degrees of renal impairment, trial 1245.48 in patients with hypertension, and the large cardiovascular outcome trial 1245.25 (on-going) tests empagliflozin in patients with high cardiovascular risk. Trial 1245.33 was conducted in patients with basal insulin as background therapy. These 4 trials (1245.36, 1245.48, 1245.25, 1245.33) were placebo-controlled, allowed different background medications, and tested 10 mg and 25 mg empagliflozin (but only empagliflozin 25 mg for the subgroups of patients with moderate or severe renal impairment in trial 1245.36). Trial 1245.28 (on-going) is active-controlled and compares 25 mg empagliflozin once daily with glimepiride (maximal tolerated dose between 1 and 4 mg) in patients with a metformin background therapy.

Tabulated summaries of the studies included in the evaluation of efficacy are shown below.

Table 4 Summary of efficacy for trial 1245.19

Title: A randomised, double-blind, placebo-controlled parallel group efficacy and safety trial of BI 10773 (10 and 25 mg administered orally once daily) over 24 weeks in patients with type 2 diabetes mellitus with insufficient glycaemic control despite a background therapy of pioglitazone alone or in combination with metformin			
Study identifier	1245.19, EudraCT No.: 2009-016154-40, CTR U12-1516		
Design	Randomised, placebo-controlled, double-blind, double-dummy, parallel group, international, multicentre. Randomisation was stratified by HbA_{1c} at screening, renal function at screening, and background medication. Add-on therapy to pioglitazone or pioglitazone plus metformin		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		24 weeks 2 weeks Min. 52 weeks (reported under different study number: 1245.31)
Hypothesis	Superiority over placebo		
Treatment groups	Empa 10		Empagliflozin 10 mg film-coated tablets once daily, 24 weeks, 165 patients randomised
	Empa 25		Empagliflozin 25 mg film-coated tablets once daily, 24 weeks, 168 patients randomised
	Placebo		Placebo tablets (double-dummy) once daily, 24 weeks, 166 patients randomised
Endpoints and definitions	Primary endpoint	HbA_{1c}	Change from baseline in HbA_{1c} after 24 weeks of treatment

	First key secondary endpoint	FPG	Change from baseline in fasting plasma glucose (FPG) after 24 weeks of treatment
	Second key secondary endpoint	Weight	Change from baseline in body weight after 24 weeks of treatment
Database lock	24 May 2012		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Full analysis set (FAS) – including all randomised and treated patients who had a baseline HbA_{1c} value. Missing data imputed as LOCF (excluding values after rescue medication). Confirmatory tests for primary and key secondary endpoints followed a hierarchical testing procedure and were based on 2-sided tests at a 2.5% level (and corresponding 97.5% confidence intervals), preserving the overall 5% level of the trial. 24 weeks

Descriptive statistics and estimate variability	Treatment group	Placebo	Empa 10	Empa 25
	Number of subject	165	165	168
	HbA_{1c} [%] Baseline mean (SE)	8.16 (0.07)	8.07 (0.07)	8.06 (0.06)
	Adj. mean change at week 24 (SE)	-0.11 (0.07)	-0.59 (0.07)	-0.72 (0.07)
	FPG [mg/dL] Baseline mean (SE)	151.93 (3.14)	152.01 (2.99)	151.86 (2.86)
	Adj. mean change at week 24 (SE)	6.47 (2.61)	-17.00 (2.63)	-21.99 (2.59)
	Weight [kg] Baseline mean (SE)	78.10 (1.57)	77.97 (1.49)	78.93 (1.54)
	Adj. mean change at week 24 (SE)	0.34 (0.21)	-1.62 (0.21)	-1.47 (0.21)

Effect estimate per comparison				
	HbA_{1c} [%] Change from baseline at week 24	Comparison groups	Empa 10	Empa 25
		Adj. mean difference to placebo (SE)	-0.48 (0.09)	-0.61 (0.09)
		97.5% confidence interval	(-0.69, -0.27)	(-0.82, -0.40)
		P-value (ANCOVA)	<0.0001	<0.0001
	FPG [mg/dL] Change from baseline at week 24	Comparison groups	Empa 10	Empa 25
		Adj. mean difference to placebo (SE)	-23.48 (3.71)	-28.46 (3.68)
		97.5% confidence interval	(-31.81, -15.15)	(-36.73, -20.19)
		P-value (ANCOVA)	<0.0001	<0.0001
	Weight [kg]	Comparison groups	Empa 10	Empa 25

	Change from baseline at week 24	Adj. mean difference to placebo (SE)	-1.95 (0.30)	-1.81 (0.30)
		97.5% confidence interval	(-2.64, -1.27)	(-2.49, -1.13)
		P-value (ANCOVA)	<0.0001	<0.0001
Notes	The robustness of the results was confirmed across a number of sensitivity analyses, both for the primary and for the key secondary endpoints. Other analysed endpoints – blood pressure, waist circumference, the pre-defined composite endpoint (change in HbA1c, blood pressure, and body weight), relative response, treat-to-target response, and use of rescue medication – supported the findings for the primary and key secondary endpoints regarding the effect of the empagliflozin treatment (both doses) compared with placebo.			

Table 5 Summary of efficacy for trial 1245.20

Title: A phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 and sitagliptin administered orally over 24 weeks, in drug naïve patients with type 2 diabetes mellitus and insufficient glycaemic control despite diet and exercise			
Study identifier	1245.20, EudraCT No.: 2009-016243-20, CTR U12-1517		
Design	Randomised, double-blind, triple-dummy, active and placebo-controlled, parallel group, international, multicentre. Randomisation was stratified by HbA_{1c} at screening, renal function at screening, and geographical region. Additional open-label arm to assess the efficacy and safety of empagliflozin 25 mg once daily in patients with type 2 diabetes and very poor glycaemic control (HbA_{1c} >10%).		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		24 weeks 2 weeks Min. 52 weeks (reported under different study number: 1245.31)
Hypothesis	Superiority over placebo		
Treatment groups	Empa 10		Empagliflozin 10 mg film-coated tablets once daily, 24 weeks, 224 patients randomised
	Empa 25		Empagliflozin 25 mg film-coated tablets once daily, 24 weeks, 224 patients randomised
	Sita 100		Sitagliptin 100 mg tablets once daily, 24 weeks, 223 patients randomised
	Placebo		Placebo tablets (triple-dummy) once daily, 24 weeks, 228 patients randomised
	OL empa 25		Empagliflozin 25 mg film-coated tablets once daily, 24 weeks, 87 patients entered
Endpoints and definitions	Primary endpoint	HbA1c	Change from baseline in HbA1c after 24 weeks of treatment.
	First key Secondary endpoint	Weight	Change from baseline in body weight after 24 weeks of treatment

	Second key Secondary endpoint	SBP and DBP	Change from baseline in blood pressure (systolic and diastolic) after 24 weeks of treatment
Database lock	27 April 2012		
Results and Analysis			

Analysis description	**Primary Analysis**
Analysis population and time point description	Full analysis set (FAS) – including all randomised and treated patients who had a baseline HbA_{1c} value. Missing data imputed as LOCF (excluding values after rescue medication). Confirmatory tests for primary and key secondary endpoints followed a hierarchical testing procedure and were based on 2-sided tests at a 2.5% level (and corresponding 97.5% confidence intervals), preserving the overall 5% level of the trial. 24 weeks

Descriptive statistics and estimate variability	Treatment group	Placebo	Empa 10	Empa 25	Sita 100
	Number of subjects	228	224	224	223
	HbA_{1c} [%] Baseline mean (SE)	7.91 (0.05)	7.87 (0.06)	7.86 (0.06)	7.85 (0.05)
	Adj. mean change at week 24 (SE)	0.08 (0.05)	-0.66 (0.05)	-0.78 (0.05)	-0.66 (0.05)
	Weight [kg] Baseline mean (SE)	78.23 (1.32)	78.35 (1.25)	77.80 (1.20)	79.31 (1.37)
	Adj. mean change at week 24 (SE)	-0.33 (0.17)	-2.26 (0.17)	-2.48 (0.17)	0.18 (0.17)
	SBP [mmHg] Baseline mean (SE)	130.4 (1.1)	133.0 (1.1)	129.9 (1.2)	132.5 (1.1)
	Adj. mean change at week 24 (SE)	-0.3 (0.8)	-2.9 (0.8)	-3.7 (0.8)	0.5 (0.8)
	DBP [mmHg] Baseline mean (SE)	78.9 (0.6)	79.2 (0.6)	78.3 (0.6)	80.1 (0.7)
	Adj. mean change at week 24 (SE)	-0.5 (0.5)	-1.0 (0.5)	-1.9 (0.5)	0.7 (0.5)

Effect estimate per comparison				
	HbA_{1c} [%] Change from baseline after 24 weeks	Comparison groups	Empa 10	Empa 25
		Adj. mean difference to placebo (SE)	-0.74 (0.07)	-0.85 (0.07)
		97.5% confidence interval	(-0.90,-0.57)	(-1.01,-0.69)
		P-value (ANCOVA)	<0.0001	<0.0001
	Weight [kg] Change from baseline after 24 weeks	Comparison groups	Empa 10	Empa 25
		Adj. mean difference to placebo (SE)	-1.93 (0.24)	-2.15 (0.24)
		97.5% confidence interval	(-2.48,-1.38)	(-2.70,-1.60)
		P-value (ANCOVA)	<0.0001	<0.0001
	SBP [mmHg]	Comparison groups	Empa 10	Empa 25

	Change from baseline after 24 weeks	Adj. mean difference to placebo (SE)	-2.6 (1.1)	-3.4 (1.1)
		97.5% confidence interval	(-5.2,0.0)	(-6.0,-0.9)
		P-value (ANCOVA)	0.0231	0.0028
	DBP [mmHg] Change from baseline after 24 weeks	Comparison groups	Empa 10	Empa 25
		Adj. mean difference to placebo (SE)	-0.6 (0.7)	-1.5 (0.7)
		97.5% confidence interval	(-2.1,0.9)	(-3.0,0.0)
		P-value (ANCOVA)	0.3987	0.0296
Notes	The robustness of the results was confirmed across a number of sensitivity analyses, both for the primary and for the key secondary endpoints. Other analysed endpoints – FPG, waist circumference, the pre-defined composite endpoint (change in HbA_{1c}, blood pressure, and body weight), relative response, treat-to-target response, and use of rescue medication – supported the findings for the primary and key secondary endpoints regarding the effect of the empagliflozin treatment (both doses) compared with placebo.			

Table 6 Summary of efficacy for trial 1245.23

Title: A phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 (10 mg, 25 mg) administered orally, once daily over 24 weeks in patients with type 2 diabetes mellitus with insufficient glycaemic control despite treatment with metformin alone or metformin in combination with a sulphonylurea		
Study identifier	1245.23, EudraCT No.: 2009-016258-41, CTR U12-1518	
Design	Randomised, placebo-controlled, double-blind, double-dummy, parallel group, international, multicentre. Randomisation was stratified by HbA1c at screening, renal function at screening, and geographical region. Add-on therapy to metformin or metformin plus sulphonylurea. Additional open-label arm to assess the efficacy and safety of empagliflozin 25 mg once daily in patients with type 2 diabetes and very poor glycaemic control (HbA_{1c} >10%).	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	24 weeks 2 weeks Min. 52 weeks (reported under different study number: 1245.31)
Hypothesis	Superiority over placebo	

Add-on therapy to metformin:

Treatment groups	Empa 10	Empagliflozin 10 mg film-coated tablets once daily, 24 weeks, 217 patients randomised
	Empa 25	Empagliflozin 25 mg film-coated tablets once daily, 24 weeks, 214 patients randomised
	Placebo	Placebo tablets (double-dummy) once daily, 24 weeks, 207 patients randomised

	OL empa 25		Empagliflozin 25 mg film-coated tablets once daily, 24 weeks, 69 patients entered
Endpoints and definitions	Primary endpoint	HbA_{1c}	Change from baseline in HbA1c after 24 weeks of treatment
	First key secondary endpoint	Weight	Change from baseline in body weight after 24 weeks of treatment
	Second key secondary endpoint	Mean daily plasma glucose (MDG)	Change from baseline in MDG after 24 weeks of treatment
Database lock	23 March 2012		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full analysis set (FAS) – including all randomised and treated patients who had a baseline HbA_{1c} value. Missing data imputed as LOCF (excluding values after rescue medication). Confirmatory tests for primary and key secondary endpoints followed a hierarchical testing procedure and were based on 2-sided tests at a 2.5% level (and corresponding 97.5% confidence intervals), preserving the overall 5% level of the trial. 24 weeks			
Descriptive statistics and estimate variability	Treatment group		Placebo	Empa 10	Empa 25
	Number of subjects		207	217	213
	HbA_{1c} [%] Baseline mean (SE)		7.90 (0.06)	7.94 (0.05)	7.86 (0.06)
	Adj. mean change at week 24 (SE)		-0.13 (0.05)	-0.70 (0.05)	-0.77 (0.05)
	Weight [kg] Baseline mean (SE)		79.73 (1.29)	81.59 (1.26)	82.21 (1.32)
	Adj. mean change at week 24 (SE)		-0.45 (0.17)	-2.08 (0.17)	-2.46 (0.17)
	MDG [mg/dL] Baseline mean (SE)		169.53 (3.27)	168.03 (2.64)	167.87 (2.82)
	Adj. mean change at week 24 (SE)		-1.99 (1.99)	-9.64 (1.89)	-14.36 (1.89)
Effect estimate per comparison	**HbA_{1c} [%]** Change from baseline at week 24	Comparison groups		Empa 10	Empa 25
		Adj. mean difference to placebo (SE)		-0.57 (0.07)	-0.64 (0.07)
		97.5% confidence interval		(-0.72, -0.42)	(-0.79, -0.48)
		P-value (ANCOVA)		<0.0001	<0.0001
	Weight [kg] Change from baseline at	Comparison groups		Empa 10	Empa 25
		Adj. mean difference to placebo (SE)		-1.63 (0.24)	-2.01 (0.24)

	week 24	97.5% confidence interval	(-2.17, -1.08)	(-2.56, -1.46)
		P-value (ANCOVA)	<0.0001	<0.0001
	MDG [mg/dL] Change from baseline at week 24	Comparison groups	Empa 10	Empa 25
		Adj. mean difference to placebo (SE)	-7.65 (2.74)	-12.37 (2.75)
		97.5% confidence interval	(-13.81, -1.48)	(-18.55, -6.19)
		P-value (ANCOVA)	0.0055	<0.0001
Notes	The robustness of the results was confirmed across a number of sensitivity analyses, both for the primary and for the key secondary endpoints. Other analysed endpoints – FPG, blood pressure, waist circumference, the pre-defined composite endpoint (change in HbA_{1c}, blood pressure, and body weight), relative response, treat-to-target response, and use of rescue medication – supported the findings for the primary and key secondary endpoints regarding the effect of the empagliflozin treatment (both doses) compared with placebo.			

Add-on therapy to metformin plus sulphonylurea:

Treatment groups	Empa 10		Empagliflozin 10 mg film-coated tablets once daily, 24 weeks, 226 patients randomised
	Empa 25		Empagliflozin 25 mg film-coated tablets once daily, 24 weeks, 218 patients randomised
	Placebo		Placebo tablets (double-dummy) once daily, 24 weeks, 225 patients randomised
	OL empa 25		Empagliflozin 25 mg film-coated tablets once daily, 24 weeks, 103 patients entered
Endpoints and definitions	Primary endpoint	HbA_{1c}	Change from baseline in HbA1c after 24 weeks of treatment
	First key secondary endpoint	Weight	Change from baseline in body weight after 24 weeks of treatment
	Second key secondary endpoint	Mean daily plasma glucose (MDG)	Change from baseline in MDG after 24 weeks of treatment
Database lock	23 March 2012		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Full analysis set (FAS) – including all randomised and treated patients who had a baseline HbA_{1c} value. Missing data imputed as LOCF (excluding values after rescue medication). Confirmatory tests for primary and key secondary endpoints followed a hierarchical testing procedure and were based on 2-sided tests at a 2.5% level (and corresponding 97.5% confidence intervals), preserving the overall 5% level of the trial. 24 weeks			
Descriptive statistics and estimate variability	Treatment group		Placebo	Empa 10	Empa 25
	Number of subject		225	225	216
	HbA_{1c} [%] Baseline mean (SE)		8.15 (0.06)	8.07 (0.05)	8.10 (0.06)
	Adj. mean change at week 24 (SE)		-0.17 (0.05)	-0.82 (0.05)	-0.77 (0.05)
	Weight [kg] Baseline mean (SE)		76.23 (1.13)	77.08 (1.22)	77.50 (1.28)
	Adj. mean change at week 24 (SE)		-0.39 (0.15)	-2.16 (0.15)	-2.39 (0.16)
	MDG [mg/dL] Baseline mean (SE)		170.45 (2.47)	170.28 (2.39)	172.72 (3.49)
	Adj. mean change at week 24 (SE)		0.00 (1.78)	-10.01 (1.80)	-13.06 (2.03)
Effect estimate per comparison	**HbA_{1c} [%]** Change from baseline at week 24	Comparison groups		Empa 10	Empa 25
		Adj. mean difference to placebo (SE)		-0.64 (0.07)	-0.59 (0.07)
		97.5% confidence interval		(-0.79, -0.49)	(-0.74, -0.44)
		P-value (ANCOVA)		<0.0001	<0.0001
	Weight [kg] Change from baseline at week 24	Comparison groups		Empa 10	Empa 25
		Adj. mean difference to placebo (SE)		-1.76 (0.22)	-1.99 (0.22)
		97.5% confidence interval		(-2.25, -1.28)	(-2.48, -1.50)
		P-value (ANCOVA)		<0.0001	<0.0001
	MDG [mg/dL] Change from baseline at week 24	Comparison groups		Empa 10	Empa 25
		Adj. mean difference to placebo (SE)		-10.02 (2.53)	-13.06 (2.70)
		97.5% confidence interval		(-15.72, -4.32)	(-19.15, -6.98)
		P-value (ANCOVA)		<0.0001	<0.0001

Notes	The robustness of the results was confirmed across a number of sensitivity analyses, both for the primary and for the key secondary endpoints. Other analysed endpoints – FPG, blood pressure, waist circumference, the pre-defined composite endpoint (change in HbA_{1c}, blood pressure, and body weight), relative response, treat-to-target response, and use of rescue medication – supported the findings for the primary and key secondary endpoints regarding the effect of the empagliflozin treatment (both doses) compared with placebo.

Inclusion and exclusion criteria

The main inclusion and exclusion criteria were harmonised across the trials. Men and women diagnosed with type 2 diabetes mellitus and with insufficient glycaemic control (HbA1c ≥7.0%; upper limit 10.0% in most trials/sites), with a BMI of ≤45 kg/m2 and at least 18 years of age (for patients in Japan the minimum age was 20 years) were to be included in the trials. Each of the trials had specific additional eligibility requirements, e.g. with regard to the permitted antidiabetic background medication (which was not provided as part of the trial medication). In general, patients with various degrees of renal impairment were eligible for the empagliflozin phase-III programme. However, the allowed degree of renal impairment differed between the trials depending on the background medication and comparator; patients with severe renal impairment (<30 mL/min/1.73 m2) were only admitted in trial 1245.36. Patients were not allowed to participate in any trial if they had a history of acute coronary syndrome, stroke, or transient ischaemic attack within 3 months (2 months for 1245.25) prior to informed consent.

Primary endpoint

The trials critical for the evaluation of efficacy used the same primary endpoint to assess antidiabetic efficacy: the change from baseline in HbA1c. Exceptions were the double-blind extensions of the pivotal trials (1245.31), in which HbA1c was a secondary endpoint (confirmatory testing was done only in the preceding trials). Another exception was the cardiovascular safety trial 1245.25, which had a safety-related primary endpoint; the change from baseline in HbA1c was an exploratory endpoint. In all trials, blood samples for the determination of HbA1c were analysed in central laboratories that held a National Glycohemoglobin Standardization Program Level I certificate.

Secondary endpoints

Four endpoints were considered secondary endpoints for the pooled analyses of efficacy, i.e. the changes from baseline in FPG, body weight, SBP, and DBP. On trial level, FPG was a key secondary endpoint in the pivotal trial 1245.19, and body weight was a key secondary endpoint in the 4 pivotal trials and in the glimepiride-controlled trial 1245.28. SBP and DBP were defined as key secondary endpoints in trials 1245.20 and 1245.28. Furthermore, in trial 1245.48 (patients with diabetes and hypertension), 24-h SBP was a co-primary endpoint and 24-h DBP was a key secondary endpoint. These key secondary endpoints were part of the testing hierarchy of the respective trial. Thus, the trial-level results for these endpoints provide confirmatory evidence.

In general, efficacy analyses followed the intention-to-treat principle and were based on the full analysis set (FAS), which included all randomised patients who received at least one dose of trial

medication and had a baseline HbA1c measurement (and in trial 1245.48 also a baseline mean 24-hour SBP measurement). Per-protocol sets (PPS) were usually defined on trial level to assess the robustness of the efficacy results. The PPS comprised all patients of the FAS who did not have any important protocol violations with a potential influence on the primary efficacy data.

The main analyses of efficacy were based on ANCOVA models and employed a last observation carried forward (LOCF) approach to impute missing data, whereby also baseline values were carried forward in case no post-baseline value was available. Values measured after a patient had taken rescue medication were excluded and imputed using the LOCF method.

Patient Populations Studied

Premature discontinuation

The rates of premature discontinuations of trial medication were low in all pivotal trials, with a consistently higher rate in the placebo groups than in the empagliflozin 10 mg and 25 mg groups. In the empagliflozin groups, a maximum of 8.9% of patients discontinued prematurely. The most frequent reasons for premature discontinuations were adverse events (other than worsening of disease under study or other pre-existing disease) in trials 1245.19, 1245.23(met), and 1245.23(met+SU), or patient refusal to continue trial medication (not due to adverse event) in trial 1245.20. Discontinuation rates were similar for the other phase III trials. In the longer (78-week) trial 1245.33 in patients with basal insulin and thus more advanced disease, premature discontinuations were more frequent (overall 27.1%) than in the pivotal trials but again numerically higher in the placebo group than in the empagliflozin groups.

Long-term efficacy analyses (>24 weeks) of the pivotal trials and their double-blind extensions (1245.31) were based on the pooling of the 4 pivotal trials. Of all patients randomised and treated in the 4 pivotal trials, 91.1% completed treatment in the 24-week pivotal trials as planned and 68.7% continued into the extension trials. For the pooled analyses in this grouping, patients who had completed the initial trial but did not enter the extension trial (for various reasons, e.g. trial site did not participate in extension trial or patient's wish) were counted as premature discontinuations. These 22.3% of patients contributed to the overall discontinuation rate of 35.8%. When these patients are not counted, the rates of premature discontinuations were 17.1% in the placebo group, 10.8% for empagliflozin 10 mg, and 12.8% for empagliflozin 25 mg.

Duration of exposure

The duration of exposure to randomised trial medication in the pivotal trials was similar across treatment groups and very close to the planned treatment duration of 24 weeks. When taking the extension trials (1245.31) into consideration, exposure tended to be shorter for placebo than for empagliflozin; median exposure was 328 days (placebo), 371 days (empagliflozin 10 mg), and 364 days (empagliflozin 25 mg). Total exposure to trial medication in the pivotal trials and their extensions amounted to 699.7 years in the placebo group, 785.4 years in the empagliflozin 10 mg group, and 759.7 years in the empagliflozin 25 mg group. In the other trials, duration of exposure was very similar in all treatment groups.

Demographic and baseline characteristics

Key demographic and baseline characteristics were generally balanced across all randomised treatment groups. In the pivotal trials, just over half (54.5%) of the patients were men. Most of the patients (51.2%) had mild renal impairment, i.e. an eGFR of 60 to <90 mL/min/1.73 m2, or normal renal function (41.4%) as assessed by eGFR calculated with the MDRD formula; the remaining 7.4% of patients had moderate renal impairment, i.e. an eGFR of 30 to <60 mL/min/1.73 m2. Overall, 55.5% of patients had a history of hypertension. Diabetes-related concomitant diagnoses such as diabetic neuropathy were relatively uncommon in the pivotal trials, with highest frequencies observed in trial 1245.23(met+SU).

Table 7 Demographic characteristics in pivotal trials and other trials

	N	Age, mean (SD) [years]	Male gender, N (%)	Race, N (%)			BMI, mean (SD) [kg/m^2]	Time since diagnosis of diabetes, N (%)
				White	Black[1]	Asian		>5 years
Pivotal trials								
1245.20	676	55.0 (11.4)	410 (60.7)	226 (33.4)	16 (2.4)	433 (64.1)	28.4 (5.7)	147 (21.7)
1245.23$_{(met)}$	637	55.7 (9.9)	361 (56.7)	338 (53.1)	6 (0.9)	289 (45.4)	29.2 (5.5)	349 (54.8)
1245.23$_{(met+SU)}$	666	57.1 (9.2)	339 (50.9)	262 (39.3)	13 (2.0)	381 (57.2)	28.2 (5.3)	516 (77.5)
1245.19	498	54.5 (9.8)	241 (48.4)	197 (39.6)	11 (2.2)	288 (57.8)	29.2 (5.5)	219 (44.0)
Pivotal total[2]	2477	55.6 (10.2)	1351 (54.5)	1023 (41.3)	46 (1.9)	1391 (56.2)	28.7 (5.5)	1231 (49.7)
Other trials								
1245.28	1545	55.9 (10.4)	854 (55.3)	1017 (65.8)	20 (1.3)	507 (32.8)	30.1 (5.3)	696 (45.0)
1245.33	374	59.0 (9.7)	212 (56.7)	261 (69.8)	32 (8.6)	79 (21.1)	32.0 (5.9)	335 (89.6)
1245.48	823	60.2 (9.0)	495 (60.1)	771 (93.7)	41 (5.0)	8 (1.0)	32.6 (5.1)	590 (71.7)
1245.36	738	63.9 (8.8)	430 (58.3)	445 (60.3)	22 (3.0)	266 (36.0)	30.7 (5.5)	625 (84.7)
1245.25	4495	63.0 (8.8)	3233 (71.9)	3153 (70.1)	240 (5.3)	1063 (23.6)	30.5 (5.4)	3673 (81.7)
1245.49	563	56.7 (9.5)	256 (45.5)	531 (94.3)	19 (3.4)	3 (0.5)	34.79 (4.06)	512 (91.0)

[1] or African American
[2] Includes 1245.19, 1245.20, 1245.23$_{(met)}$, and 1245.23$_{(met+SU)}$

A summary of the most important demographic and baseline characteristics is presented in Table 8.

Table 8 Baseline efficacy characteristics in pivotal trials and other trials.

	N	Baseline HbA_{1c}, mean (SD) [%]	Baseline FPG, mean (SD) [mg/dL]	Baseline weight, mean (SD) [kg]	Baseline blood pressure, mean (SD) [mmHg]	
					SBP	DBP
Pivotal trials						
1245.20	676	7.88 (0.84)	153.4 (34.0)	78.13 (18.83)	131.1 (16.8)	78.8 (9.5)
$1245.23_{(met)}$	637	7.90 (0.85)	153.3 (33.0)	81.19 (18.79)	129.4 (14.6)	78.7 (8.1)
$1245.23_{(met+SU)}$	666	8.10 (0.83)	153.0 (34.2)	76.93 (18.00)	128.9 (14.1)	78.6 (8.8)
1245.19	498	8.09 (0.88)	151.9 (38.5)	78.34 (19.70)	126.1 (13.2)	76.9 (8.4)
Pivotal total[1]	2477	7.99 (0.85)	153.0 (34.7)	78.64 (18.84)	129.1 (15.0)	78.3 (8.8)
Other trials						
1245.28	1545	7.92 (0.84)	149.9 (33.9)	82.78 (19.19)	133.5 (15.9)	79.5 (9.4)
1245.33	374	8.23 (0.82)	143.0 (48.7)	91.77 (21.35)	133.5 (15.5)	78.4 (10.0)
1245.48	823	7.90 (0.74)	159.9 (37.1)	95.17 (18.22)	142.1 (12.3)	83.9 (7.0)
1245.36	738	8.04 (0.82)	145.4 (41.9)	85.0 (20.0)	136.9 (18.1)	75.9 (9.6)
1245.25	4495	8.09 (0.86)	151.8 (43.8)	85.97 (19.15)	134.8 (17.1)	76.2 (9.8)
1245.49	563	8.34 (0.73)	153.6 (47.6)	96.0 (17.5)	133.3 (15.5)	78.8 (8.6)

[1] Includes 1245.19, 1245.20, $1245.23_{(met)}$, and $1245.23_{(met+SU)}$

HbA1c

All pivotal trials had HbA1c change from baseline at 24 weeks as their primary endpoint. In each pivotal trial, both doses of empagliflozin provided statistically significant ($p<0.0001$) and clinically meaningful reductions in HbA1c compared with placebo after 24 weeks of treatment (Figure 1).

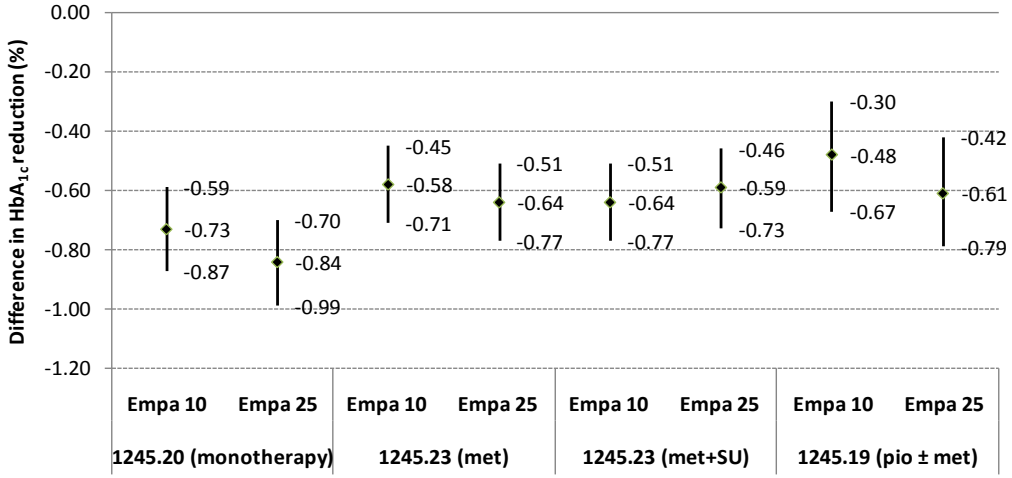


Figure 1 Adjusted mean difference (with 95% confidence intervals) between empagliflozin and placebo in HbA1c after 24 weeks for the pivotal trials.

In the monotherapy study 1245.20, After 24 weeks, compared to placebo, empagliflozin monotherapy was associated with a clinically relevant reduction in HbA1c of -0.74% (10 mg) and -0.85% (25 mg) (Figure 2). The exploratory comparison of both empagliflozin doses vs. sitagliptin provided a similar treatment effect of empagliflozin (empagliflozin 10 mg -0.74% (95% CI: -0.90 to -0.57%), empagliflozin 25 mg -0.85% (95% CI -1.01 to - 0.69%) vs. placebo -0.73% (95% CI: -0.88 to -0.59%)).

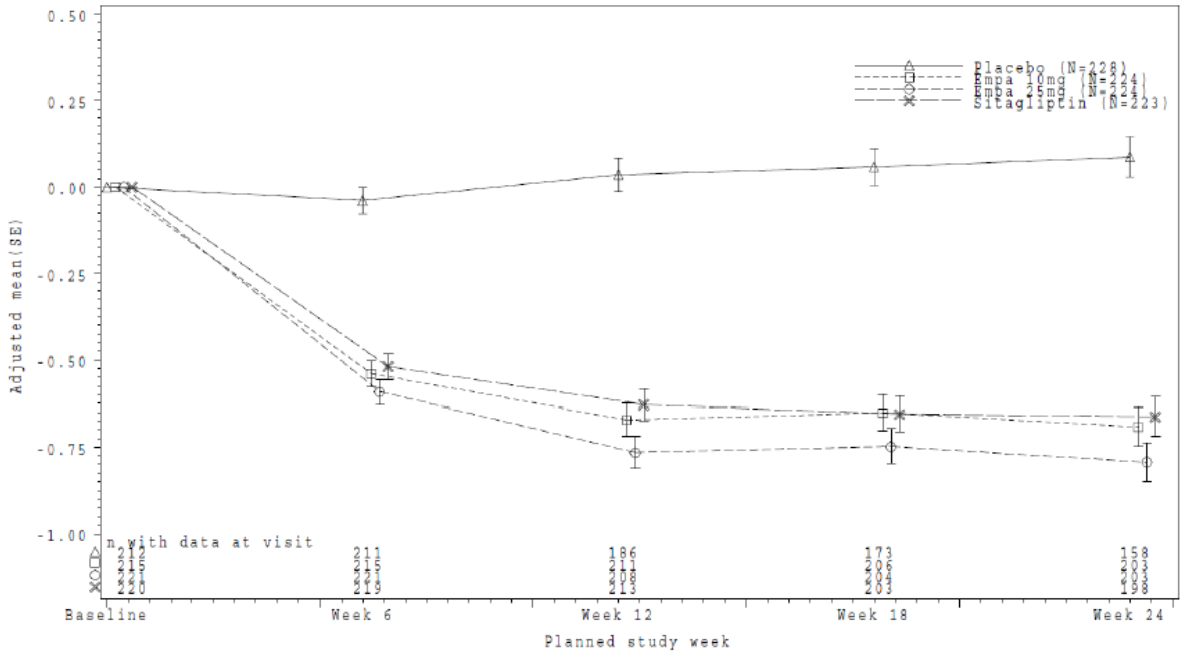


Figure 2 Monotherapy (Study 1245.20). Adjusted mean change in HbA1c (%) over time

In study 1245.23 (met), compared to placebo, empagliflozin as add on to metformin was associated with a reduction in HbA1c of -0.57 (10 mg) and -0.64 (25 mg) after 24 weeks of treatment (**Figure 3**).

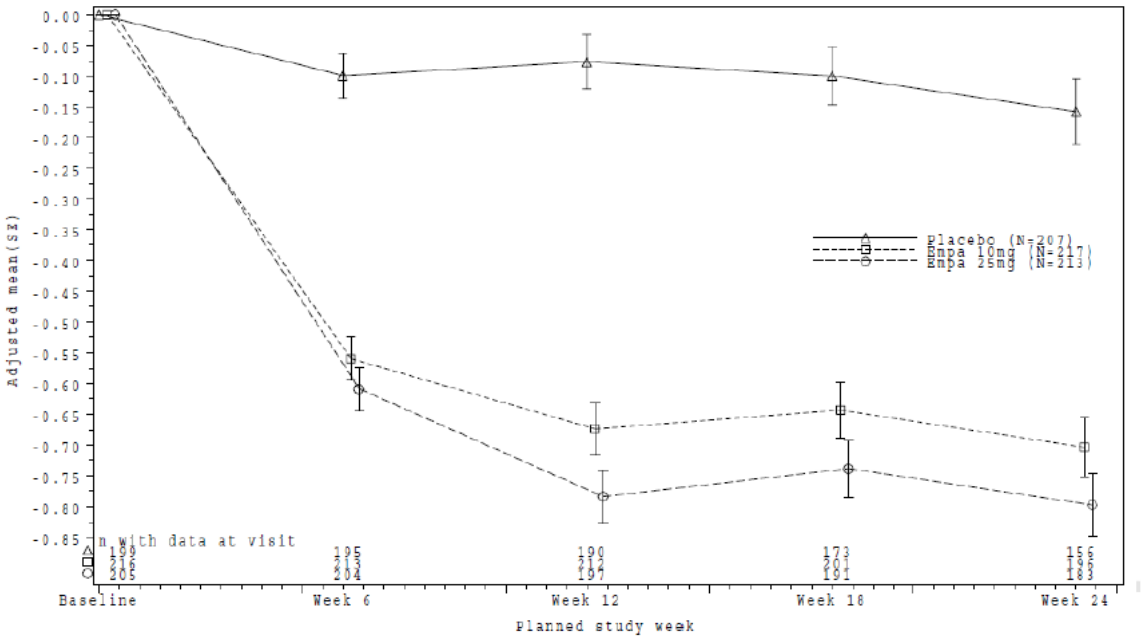


Figure 3 Add-on to metformin (Study 1245.23 met). Adjusted mean change in HbA1c (%) over time

In study 1245.23 (met plus SU), compared to placebo, empagliflozin as add on to metformin plus SU was associated with a reduction in HbA1c of -0.64% (10 mg) and -0.59% (25 mg) (Figure 4). The mean dose of metformin was 1815 (454) mg.

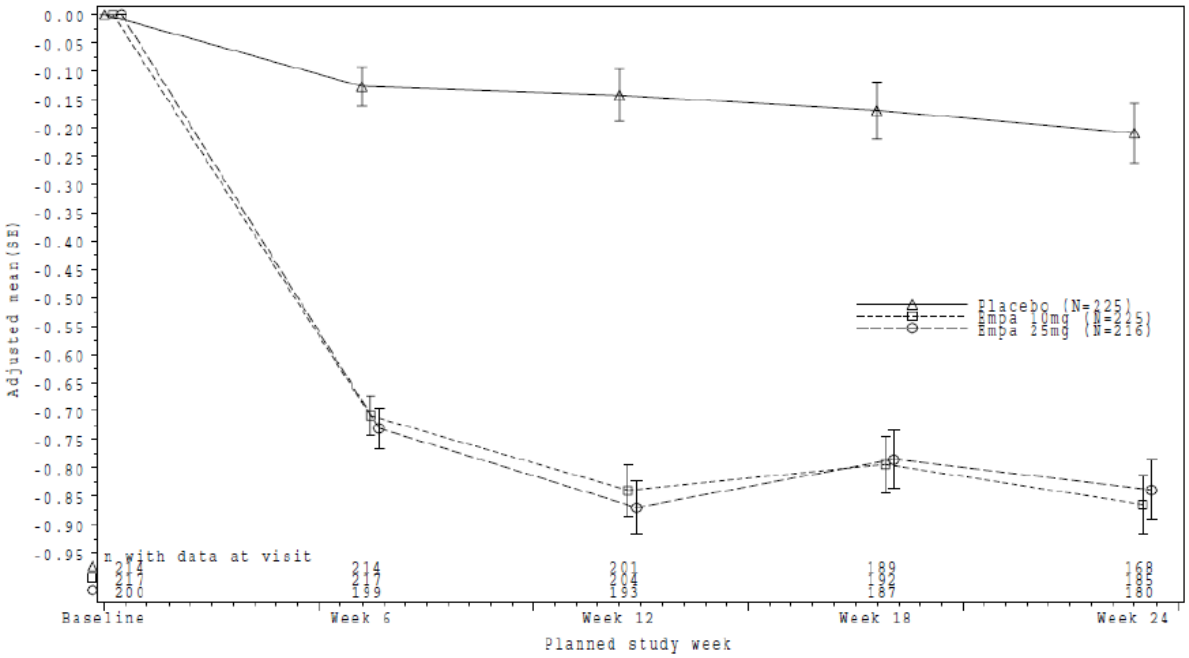


Figure 4 Add-on to metformin plus sulphonylurea (Study 1245.23 met+SU). Adjusted mean change in HbA1c (%) over time.

In study 1245.19, compared to placebo, empagliflozin as add on to pioglitazone with or without metformin was associated with a reduction in HbA1c of -0.48% (10 mg) and -0.61% (25 mg) (Figure 5). About 3 quarters of the patients (75.5%) had a background therapy of metformin plus pioglitazone; the rest had a background therapy of pioglitazone alone. Efficacy of empagliflozin was similar in both subgroups.

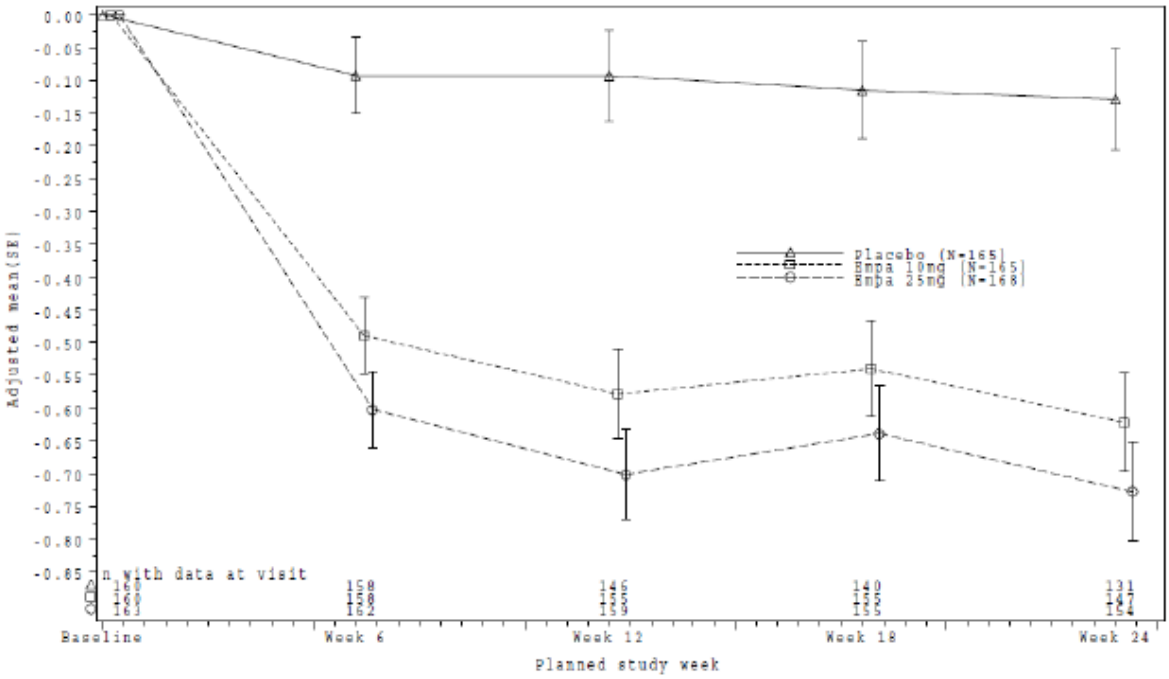


Figure 5 Add-on to pioglitazone with or without metformin (Study 1245.19). Adjusted mean change in HbA1c (%) over time – FAS (OC)

In the pivotal trials, the proportion of patients achieving HbA1c <7.0% was analysed. In the combined pivotal trials, 31.5% of patients in the empagliflozin 10 mg group, 37.2% in the empagliflozin 25 mg group, and 10.5% in the placebo group achieved this target (among patients with a baseline HbA1c ≥7.0%).

In trial 1245.33, empagliflozin was investigated in patients with insulin background therapy. The primary endpoint change in HbA1c was analysed after 18 weeks of treatment, until when the dose of basal insulin had to remain unchanged. The 25 mg dose resulted in a numerically larger reduction than 10 mg empagliflozin) (Figure 6). In the empagliflozin groups, 18.0% (10 mg) and 19.5% (25 mg) of patients achieved an HbA1c value below 7.0%, compared with 5.5% of patients in the placebo group. During the additional 60-week period, the dose of insulin could be adjusted at the discretion of the investigator for any confirmed fasting plasma glucose (FPG) levels >110 mg/dL. After 78 weeks, the placebo-adjusted changes from baseline in mean HbA1c were: -0.46% (97.5% CI: -0.73, -0.19, p=0.0001) for the empagliflozin 10 mg group and -0.62% (97.5% CI: -0.90, -0.34, p<0.0001) for the empagliflozin 25 mg group. For the key secondary endpoint of basal insulin dose, the adjusted mean differences from placebo at Week 78 were -6.66 IU in the empagliflozin 10 mg group (97.5% CI: -11.56, -1.77) and -5.92 IU in the empagliflozin 25 mg group (97.5% CI: -11.00, -0.85).

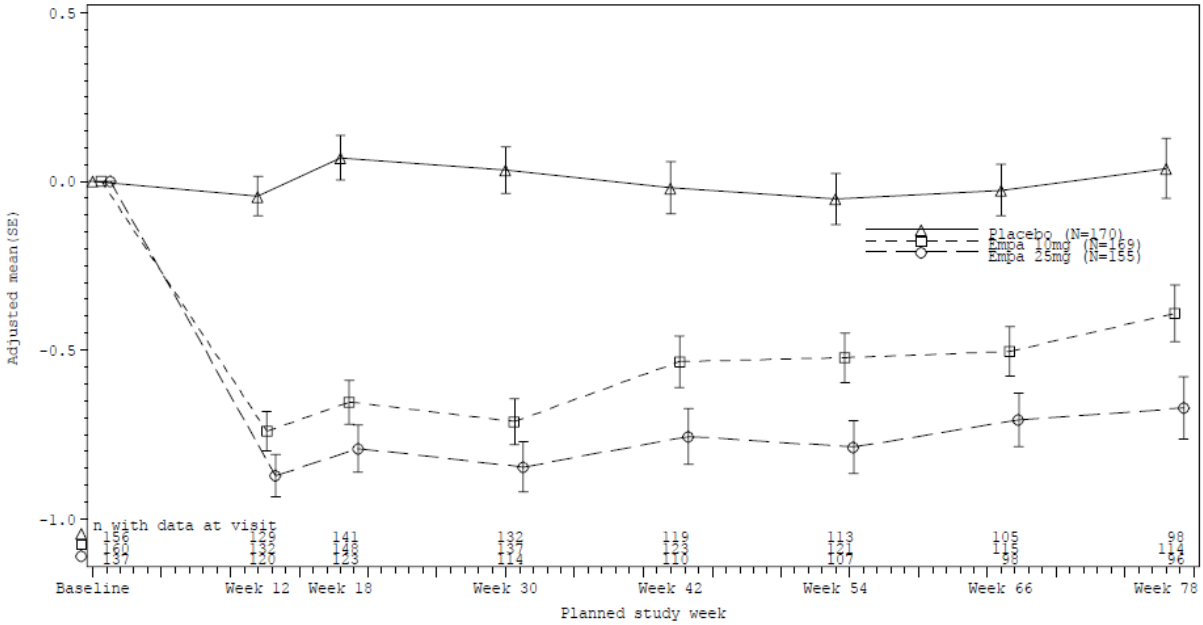


Figure 6 HbA1c (%) change from baseline MMRM results over time –FAS (OC-18)

During the registration process, a second study in patients with an insulin background therapy was submitted. Study 1245.49, a randomized, blinded placebo-controlled 52-week study, enrolled 563 subjects in total, 186 subjects were treated with 10 mg empagliflozin and 189 subjects with 25 mg empagliflozin, as add-on to multiple daily injection insulin therapy with or without metformin in type 2 diabetes. In this study, subjects maintained a stable insulin dose for the first 18 weeks and the primary outcome was the change in HbA1c after 18 weeks. Thereafter from week 18 to week 40, insulin doses were adjusted treat-to-target and for week 40 to 52, insulin doses maintained stable. Change in HbA1c was -0.44 (97.5% CI -0.61;-0.27) for 10 mg empagliflozin and -0.52 (97.5%CI -0.69;-0.35) for 25 mg empagliflozin, compared to placebo. After 52 weeks, the adjusted mean changes in insulin dose from baseline compared with placebo were -8.83 IU/day (97.5% CI: -15.69, -1.97; p=0.0040) for empagliflozin 10 mg and -11.22 IU/day (97.5% CI: -18.09, -4.36, p=0.0003) for empagliflozin 25 mg. The placebo-adjusted mean changes in HbA1c values at 52 weeks were -0.38% (97.5% CI: -0.62% to -0.13%) for 10 mg and -0.46% (97.5% CI: -0.70% to -0.22%) for 25 mg.

The non-inferiority of empagliflozin to an established standard-of-care comparator was investigated in the glimepiride-controlled trial 1245.28. In this on-going trial, an interim analysis was performed following 52 weeks of treatment with 25 mg empagliflozin or 1 to 4 mg glimepiride. The actual mean daily dose of glimepiride taken during the treatment period was 2.71 mg (SD 1.24 mg). The non-inferiority margin was defined as 0.3% for the primary analysis of HbA1c change from baseline. It was met with a p-value of <0.0001. The adjusted mean changes from baseline (ANCOVA) after 52 weeks were -0.73% in the empagliflozin group and -0.66% in the glimepiride group (Figure 7). Of the patients with a baseline HbA1c ≥7.0%, similar proportions in both groups achieved a HbA1c value <7.0% after 52 weeks (empagliflozin: 38.7%, glimepiride: 39.0%).

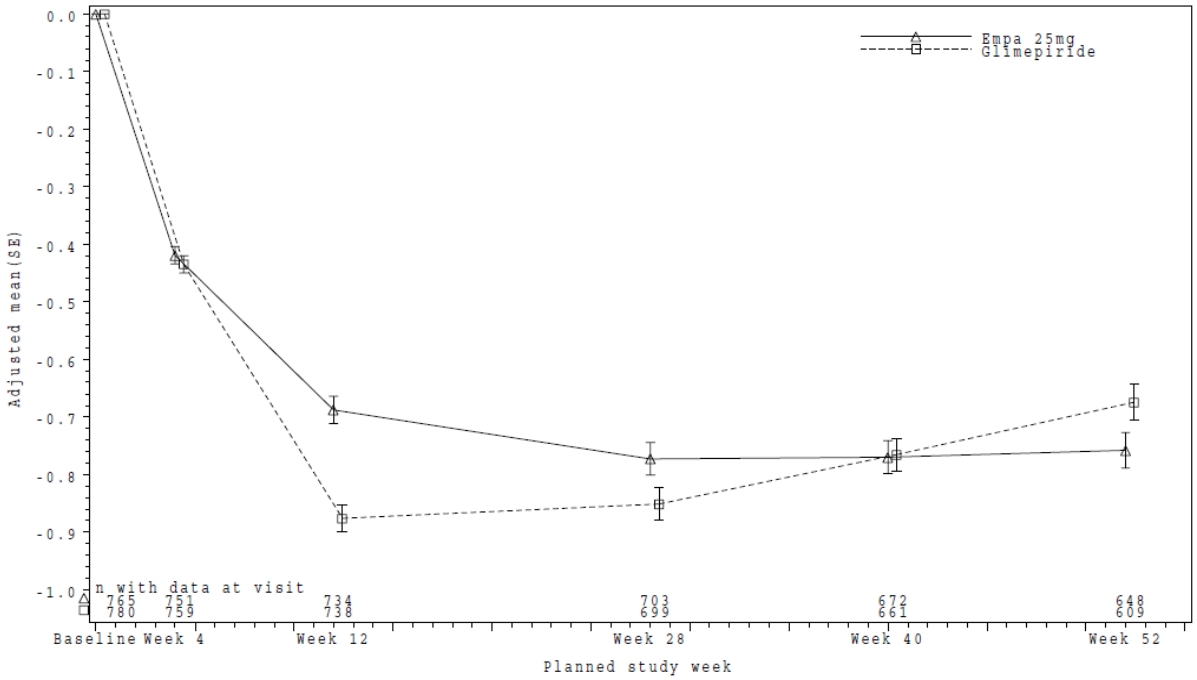


Figure 7 Adjusted mean change from baseline up to 52 weeks in HbA1c [%] in the glimepiride-controlled trial 1245.28

In the 12-week trial in patients with type 2 diabetes and hypertension (trial 1245.48), the primary analysis showed that, compared to placebo, there was a relevant decrease in HbA1c (-0.62% (95% CI: -0.72 to -0.52%) and 0.65% (95% CI: -0.75 to -0.55%) for empagliflozin 10 and 25 mg, respectively). This was confirmed by the proportions of patients who achieved an HbA1c value below 7.0% at the end of treatment: 7.1% for placebo, 30.9% for empagliflozin 10 mg, and 29.9% for empagliflozin 25 mg.

In the trial in patients with renal impairment (trial 1245.36), only the higher empagliflozin dose (25 mg) was investigated in patients with moderate or severe renal impairment. In patients with mild renal impairment, both doses of empagliflozin (10 mg and 25 mg) were tested. In comparison to placebo, the change in HbA1c at Week 24 in patients with mild (i.e. GFR 60-90ml/min) renal impairment was -0.52% (95% CI: -0.72 to -0.32%) for empagliflozin 10 mg and -0.68% (-0.88 to -0.49%) for empagliflozin 25 mg. In patients with moderate (i.e. GFR 30-60 ml/min) renal impairment, the placebo-adjusted treatment effect for empagliflozin 25 mg was -0.42% (-0.56 to -0.28%). The patients with moderate renal impairment were subdivided in patients with GFR 45-60 and 30-45 ml/min. The adjusted mean treatment differences for empagliflozin 25 mg compared with placebo were -0.46 and -0.39%, respectively. The categorical response (HbA1c <7.0%) at Week 24 were in line with the results for HbA1c change from baseline: 17.0% (empagliflozin 10 mg) and 24.2% (empagliflozin 25 mg) of the patients with mild renal impairment achieved this target (placebo: 6.7%). Among patients with moderate renal impairment, 12.0% in the empagliflozin 25 mg group reached the target (placebo: 7.9%). For the small group of patients with severe renal impairment (37 patients per treatment group), descriptive statistics revealed no reduction of HbA1c compared with placebo.

Fasting plasma glucose

The change from baseline in FPG was a secondary endpoint in all of the pivotal placebo-controlled trials. In each pivotal trial, both doses of empagliflozin provided reductions in FPG after 24 weeks of treatment compared with placebo. In the placebo groups, mean FPG increased slightly from baseline to 24 weeks. After 52 weeks in the on-going trial 1245.28, there were clinically meaningful reductions in FPG in both the empagliflozin and the glimepiride groups. However, the reduction was larger in the empagliflozin group than in the glimepiride group. In each of the other individual trials (1245.33, 1245.48, 1245.36), empagliflozin provided reductions in FPG compared with placebo. The FPG reductions were generally in a similar range as for the pivotal trials.

Body weight

The change from baseline in body weight at 24 weeks was defined as a key secondary endpoint in all pivotal trials. In each pivotal trial, both doses of empagliflozin were superior ($p<0.0001$) to placebo, with similar reductions in each trial (Figure 8).

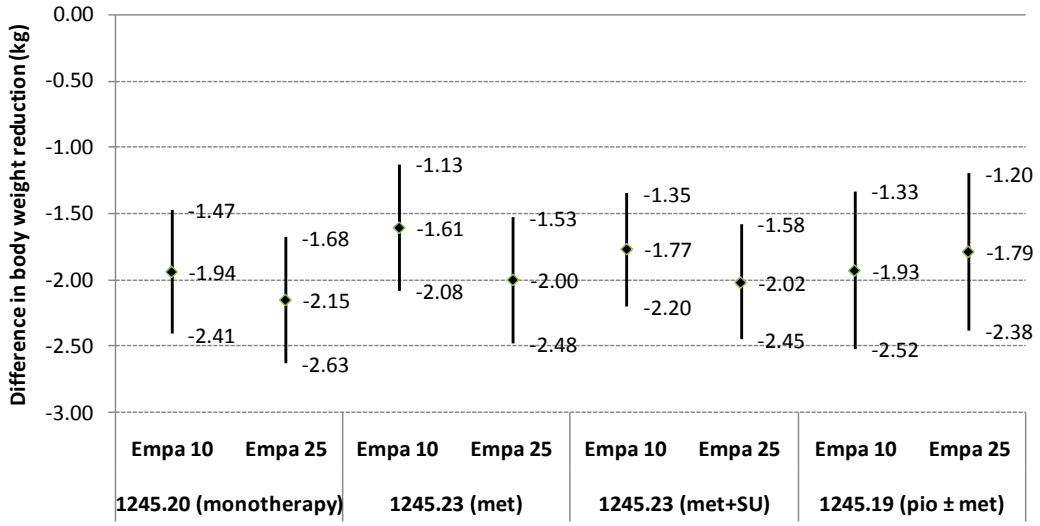


Figure 8 Adjusted mean difference (with 95% confidence intervals) between empagliflozin and placebo in body weight after 24 weeks for the pivotal trials – FAS (LOCF)

Treatment with glimepiride led to a 1.60 kg increase in mean body weight after 52 weeks. Mean body weight decreased by 3.21 kg in the empagliflozin 25 mg group. The resulting adjusted mean difference between treatment groups of 4.81 kg (95% CI: -5.12, -4.50) demonstrated superiority of empagliflozin 25 mg to the sulphonylurea glimepiride.

Body weight was an exploratory endpoint in trials 1245.33, 1245.48, 1245.36. In each trial, empagliflozin provided reductions in body weight compared with placebo. The reductions were generally in a similar range as for the pivotal trials.

The additional add-on to insulin study (1245.49) also investigated the change in body weight. Compared with placebo, the adjusted mean changes from baseline at 52 weeks were -2.39 kg

(97.5% CI: -3.54 to -1.24 kg; p<0.0001) for empagliflozin 10 mg and -2.48 kg (97.5% CI: -3.63 to -1.33, p<0.0001) for empagliflozin 25 mg.

Blood pressure

Blood pressure was analysed as an efficacy endpoint. In the pivotal trials, empagliflozin was associated with a reduction in blood pressure. Results for SBP and DBP are summarised in Figure 9.

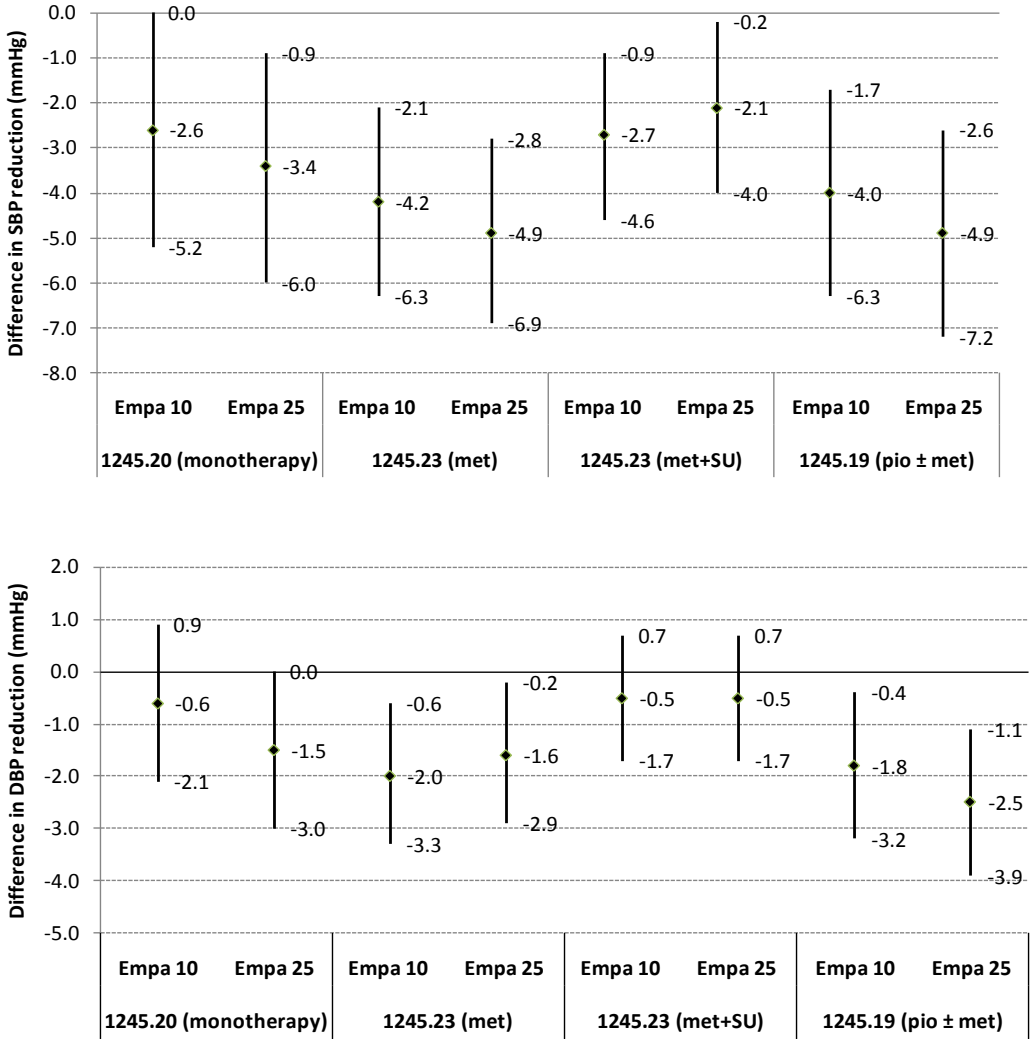


Figure 9 Adjusted mean difference (with confidence intervals) between empagliflozin and placebo in SBP and DBP after 24 weeks for the pivotal trials.

In trial 1245.28, treatment with empagliflozin was superior to glimepiride for both SBP and DBP changes from baseline. After 52 weeks, the adjusted mean difference in SBP to glimepiride was -5.8 mmHg (97.5% CI: -7.3, -4.4) with p<0.0001. The corresponding treatment difference for DBP was -2.8 mmHg (97.5% CI: -3.7, -2.0) with p<0.0001.

In the trial in patients with hypertension (trial 1245.48) ambulatory blood pressure monitoring (ABPM) was employed. Both doses of empagliflozin were superior to placebo for 24-h SBP and 24-h DBP changes from baseline. After the 12-week treatment period, the adjusted mean treatment differences for 24-h SBP were -3.44 mmHg (95% CI: -4.78,-2.09) for empagliflozin 10 mg and -4.16 mmHg (95% CI: 5.50,-2.83) for empagliflozin 25 mg. For 24-h DBP, the corresponding differences to placebo were 1.36 mmHg (95% CI: -2.15,-0.56) for empagliflozin 10 mg and -1.72 mmHg (95% CI: 2.51,-0.93) for empagliflozin 25 mg.

Changes in SBP and DBP were analysed as exploratory endpoints in the other placebo-controlled trials (1245.33, 1245.36). Results were in a similar range as for the pivotal trials (with somewhat smaller reductions in trial 1245.33).

Rescue medication

In most trials, rescue medication was to be initiated during the first 12 weeks of treatment only if a patient had a confirmed glucose level of >240 mg/dL after an overnight fast (and if the glucose level was >200 mg/dL during the subsequent 12 weeks). In each of the pivotal trials, a lower proportion of patients in the empagliflozin groups than in the placebo group required antidiabetic rescue medication (i.e. increase in dose of background medication or initiation of a new drug). In the pooled analysis of the pivotal trials (EFF-2), 4.1% of patients in the empagliflozin 10 mg group and 2.4% in the empagliflozin 25 mg group required rescue medication in the first 24 weeks, compared with 15.8% in the placebo group. After 52 weeks, the picture was similar, with higher overall frequencies. The use of rescue medication in the first 24 weeks of trial 1245.36 (patients with renal impairment) and the first 18 weeks of trial 1245.33 (patients with basal insulin) was consistent with the observations made for the pivotal trials. In the shorter 12-week trial 1245.48 (patients with hypertension), few patients required rescue medication and frequencies were similar across treatment groups. In the active-controlled trial 1245.28, fewer patients in the empagliflozin group than in the glimepiride group needed rescue medication: after 52 weeks, frequencies of patients requiring rescue medication were 7.3% for empagliflozin and 13.3% for glimepiride.

Analysis performed across trials (pooled analyses)

The empagliflozin effects were assessed in a number of subgroups for various demographic and baseline characteristics. The subgroup analyses used the 24-week data from the pooling of the pivotal trials. For all endpoints tested, the efficacy of empagliflozin compared with placebo was consistent across the subgroup categories for gender, race, baseline BMI, and time since diagnosis of diabetes. Empagliflozin effects compared with placebo were largely homogeneous across the 4 geographical regions.

Possible treatment-by-subgroup interactions for renal impairment at baseline were observed for HbA1c, FPG, and SBP. There were no patients with severe renal impairment in the pivotal trials, since these patients were not allowed in the pivotal trials. The change in HbA1c at Week 24 in patients with mild (i.e. GFR 60-90ml/min) renal impairment was 0.68% in comparison to placebo. In patients with moderate (i.e. GFR 30-60 ml/min) renal impairment, the placebo-adjusted treatment effect was -0.42%. The patients with moderate renal impairment were

subdivided in patients with GFR 45-60 and 30-45 ml/min. The adjusted mean treatment differences for empagliflozin 25 mg compared with placebo were -0.46 and -0.39%, respectively. In patients with severe renal insufficiency, there was no treatment effect of empagliflozin 25 mg compared with placebo after either 24 weeks or 52 weeks of treatment. In the pivotal studies, the effect of empagliflozin on HbA1c in individuals with GFR 45-60 ml/min was of borderline significance (-0.44 for empagliflozin 10 mg and -0.31 for empagliflozin 25 mg). For patients with GFR 30-45 ml/min, efficacy was not acceptable (-0.27% and -0.18%, respectively).

The subgroup analyses by baseline HbA1c showed that both doses of empagliflozin provided clinically meaningful reductions in HbA1c in each of the individual baseline HbA1c categories. The adjusted mean difference in the HbA1c change from baseline between empagliflozin (both doses) and placebo increased with increasing baseline HbA1c. In the lowest baseline category (HbA1c <8.0%) the treatment difference to placebo was -0.40% for empagliflozin 10 mg and -0.46% for empagliflozin 25 mg, whereas in the highest baseline category (HbA1c ≥9.0%) the treatment difference was -1.14% for empagliflozin 10 mg and -1.18% for empagliflozin 25 mg.

Longer-term effects

The pivotal trials had a treatment duration of 24 weeks. However, as described above several of the trials had a longer treatment duration. Active-controlled confirmatory data for up to 52 weeks comparing 25 mg empagliflozin with glimepiride are available from the interim analysis of trial 1245.28. This trial showed empagliflozin 25 mg to be non-inferior to glimepiride for HbA1c reductions and superior to glimepiride for body weight and the occurrence of confirmed hypoglycaemic adverse events as well as systolic and diastolic blood pressure. Furthermore, efficacy of empagliflozin compared with placebo over 52 weeks was investigated in patients with renal impairment in trial 1245.36. Empagliflozin compared with placebo was also efficacious for up to 78 weeks in patients treated with basal insulin in trial 1245.33. In each of these placebo-controlled trials, sustained empagliflozin efficacy was shown not only for glycaemic control (HbA1c, FPG) but also for body weight and blood pressure reductions.

The interim data from the double-blind extensions (1245.31) of the 4 pivotal trials also provide evidence of efficacy for 2 doses of empagliflozin (10 mg and 25 mg) for up to 52 weeks. For the pooling of the extension of these pivotal trials, the HbA1c values at baseline were 7.98% in the empagliflozin 10 mg group, 7.96% in the empagliflozin 25 mg group, and 8.02% in the placebo group. The efficacy of empagliflozin was almost maximal after 12 weeks and was sustained over the 52-week analysis period. The difference to placebo in the adjusted mean change in HbA1c at 24 weeks (i.e. the time point of the primary analysis of the pivotal trials) was -0.55% (95% CI: -0.63, -0.47) for the empagliflozin 10 mg group and -0.60% (95% CI: -0.68, -0.53) for the empagliflozin 25 mg group. At 52 weeks, the treatment differences to placebo were almost identical to the 24-week time point and were -0.55% (95% CI: -0.66, -0.45) for empagliflozin 10 mg and -0.59% (95% CI: -0.69, -0.48) for empagliflozin 25 mg.

Empagliflozin compared to metformin and sitagliptin

The phase IIb dose-finding monotherapy trial 1245.9 tested various doses of empagliflozin in drug-naïve patients, with immediate-release metformin as an open-label comparator (1000 mg twice daily or maximum tolerated dose). The allocation to empagliflozin and metformin was

randomised, but not blinded. The effect of metformin on HbA1c was -0.85%, the effect of empagliflozin 25 mg was -0.72%.

In study 1245.20, the exploratory comparison of both empagliflozin doses vs. sitagliptin 100 mg demonstrated that treatment with empagliflozin showed a similar reduction in HbA1c compared to treatment with sitagliptin (empagliflozin 10 mg -0.74%; empagliflozin 25 mg -0.85% vs. sitagliptin 100 mg -0.73%). Treatment with both empagliflozin 10 mg and 25 mg reduced body weight and BP compared with sitagliptin treatment.

Open label empagliflozin in patients with HbA1c above 10.0%

In the pivotal trials 1245.20 (monotherapy), 1245.23(met), and 1245.23(met+SU), patients with HbA1c above 10% at baseline were offered the possibility to receive open-label treatment with the high empagliflozin dose (25 mg). In total, 257 patients were assigned to and treated with open-label treatment with 25 mg empagliflozin (39% with metformin plus sulphonylurea background, 27% with metformin background, and 34% without background treatment). These patients were treated for up to 24 weeks, i.e. they did not have the option to continue into the extension trial. The proportion of the patients who prematurely discontinued trial medication in the monotherapy setting (1245.20) was only slightly higher than in the randomised empagliflozin groups of this trial. However, in trials 1245.23(met) and 1245.23(met+SU), premature discontinuations among patients with open-label empagliflozin were about twice as frequent as in the randomised empagliflozin groups. For open-label treatment, the most frequent reason leading to premature discontinuation generally was patient refusal to continue trial medication (not due to adverse event).

Substantial reductions of mean HbA1c and mean FPG were achieved in the open-label empagliflozin group of all 3 trials. For all patients in the open-label group (observed cases), the mean HbA1c change from baseline to 24 weeks was -3.27%, and the mean FPG change was 66.2 mg/dL. Despite their very high baseline values, a considerable proportion of patients (15.2%) met the HbA1c target of <7.0%. Furthermore, reductions of body weight, SBP, and DBP were observed and were in a similar range as for the randomised empagliflozin groups.

Clinical studies in special populations

A study in patients with hypertension was performed. In this study, various antidiabetic drugs were used as background medication. The findings in this study in patients with hypertension were similar to those in the other studies. Compared to placebo, there was a relevant decrease in HbA1c (-0.62% and -0.65% for empagliflozin 10 and 25 mg, respectively). In addition, blood pressure was lower with empagliflozin (-3.4 and -4.2 mmHg for empagliflozin 10 and 25 mg respectively). This decrease in blood pressure may be clinically relevant, however, the diuretic effect of empagliflozin may also be associated with adverse events.

Empagliflozin was investigated in a specific trial in patients with various degrees of renal insufficiency. The most frequent reason for premature treatment discontinuation was adverse events; reported for 4.5% of patients with mild renal impairment, 4.3% of patients with moderate renal impairment, and 18.9% of patients with severe renal impairment. Premature treatment discontinuation was very high for patients with severe renal insufficiency. The change in HbA1c at Week 24 in patients with mild (i.e. GFR 60-90ml/min) renal impairment was 0.68%

in comparison to placebo. In patients with moderate (i.e. GFR 30-60 ml/min) renal impairment, the placebo-adjusted treatment effect was -0.42%. The patients with moderate renal impairment were subdivided in patients with GFR 45-60 and 30-45 ml/min. The adjusted mean treatment differences for empagliflozin 25 mg compared with placebo were -0.46 and -0.39%, respectively. In patients with severe renal insufficiency, there was no treatment effect of empagliflozin 25 mg compared with placebo after either 24 weeks or 52 weeks of treatment. In the pivotal studies, the effect of empagliflozin on HbA1c in individuals with GFR 45-60 ml/min was of borderline significance (-0.33% for empagliflozin 25 mg, n=50 and -0.48% for empagliflozin 10 mg, n=51). For patients with GFR 30-45 ml/min, efficacy was also not acceptable (-0.18% for empagliflozin 25 mg). These data suggest that, similar to dapagliflozin and canagliflozin, treatment effects diminish with decreasing renal function. Treatment effects of empagliflozin in patients with GFR 45-60ml/min are of borderline significance.

Subgroup analyses of the pivotal trials demonstrate that the treatment effect of empagliflozin in patients older than 75 years is only -0.21 and -0.33%. Similar findings were shown in the elderly in the cardiovascular safety trial (-0.20% and -0.30%). A further post-hoc analysis of the cardiovascular safety study suggested that efficacy in individuals>75 years with a renal function >60 ml/min may be acceptable (-0.48% for empagliflozin 25 mg). However, in the subgroup of elderly patients >75 years and renal function 45-60 ml/min efficacy was not acceptable (-0.37%).

Supportive studies

Combination with insulin

The use of empagliflozin in combination with insulin was investigated in two separate trials.

Study 1245.33 consisted of two parts. During the first part, a fixed insulin dose is used for 18 weeks (except for rescue therapy). After that, an adjustable dose of insulin was used for 60 weeks. As could be expected, diabetes duration was longer than in studies in patients not using insulin. Compared to placebo without changes in insulin dose, empagliflozin as add on to insulin was associated with a clinically relevant reduction in HbA1c of -0.56 (10 mg) and -0.70 (25 mg) at 18 weeks. After these 18 weeks, insulin dose adjustments were allowed. The adjusted mean differences from placebo at Week 78 were -6.66 IU in the empagliflozin 10 mg group and -5.92 IU in the empagliflozin 25 mg group. Despite these changes in insulin dose, compared to placebo after 78 weeks, empagliflozin as add on to insulin was associated with a clinically relevant reduction in HbA1c of -0.46 (10 mg) and -0.62 (25 mg). In addition, there were reductions in body weight with both doses of empagliflozin at Week 18 that were sustained through Week 78; the difference versus placebo for the adjusted mean change in body weight from baseline at Week 78 -3.63 kg for the empagliflozin 10 mg group and -3.12 kg for the empagliflozin 25 mg group.

It should be noted that the changes in insulin dose were small and not clinically relevant. In addition, there was a remarkable difference in baseline HbA1c between the groups. Compared to the placebo, HbA1c was 0.16% and 0.24% higher in the empagliflozin 10 and 25 mg groups, respectively. This may have caused an overestimation of treatment effects. Nevertheless, the changes in HbA1c are considered clinically relevant.

Study 1245.49 was a similar study. This randomized, blinded placebo-controlled 52-week study investigated empagliflozin as add-on to multiple daily injection insulin therapy with or without metformin in type 2 diabetes. In this study, subjects maintained a stable insulin dose for the first 18 weeks. Change in HbA1c was -0.44 (97.5% CI -0.61;-0.27) for 10 mg empagliflozin and -0.52 (97.5%CI -0.69;-0.35) for 25 mg empagliflozin, compared to placebo. After 52 weeks, the adjusted mean changes in insulin dose from baseline compared with placebo were -8.83 IU/day for empagliflozin 10 mg and -11.22 IU/day for empagliflozin 25 mg. The placebo-adjusted mean changes in HbA1c values at 52 weeks were -0.38% for 10 mg and -0.46% for 25 mg.

Based on these studies, combination with insulin is acceptable.

Non-inferiority trial

The effects of empagliflozin were compared to SU in a non-inferiority study. The decrease in HbA1c was numerically greater with empagliflozin compared to glimepiride (-0.73% vs. -0.66%). In addition, 60% of the patients in the glimepiride group was taking less than the maximum allowed dose of 4 mg, whereas all patient in the empagliflozin group were treated with the maximum dose of 25 mg. This may underestimate the treatment effect of glimepiride in comparison to empagliflozin. However, this is also observed in clinical practice. It may be difficult to uptitrate glimepiride due to higher risk of hypoglycaemia. Efficacy of empagliflozin was numerically larger than that of glimepiride and statistical non-inferiority was established. Therefore, a formal non-inferiority claim is acceptable.

Treatment with glimepiride led to a 1.6 kg increase in mean body weight after 52 weeks, whereas mean body weight decreased by 3.2 kg in the empagliflozin 25 mg group.

2.5.3. Discussion on clinical efficacy

Empagliflozin is an orally administered, selective inhibitor of the sodium-dependent glucose co-transporter-2 (SGLT-2) in the kidney. It is intended for use in patients with type 2 diabetes mellitus. The blood glucose-lowering effect of empagliflozin is independent of insulin secretion or action. Empagliflozin's insulin-independent mode of action results in a low risk of hypoglycaemia. Further effects of SGLT 2 inhibition include weight loss due to potential calorie loss through urinary glucose excretion and a reduction in blood pressure due to a diuretic effect.

A total of 11250 randomised and treated patients are included in the evaluation of efficacy presented. Of these, 3021 patients were randomised to empagliflozin 10 mg and 3994 patients were randomised to empagliflozin 25 mg. Another 3081 patients were randomised to receive placebo and 1154 patients were randomised to an active comparator. At Day 120 an additional (add-on to insulin) study was submitted. Study 1245.49 enrolled 563 subjects of whom 186 received empagliflozin 10 mg and 189 empagliflozin 25 mg.

Dose finding

In the dose findings studies, the 25 mg dose of empagliflozin provided better efficacy than the 10 mg dose. The 50 mg dose was only investigated in study 1245.10. In this study, there was no additional benefit of the 50 mg dose in terms of efficacy. The selection of the 10 mg and 25 mg

dose for the phase III studies is reasonable. In each of the pivotal phase III trials except for 1245.23 (met+SU) the reduction in HbA1c from baseline at 24 weeks was greater for empagliflozin 25 mg than for empagliflozin 10 mg. The pooled data of the pivotal trials (EFF-2) showed that the adjusted mean change from baseline in HbA1c after 24 weeks of treatment was -0.70% for empagliflozin 10 mg and -0.76% for empagliflozin 25 mg. Although the 25 mg performed better, the lower dose also showed clinically significant changes in HbA1c. It could be useful to start treatment with this lower dose and then increase the dose if necessary. Therefore the CHMP questioned why the Applicant abandoned the 10 mg dose. The Applicant responded by re-introducing the 10 mg dose as a starting dose. In principle, this approach is supported from a clinical efficacy and safety point of view.

Pivotal studies

Treatment with empagliflozin 10 mg or 25 mg once daily resulted in improvement of glycaemic control with modest reductions of HbA1c and FPG. The 4 pivotal trials demonstrated the superiority of both doses of empagliflozin to placebo after 24 weeks

Monotherapy: Comparison of the test agent to placebo in the monotherapy setting is always required to evaluate the genuine glucose lowering effect and safety profile of the new agent, independent of whether the marketing authorisation is intended for monotherapy or add-on therapy. After 24 weeks, compared to placebo, empagliflozin monotherapy was associated with a clinically relevant reduction in HbA1c of -0.74 (10 mg) and -0.85 (25 mg). These reductions were similar compared to the effect of sitagliptin 100 mg (-0.73). With empagliflozin, there were small changes in body weight (-1.9 and -2.2kg, respectively), but not with sitagliptin (+0.5kg).

However, if an indication for first line (unrestricted) monotherapy is intended, a monotherapy study comparing the test drug to metformin is always needed. A formal comparison was not performed, but dose finding study 1245.9 included empagliflozin and metformin. The allocation to empagliflozin and metformin was randomised, but not blinded. Nevertheless, a comparison can be performed. The effect of metformin on HbA1c was larger (-0.85%) compared to empagliflozin 25 mg (-0.72%).

An additional issue is the fact that, other efficacy measures such as effects on micro- and macrovascular endpoints may need to be evaluated before a first line monotherapy indication would be considered approvable. For empagliflozin, micro- and macrovascular endpoints have not been studied.

Taken together, a first line indication for empagliflozin is not acceptable. Therefore, the Applicant claims a restricted monotherapy indication: When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate. Patients with renal insufficiency were investigated in a specific trial (see below). Patients with gastrointestinal complaints with metformin were not specifically investigated, but this is not considered to be an important issue. With respect to heart failure, there is no experience in clinical studies with empagliflozin in NYHA class III-IV.

Add-on to metformin with and without SU: The use of empagliflozin as add-on to metformin with and without SU is relevant for clinical practice. Compared to placebo, empagliflozin as add on to metformin was associated with a clinically relevant reduction in HbA1c of -0.57 (10 mg) and -

0.64 (25 mg). In addition, compared to placebo, empagliflozin as add on to metformin plus SU was also associated with a clinically relevant reduction in HbA1c of -0.64 (10 mg) and -0.59 (25 mg). There were small decreases in body weight (-1.6 to -2.0 kg). The efficacy of the combination of empagliflozin with metformin and metformin plus SU is acceptable.

Add-on to pioglitazone with and without metformin: The use of empagliflozin as add-on to pioglitazone with and without metformin is relevant. Compared to placebo, empagliflozin as add on to pioglitazone was associated with a clinically relevant reduction in HbA1c of -0.48 (10 mg) and -0.61 (25 mg). There were small decreases in body weight (-2.0 and -1.8 kg, respectively). The majority of patients were treated with pioglitazone with metformin. Only a minority of the patients was treated with empagliflozin in combination with pioglitazone without metformin. However, efficacy was similar in both subgroups.

Other outcome measures in pivotal studies: In these pivotal trials, body weight was decreased with empagliflozin. The treatment difference to placebo at 24 weeks was 1.8 kg for the empagliflozin 10 mg group and 2.0 kg for the empagliflozin 25 mg group. In the pivotal studies, in comparison to placebo, empagliflozin was associated with a lower systolic (-2.1 to -4.9 mmHg) and diastolic blood pressure systolic (-0.5 to -2.5 mmHg). The sub-studies investigating the effects on mean daily glucose, body composition and the meal tolerance tests are of interest. However, it is not known whether or not the effects are of clinical relevance.

Combination with insulin

The use of empagliflozin in combination with insulin was investigated in two separate trials.

Study 1245.33 consisted of two parts. During the first part, a fixed insulin dose is used for 18 weeks (except for rescue therapy). After that, an adjustable dose of insulin was used for 60 weeks. As could be expected, diabetes duration was longer than in studies in patients not using insulin. Compared to placebo without changes in insulin dose, empagliflozin as add on to insulin was associated with a clinically relevant reduction in HbA1c of -0.56 (10 mg) and -0.70 (25 mg) at 18 weeks. After these 18 weeks, insulin dose adjustments were allowed. The adjusted mean differences from placebo at Week 78 were -6.66 IU in the empagliflozin 10 mg group and -5.92 IU in the empagliflozin 25 mg group. Despite these changes in insulin dose, compared to placebo after 78 weeks, empagliflozin as add on to insulin was associated with a clinically relevant reduction in HbA1c of -0.46 (10 mg) and -0.62 (25 mg). In addition, there were reductions in body weight with both doses of empagliflozin at Week 18 that were sustained through Week 78; the difference versus placebo for the adjusted mean change in body weight from baseline at Week 78 -3.63 kg for the empagliflozin 10 mg group and -3.12 kg for the empagliflozin 25 mg group.

It should be noted that the changes in insulin dose were small and not clinically relevant. In addition, there was a remarkable difference in baseline HbA1c between the groups. Compared to the placebo, HbA1c was 0.16% and 0.24% higher in the empagliflozin 10 and 25 mg groups, respectively. This may have caused an overestimation of treatment effects. Nevertheless, the changes in HbA1c are considered clinically relevant.

Study 1245.49 was a similar study. This randomized, blinded placebo-controlled 52-week study investigated empagliflozin as add-on to multiple daily injection insulin therapy with or without

metformin in type 2 diabetes. In this study, subjects maintained a stable insulin dose for the first 18 weeks. Change in HbA1c was -0.44 (97.5% CI -0.61;-0.27) for 10 mg empagliflozin and -0.52 (97.5%CI -0.69;-0.35) for 25 mg empagliflozin, compared to placebo. After 52 weeks, the adjusted mean changes in insulin dose from baseline compared with placebo were -8.83 IU/day for empagliflozin 10 mg and -11.22 IU/day for empagliflozin 25 mg. The placebo-adjusted mean changes in HbA1c values at 52 weeks were -0.38% for 10 mg and -0.46% for 25 mg.

Based on these studies, combination with insulin is acceptable.

Non-inferiority trial

The effects of empagliflozin were compared to SU in a non-inferiority study. The decrease in HbA1c was numerically greater with empagliflozin compared to glimepiride (-0.73% vs. -0.66%). In addition, 60% of the patients in the glimepiride group was taking less than the maximum allowed dose of 4 mg, whereas all patient in the empagliflozin group were treated with the maximum dose of 25 mg. This may underestimate the treatment effect of glimepiride in comparison to empagliflozin. However, this is also observed in clinical practice. It may be difficult to uptitrate glimepiride due to higher risk of hypoglycaemia. Efficacy of empagliflozin was numerically larger than that of glimepiride and statistical non-inferiority was established. Therefore, a formal non-inferiority claim is acceptable.

Treatment with glimepiride led to a 1.6 kg increase in mean body weight after 52 weeks, whereas mean body weight decreased by 3.2 kg in the empagliflozin 25 mg group.

Special populations

A study in patients with hypertension was performed. In this study, various antidiabetic drugs were used as background medication. The findings in this study in patients with hypertension were similar to those in the other studies. Compared to placebo, there was a relevant decrease in HbA1c (-0.62% and -0.65% for empagliflozin 10 and 25 mg, respectively). In addition, blood pressure was lower with empagliflozin (-3.4 and -4.2 mmHg for empagliflozin 10 and 25 mg respectively). This decrease in blood pressure may be clinically relevant, however, the diuretic effect of empagliflozin may also be associated with adverse events.

Empagliflozin was investigated in a specific trial in patients with various degrees of renal insufficiency. The most frequent reason for premature treatment discontinuation was adverse events; reported for 4.5% of patients with mild renal impairment, 4.3% of patients with moderate renal impairment, and 18.9% of patients with severe renal impairment. Premature treatment discontinuation was very high for patients with severe renal insufficiency. The change in HbA1c at Week 24 in patients with mild (i.e. GFR 60-90ml/min) renal impairment was 0.68% in comparison to placebo. In patients with moderate (i.e. GFR 30-60 ml/min) renal impairment, the placebo-adjusted treatment effect was -0.42%. The patients with moderate renal impairment were subdivided in patients with GFR 45-60 and 30-45 ml/min. The adjusted mean treatment differences for empagliflozin 25 mg compared with placebo were -0.46 and -0.39%, respectively. In patients with severe renal insufficiency, there was no treatment effect of empagliflozin 25 mg compared with placebo after either 24 weeks or 52 weeks of treatment. In the pivotal studies, the effect of empagliflozin on HbA1c in individuals with GFR 45-60 ml/min was of borderline

significance (-0.33% for empagliflozin 25 mg, n=50 and -0.48% for empagliflozin 10 mg, n=51). For patients with GFR 30-45 ml/min, efficacy was also not acceptable (-0.18% for empagliflozin 25 mg). These data suggest that, similar to dapagliflozin and canagliflozin, treatment effects diminish with decreasing renal function. Treatment effects of empagliflozin in patients with GFR 45-60ml/min are of borderline significance.

Subgroup analyses of the pivotal trials demonstrate that the treatment effect of empagliflozin in patients older than 75 years is only -0.21 and -0.33%.

2.5.4. Conclusions on the clinical efficacy

In clinical trials two doses were used: 10 mg and 25 mg. In general, the 25 mg dose performed slightly better, but 10 mg might be considered as a starting dose. During the procedure, the 10 mg dose was added to the dossier following the CHMP request.

The Applicant claimed a restricted monotherapy indication: When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate. An indication for empagliflozin monotherapy in patients for whom metformin is not appropriate due to gastrointestinal complaints may be acceptable. However, other contraindications for metformin, such as heart failure and moderate or severe renal insufficiency are not acceptable. Patients with heart failure have not been investigated. In the trial in patients with renal impairment, treatment effects of empagliflozin in patients with mild renal impairment (GFR 60-90 ml/min) were clinically relevant (-0.68%), but treatment effects of empagliflozin in patients with GFR<45-60 ml/min are of borderline significance. Efficacy of empagliflozin add-on to metformin, add-on to metformin plus SU, add-on to pioglitazone with and without metformin and add-on to basal insulin is acceptable.

Subgroup analyses of the trial in patients with renal impairment suggest that the reduced efficacy in patients >75 years is explained by renal impairment. In individuals >75 years with a renal function >60 ml/min efficacy may be acceptable.

2.6. Clinical safety

The safety assessment focused on patients with type 2 diabetes, who were treated in mostly randomised, double-blind trials. All patients treated with at least 1 dose of trial medication in any randomised period (i.e. excluding placebo run-in or washout periods) were included in the patient set evaluated (TS, treated set). This application is supported by safety data from 48 clinical trials, including 13 phase IIb/III trials, 5 dose-finding phase II trials, and 30 phase I trials (see also the description of the clinical development programme above). Some phase III trials were still on-going at the time of the integrated analysis for this application (1245.25, 1245.28, 1245.31). For these trials, all safety data available at the time of data cut-off for the pre-specified interim analysis of each trial are included in this application.

To better support an integrated analysis of safety, the trial data were pooled. Six poolings were devised to adequately analyse the different aspects of the safety profile of empagliflozin: the pivotal phase III trials (2 different poolings; SAF-2 and SAF-3), all monotherapy trials (SAF-1),

all trials in patients with type 2 diabetes (2 poolings; SAF-4 and SAF-5), and all trials in healthy subjects (SAF-6); for an overview.

Patient exposure

The largest pooling, SAF-5 (all patients), included 12873 treated patients, of which 8197 were treated with empagliflozin (10 mg: 3311 patients; 25 mg: 4285 patients; doses <10 mg [1 mg, 2.5 mg, 5 mg]: 382 patients; doses > 25 mg [50 mg, 100 mg]: 219 patients). Of these, 4415 patients were treated with empagliflozin for more than 52 weeks (10 and 25 mg only) and 1486 patients for more than 76 weeks (10 and 25 mg only).

Across all SAFs, exposure was lower in the placebo groups than in the empagliflozin groups (10 mg or 25 mg). The higher exposure in the empagliflozin groups is a result of the generally higher discontinuation rates in the placebo groups in the different trials, and of the trial designs. Particularly, trial 1245.28, a 52-week active comparator trial without a placebo control and testing only the 25 mg dose of empagliflozin, contributed to the exposure differences between treatment groups.

In SAF-5 (all patients), mean and median exposure was similar in all treatment groups except placebo and empagliflozin 10 mg. The slightly higher exposure in the empagliflozin 25 mg and 'all comparator' group can be explained by trial 1245.28, the active comparator trial contributing 12% of all patients to SAF-5.

Table 9 Exposure to trial medication for SAF-5 (all patients) – TS

	Placebo	**Empa 10**	**Empa 25**	**All empa[2]**	**All comparators[3]**
Number of patients[1], N (%)	3522 (100.0)	3630 (100.0)	4602 (100.0)	8400 (100.0)	4676 (100.0)
Cumulative exposure, N (%)					
≥24 weeks	2464 (70.0)	2856 (78.7)	3738 (81.2)	6603 (78.6)	3514 (75.1)
≥52 weeks	1423 (40.4)	1720 (47.4)	2541 (55.2)	4415 (52.6)	2333 (49.9)
≥76 weeks	317 (9.0)	601 (16.6)	881 (19.1)	1486 (17.7)	724 (15.5)
Exposure [days]					
Mean (SD)	286.0 (169.8)	327.8 (173.7)	353.0 (176.2)	340.4 (181.2)	326.9 (183.2)
Median	307.0	351.0	367.0	364.0	363.0
Range	1 to 697	1 to 703	1 to 717	1 to 717	1 to 715
Total exposure [years]	2758.1	3258.2	4448.1	7827.8	4184.4

[1] Overall patient numbers are higher than the actual number of patients treated, as this pooling included trials with a planned re-randomisation during treatment (1245.24, 1245.38) and a patient is shown in both treatment groups if he/she was re-randomised to a different trial drug or dose.

[2] Empagliflozin doses included: 1 mg, 2.5 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg

[3] All comparators included: placebo, sitagliptin, metformin, and glimepiride

SAF-3 (pivotal trials) included 1652 patients treated with 10 or 25 mg empagliflozin and 1048 patients treated with a comparator (placebo or sitagliptin).

Table 10 Exposure to trial medication for SAF-3 (pivotal trials) – TS

	Placebo	**Empa 10**	**Empa 25**
Number of patients, N (%)	825 (100.0)	830 (100.0)	822 (100.0)
Cumulative exposure, N (%)			
≥24 weeks	707 (85.7)	771 (92.9)	747 (90.9)
≥52 weeks	361 (43.8)	434 (52.3)	414 (50.4)
≥76 weeks	65 (7.9)	82 (9.9)	80 (9.7)
Exposure [days]			
Mean (SD)	309.6 (155.6)	344.9 (145.7)	338.5 (151.3)
Median	328.0	370.5	364.0
Range	1 to 625	1 to 636	1 to 636
Total exposure [years]	699.2	783.8	761.7

Adverse events

The analysis of adverse events was based on treatment-emergent adverse events, i.e. those with an onset between the first and the last intake of trial medication plus 7 days. Adverse event analyses are based on the number of patients with adverse events, not the number of adverse events. Adverse events were coded with the MedDRA coding dictionary, version 15.0.

In SAF-3 (pivotal trials) the overall frequency of patients with adverse events was 70.9% ('all empa') and 72.1% ('all comparators'). Frequencies of most adverse event categories were similar between groups. However, investigator-assessed drug-related adverse events had a higher frequency in the 'all empa' group (21.3%) than the 'all comparators' group (16.2%).

Table 11 Overview of adverse events in SAF-3 (pivotal trials with extension) – TS

	Placebo		Empa 10 mg		Empa 25 mg	
SAF-3 (pivotal trials with extension)						
Number of patients, N (%)	825	(100.0)	830	(100.0)	822	(100.0)
Exposure, mean (SD) [days]	309.6	(155.6)	344.9	(145.7)	338.5	(151.3)
Patients with any adverse event, N (%)	611	(74.1)	596	(71.8)	576	(70.1)
Investigator-defined drug-related adverse events	146	(17.7)	185	(22.3)	167	(20.3)
Serious adverse events	61	(7.4)	59	(7.1)	48	(5.8)
Adverse events of severe intensity	52	(6.3)	34	(4.1)	37	(4.5)
Adverse events leading to discontinuation of trial medication	35	(4.2)	25	(3.0)	34	(4.1)

A patient may be counted in more than 1 adverse event category

In SAF-5 (all patients), about 70% of patients reported adverse events. Serious events and events of severe intensity were reported more frequently in the comparator groups than in the empagliflozin groups, and investigator-assessed drug-related events were reported more frequently in the empagliflozin groups than in the comparator groups, see Table . Adverse event frequencies in SAF-4 were very similar to those in SAF-5.

The frequencies of adverse events of special interest were similar across treatments and across SAFs. The exceptions were confirmed hypoglycaemia and genital infection. The occurrence of hypoglycaemia was linked to the antidiabetic background medication, with the lowest frequency of hypoglycaemic events in patients on monotherapy, and the highest frequency in patients who concomitantly received insulin. Genital infections were more frequent in the empagliflozin groups than in the comparator groups.

Table 12 Overview of adverse events in SAF-5 (all patients) – TS

Table 12 Overview of adverse events in SAF-5 (all patients) – TS	**Placebo**		**Empa 10 mg**		**Empa 25 mg**		**All comparators[1]**	
Number of patients, N (%)	3522	(100.0)	3630	(100.0)	4602	(100.0)	4676	(100.0)
Exposure, mean (SD) [days]	286.0	(169.8)	327.8	(173.7)	353.0	(176.2)	326.9	(183.2)
Patients with any adverse event, N (%)	2415	(68.6)	2472	(68.1)	3199	(69.5)	3291	(70.4)
Investigator-defined drug- related adverse events	536	(15.2)	747	(20.6)	917	(19.9)	803	(17.2)
Serious adverse events	446	(12.7)	347	(9.6)	474	(10.3)	529	(11.3)
Adverse events of severe intensity	291	(8.3)	222	(6.1)	297	(6.5)	363	(7.8)
Adverse events leading to discontinuation of trial medication	188	(5.3)	174	(4.8)	226	(4.9)	222	(4.7)
Patients with adverse events of special interest, N (%)								
Confirmed hypoglycaemic events[2]	443	(12.6)	457	(12.6)	501	(10.9)	614	(13.1)
Urinary tract infection (BIcMQ)	284	(8.1)	324	(8.9)	406	(8.8)	380	(8.1)
Genital infection (BIcMQ)	35	(1.0)	160	(4.4)	218	(4.7)	52	(1.1)
Volume depletion (BIcMQ)	49	(1.4)	52	(1.4)	67	(1.5)	57	(1.2)
Hepatic injury (SMQ)	54	(1.5)	43	(1.2)	65	(1.4)	87	(1.9)
Bone fracture (BIcMQ)	55	(1.6)	59	(1.6)	51	(1.1)	72	(1.5)
Decreased renal function (SMQ)	36	(1.0)	41	(1.1)	58	(1.3)	40	(0.9)
Malignancy (BIcMQ)	32	(0.9)	37	(1.0)	51	(1.1)	42	(0.9)
Malignancy (BIcMQ) with an onset after ≥6 months of exposure	16	(0.5)	22	(0.6)	25	(0.5)	25	(0.5)

SMQ = Standardised MedDRA query; BIcMQ = BI-customised MedDRA query (used if SMQ not available)

[1] Including placebo, sitagliptin, metformin, and glimepiride

[2] An adverse event (not restricted to the PT hypoglycaemia) assessed by the investigator to be a hypoglycaemic adverse event and with documentation of plasma glucose ≤70 mg/dL or assistance of another person required

Most frequently reported adverse events

The frequencies of patients with any adverse events were similar between treatment groups. The most common adverse events belonged to the MedDRA System Organ Class (SOC) infections and infestations, with similar frequencies for all treatment groups in all SAFs and trials. At the MedDRA Preferred Term (PT) level, the most frequent events were nasopharyngitis (with similar frequencies for all groups), urinary tract infection (with similar frequencies for all groups), hyperglycaemia (with higher frequencies in the comparator groups than in the empagliflozin groups), and hypoglycaemia (with higher frequencies in the empagliflozin groups than in the comparator groups). Differences between the 2 doses of empagliflozin (10 mg and 25 mg) were small with no clear distinction between the 2 doses. Adverse events with a frequency of more than 5% in any treatment group are presented for SAF-3 in **Table** 13.

Table 13 Frequency of patients with adverse events with a frequency of >5% in any group at MedDRA SOC or PT-level in SAF-3 (pivotal trials with extension), sorted by overall frequency – TS

System organ class Preferred term	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)
Number of patients, N (%)	825 (100.0)	830 (100.0)	822 (100.0)
Exposure, mean (SD) [days]	309.6 (155.6)	344.9 (145.7)	338.5 (151.3)
Patients with any adverse event, N (%)	611 (74.1)	596 (71.8)	576 (70.1)
Infections and infestations	303 (36.7)	298 (35.9)	298 (36.3)
Nasopharyngitis	80 (9.7)	91 (11.0)	75 (9.1)
Urinary tract infection	81 (9.8)	90 (10.8)	67 (8.2)
Upper respiratory tract infection	55 (6.7)	34 (4.1)	56 (6.8)
Metabolism and nutrition disorders	266 (32.2)	190 (22.9)	163 (19.8)
Hyperglycaemia	179 (21.7)	46 (5.5)	37 (4.5)
Hypoglycaemia	44 (5.3)	64 (7.7)	50 (6.1)
Dyslipidaemia	39 (4.7)	42 (5.1)	34 (4.1)
Musculoskeletal and connective tissue disorders	127 (15.4)	124 (14.9)	137 (16.7)
Gastrointestinal disorders	123 (14.9)	145 (17.5)	112 (13.6)
Nervous system disorders	91 (11.0)	94 (11.3)	108 (13.1)
Investigations	96 (11.6)	68 (8.2)	70 (8.5)
General disorders and administration site conditions	72 (8.7)	78 (9.4)	62 (7.5)
Renal and urinary disorders	44 (5.3)	67 (8.1)	57 (6.9)
Skin and subcutaneous tissue disorders	43 (5.2)	53 (6.4)	72 (8.8)
Injury, poisoning, and procedural complications	55 (6.7)	57 (6.9)	52 (6.3)
Respiratory, thoracic, and mediastinal disorders	40 (4.8)	49 (5.9)	42 (5.1)

Source data: [U12-2707, Appendix 2, Tables 4.3.1 and 5.2.3.1]

Adverse events leading to premature discontinuation of trial medication

The proportion of patients with adverse events leading to discontinuation of trial medication was generally similar for all treatment groups. In most trials, the frequency of adverse events leading to discontinuation was numerically higher in the placebo group than in the empagliflozin groups. The same was true when trials were pooled, although in a few trials, the frequency of such events was lower in the placebo group than in the empagliflozin groups. In SAF-5, the proportions of patients who discontinued due to adverse events were almost identical between the empagliflozin doses (4.8% for empagliflozin 10 mg, 4.9% for empagliflozin 25 mg). When adjusting for exposure, the incidence rates (events per 100 patients years) across SAFs were consistently highest in the placebo groups and lowest in the empagliflozin 10 mg or 25 mg

groups (SAF-3: placebo: 5.0; empagliflozin 10 mg: 3.2; empagliflozin 25 mg: 4.5; SAF-5: placebo: 6.8; empagliflozin 10 mg: 5.4; empagliflozin 25 mg: 5.1; 'all comparators': 5.3).

Serious adverse event/deaths/other significant events

Deaths

All-cause mortality in the pooled analysis of placebo-controlled Phase III trials with a treatment duration > 12 weeks (1245.19, 1245.20, 1245.23 (met), 1245.23 (met+SU), 1245.31, 1245.33, 1245.36, excluding 1245.25 [CVOT] and 1245.28 [H2H vs glimepiride]) was 9 patients on placebo, 2 patients on empagliflozin 10 mg, 5 patients on empagliflozin 25 mg and 7 on all empagliflozin (HR [95%CI] Empa 10 mg vs Placebo: 0.33 [0.07, 1.57]; HR [95%CI] Empa 25 mg vs Placebo: 0.54 [0.18, 1.62]; HR [95%CI] pooled Empa vs Placebo: 0.45 [0.17, 1.23]).

Adverse events of special interest

Based on scientific considerations and regulatory advice, the largest pooling (SAF-5, all patients) was searched for events of special interest.

Hypoglycaemic events

Hypoglycaemia was thoroughly monitored in all clinical trials. A hypoglycaemic event was considered 'confirmed' if the plasma glucose level was ≤70 mg/dL or when the patient required the assistance of another person, and the event was considered 'severe' when the patient required the assistance of another person. The analysis presented here is based on confirmed hypoglycaemic adverse events.

The analysis showed that treatment with empagliflozin did not lead to an increase of hypoglycaemic events in most trials. For trials in patients with metformin and sulphonylurea background medication, the frequencies of confirmed hypoglycaemic events were higher in the empagliflozin groups than in the placebo groups.

Table 14 Frequency of patients with confirmed hypoglycaemic adverse events - TS

Background antidiabetic medication	Trial no.	Placebo / N (%)	Empa 10 mg / N (%)	Empa 25 mg / N (%)
None	1245.20	1 / 229 (0.4)	1 / 224 (0.4)	1 / 223 (0.4)
	1245.31[1] *(mono)*	/ 229 (0.9)	/ 224 (0.9)	/ 223 (0.9)
Metformin	1245.23*(met)*	1 / 206 (0.5)	4 / 217 (1.8)	3 / 214 (1.4)
	1245.31[1] *(met)*	/ 206 (1.5)	/ 217 (2.8)	/ 214 (1.9)
	1245.28[2]*(52 weeks)*	A	A	2 / 765 (1.6)
Metformin + SU	1245.23 *(met+SU)*	19 / 225 (8.4)	36 / 224 (16.1)	25 / 217 (11.5)
	1245.31[1] *(met+SU)*	7 / 225 (12.0)	5 / 224 (20.1)	3 / 217 (15.2)
Pioglitazone ± metformin	1245.19	3 / 165 (1.8)	2 / 165 (1.2)	4 / 168 (2.4)
	1245.31[1]*(pio±met)*	/ 165 (2.4)	/ 165 (1.8)	/ 168 (3.0)
Basal insulin ± metformin ± SU	1245.33 *(18 weeks)*	35 / 170 (20.6)	33 / 169 (19.5)	44 / 155 (28.4)
	1245.33 *(78 weeks)*	60 / 170 (35.3)	61 / 169 (36.1)	56 / 155 (36.1)
Any	1245.48	3 / 272 (4.8)	8 / 276 (6.5)	7 / 276 (6.2)
	1245.36	8 / 319 (27.6)	6 / 98 (26.5)	8 / 321 (27.4)

Severe hypoglycaemic adverse events (assistance of another person required) were very infrequent. In the pivotal trials and in trial 1245.48, severe events were not reported at all. In trial 1245.28 (background medication: metformin), 1 case (0.1%) was reported in the glimepiride group. In trial 1245.33 (background medication: basal insulin ± metformin ± sulphonylurea), 2 cases (1.3%) were reported in the empagliflozin 25 mg group. In trials 1245.36 (renal impairment; any background medication) and (1245.36: placebo: 1.9%, empagliflozin 10 mg: 1.0%, empagliflozin 25 mg: 1.6%).

Cardiovascular events

To investigate the cardiovascular safety of empagliflozin treatment, a pre-specified meta-analysis was performed. The primary endpoint of this analysis was the composite 4-point MACE (major adverse cardiovascular events) endpoint, which consisted of cardiovascular death (including fatal stroke and fatal myocardial infarction), non-fatal myocardial infarction, non-fatal stroke, and hospitalisation due to unstable angina. All events were centrally adjudicated by an independent adjudication committee that was blinded to the treatment allocation of patients.

The meta-analysis of the pooled placebo-controlled Phase III trials with a treatment duration > 12 weeks (1245.19, 1245.20, 1245.23 (met), 1245.23 (met+SU), 1245.31, 1245.33, 1245.36, excluding 1245.25 [CVOT] and 1245.28 [H2H vs glimepiride]) included 1314 patients on placebo and 2395 patients on all empagliflozin (1098 patients on empagliflozin 10 mg, and 1297 patients on empagliflozin 25 mg). For the primary endpoint based on the treated set, the incidence was 1.98% for the placebo group (26 patients with event) and 0.92% in the all empagliflozin group (22 patients with event), with an incidence rate of 22.2 events (placebo) vs 9.8 events (all empagliflozin) per 1000 years at risk. The hazard ratio (HR) [95% CI] based on Cox regression of all empagliflozin vs placebo was 0.48 [0.27, 0.85].

Urinary tract infection

Urinary tract infections were identified as possible risks in the phase III protocols and respective patient information leaflets, but infections did not have to be specifically monitored or followed up on the case report form.

Across all trials and SAFs, the frequencies of urinary tract infection (BIcMQ) were similar for all treatment groups, as were the exposure-adjusted incidence rates. For the pooling of all patients (SAF 5), the overall frequency of urinary tract infection was 8.1% for the placebo group (incidence rate per 100 patient years: 10.9), 8.9% (10.5) for the empagliflozin 10 mg group, 8.8% (9.6) for the empagliflozin 25 mg group, and 8.1% (9.6) for the 'all comparators' group.

Very few patients reported events of severe intensity (≤0.3% per group in SAF-5) or events requiring or prolonging hospitalisation (≤0.4% per group). Cases of acute pyelonephritis, urosepsis, and sepsis with a possible urinary tract source of sepsis (and not previously reported as PT urosepsis) were very rare, with similar frequencies across treatment groups.

As would be expected, the proportion of patients who had urinary tract infection was higher in patients with a history of chronic or recurrent urinary tract infections at baseline, than in patients without such a history (patients with history: 'all empa': 26.9%, 'all comparators': 24.2%; patients without history: 'all empa': 7.8%, 'all comparators': 7.7%).

The time of onset of UTI in the empagliflozin groups is shorter than in the placebo group during the first 80 days, most likely due to symptomatic UTIs.

The Applicant has included urinary tract infections as an important identified risk in the RMP. As a proactive step to ensure patient safety, the Applicant proposes a PASS to evaluate the risk of UTI in empagliflozin-treated patients.

Genital infection

Genital infections had been mentioned as possible risks in the phase III protocols and respective patient information leaflets, but infections did not have to be specifically monitored or followed up on the case report form. Across all trials and SAFs, the frequencies of genital infection (BIcMQ) were consistently higher in the empagliflozin groups than in the comparator groups (SAF-5: placebo: 1.0%; empagliflozin 10 mg: 4.4%; empagliflozin 25 mg: 4.7%, 'all comparators': 1.1%), for both absolute frequencies and exposure-adjusted incidence rates.

The proportion of patients who had genital infection was approximately 2-fold higher for women than for men, irrespective of the treatment group. In both genders, patients in the empagliflozin groups had a 4-fold higher rate of genital infections than patients in the comparator groups (women: 'all empa': 6.9%, 'all comparators': 1.7%; men: 'all empa': 3.3%, 'all comparators': 0.7%).

The Applicant has included genital infections as an important identified risk in the updated RMP. As a proactive step to ensure patient safety, the Applicant proposes a PASS to evaluate the risk of genital infection in empagliflozin-treated patients.

Volume depletion

There was no special exclusion criterion for patients at risk for volume depletion in the trial protocols. The risk for blood pressure lowering and fluid loss had been mentioned in phase III protocols and the patient information leaflets, but there was no special reporting or follow-up required for adverse events possibly caused by volume depletion.

Across all trials, the frequencies of volume depletion were very low and similar for all treatment groups (SAF-5: placebo: 1.4%; empagliflozin 10 mg: 1.4%; empagliflozin 25 mg: 1.5%, 'all comparators': 1.2%), for both absolute frequencies and exposure-adjusted incidence rates per 100 patient years. In SAF-5 (all patients), the most common adverse events were hypotension ('all empa': 0.6%; 'all comparator': 0.7%) and syncope ('all empa': 0.5%; 'all comparator': 0.3%).

For patients taking any types of diuretics at baseline, the frequency for volume depletion was about twice as high as for those not taking diuretics at baseline. In patients using diuretics, frequency for volume depletion was slightly higher for patients using empagliflozin compared to comparators (SAF-5: patients with diuretics use at baseline: placebo: 2.2%, empagliflozin 10 mg: 2.5%, empagliflozin 25 mg: 2.7%; 'all comparators': 2.2%; patients without diuretics use at baseline: placebo: 1.0%; empagliflozin 10 mg: 0.9%, empagliflozin 25 mg: 0.9%; 'all comparators': 2.1%). The same was true for patients taking loop diuretics at baseline (SAF-5: patients with loop diuretics use at baseline: placebo: 2.9%, empagliflozin 10 mg: 4.9%, empagliflozin 25 mg: 3.0%; 'all comparators': 2.8%; patients without loop diuretics use at baseline placebo: 1.2%, empagliflozin 10 mg: 1.2%, empagliflozin 25 mg: 1.3%, 'all comparators': 1.1%).

The frequency of volume depletion increased with age and renal impairment. For most age and renal impairment categories, the frequencies were comparable in the empagliflozin and the comparator groups. The frequency of volume depletion was higher in the empagliflozin groups for the age category 75 years and older (SAF 5: placebo: 5 patients, 2.1%; empagliflozin 10 mg: 5 patients; 2.3%; empagliflozin 25 mg: 12 patients; 4.4%).

Decreased renal function

Decreased renal function was a pre-specified event in the phase III trial protocols. The frequencies of decreased renal function (SMQ) were very low for all SAFs. In SAF-5 (all patients), the frequency was 1.0% in the placebo group, 1.1% in the 10 mg empagliflozin group, 1.3% in

the 25 mg empagliflozin group, and 0.9% in the 'all comparators' group. The most common adverse event was renal impairment, reported with higher frequency in the empagliflozin groups (placebo: 0.5%, empagliflozin 10 mg: 0.7%, empagliflozin 25 mg: 0.7%; 'all comparators': 0.4%).

A similar percentage of patients in all groups were reported with serum creatinine ≥2x baseline and above the ULN. There was no clinically meaningful change from baseline in mean eGFR values in any treatment group. Empagliflozin groups showed a small initial decrease in eGFR, but the levels gradually increased over time. In trials with a longer follow up period after the last dose of trial medication, eGFR returned to baseline levels within 2 to 3 weeks after discontinuation of empagliflozin.

Hepatic injury

Hepatic injury was a pre-specified event in the phase III trial protocols. There was no evidence of an increased risk of hepatic injuries for patients treated with empagliflozin; the frequencies of hepatic injury (SMQ) were very low and similar for all treatment groups, for both absolute frequencies and exposure-adjusted incidence rates. In SAF-5 (all patients), the frequency was 1.5% in the placebo group, 1.2% in the 10 mg empagliflozin group, 1.4% in the 25 mg empagliflozin group, and 1.9% in the 'all comparators' group. The most common adverse events were hepatic steatosis, increased ALT, and increased AST. Hyperbilirubinaemia was reported with higher frequency in the empagliflozin 25 mg group (empagliflozin 10 mg: <0.1%; empagliflozin 25 mg: 0.2%; 'all comparators': 0%); all other events were generally balanced across the groups

Assessments for drug-induced liver injuries (DILI) were made according to the FDA guideline on the evaluation of DILI. A total of 7 patients had laboratory values consistent with a biochemical Hy's law laboratory constellation (ALT or AST ≥3x ULN with concomitant or subsequent total bilirubin ≥2x ULN within 30 days and with the maximum alkaline phosphatase value in the 30-day period <2x ULN): 2 patients in the empagliflozin 10 mg group, 3 patients in the empagliflozin 25 mg group, 1 patient post-treatment in the empagliflozin 25 mg group, and 1 patient during the screening period. These cases did, however, not qualify for drug-induced liver injury (according to Hy's law) because plausible alternative aetiologies for hepatic dysfunction were present in the patients' medical history, concomitant diagnoses, or concomitant therapy (for instance hepatitis, pancreatic cancer, or liver cirrhosis).

A total of 4 patients had elevated ALT or AST levels (≥3x ULN) with a concomitant or subsequent increase in total bilirubin ≥2x ULN within 30 days, but with the maximum alkaline phosphatase value in the 30-day period >2x ULN: 1 patient in the empagliflozin 10 mg group, 2 patients in the empagliflozin 25 mg group, and 1 patient in the glimepiride group. Plausible alternative aetiologies were present in the patients' medical history, concomitant diagnoses, or concomitant therapy.

Additionally, a total of 7 patients had ALT or AST values ≥10x ULN not associated with elevated bilirubin levels: 4 patients in the empagliflozin 25 mg group, 1 patient post-treatment in the empagliflozin 100 mg group, 1 patient post-treatment in the placebo group, and 1 patient during

the screening period. Again, plausible alternative aetiologies were present in the patients' medical history, concomitant diagnoses, or concomitant therapy.

During the registration process, it became clear that the number of patients with serious hepatic adverse events is remarkably higher in the empagliflozin groups compared to placebo and comparators. 22 patients are reported with serious liver enzyme elevation (ALT/AST >=3x ULN with total bilirubin >=2x ULN or ALT/AST >=10x ULN) during or after treatment. Of these 22 patients 19 were reported during or after treatment with empagliflozin, whereas no cases were reported during treatment with placebo and only 2 cases were reported after treatment with placebo. One case was reported during treatment with glimepiride. In all but one of these cases the independent committee of hepatic experts judged that the causal relationship with the treatment was not probable. The occurrence of serious liver enzyme elevations was low and there were no imbalances unfavourable for empagliflozin in less severe signs of liver impairment (ALT and/or AST ≥3x ULN or total bilirubin ≥2x ULN). There was, however, a slight imbalance for elevations of ALT and/or AST ≥ 5x ULN (0.1% for placebo and 0.2% for both empa 10 and 25 mg). A higher frequency was seen for ALT and/or AST ≥ 10x ULN and ≥ 20x ULN.

The frequency of patients with elevated liver enzymes during the treatment period was not importantly influenced by history of liver or pancreatic disease at baseline or not. This means that the risk of liver injury cannot be diminished by limiting the use of empagliflozin to individuals without a history of liver or pancreatic disease.

Bone fracture

Bone fractures reported as adverse events

Bone fracture (BIcMQ) was evaluated because of regulatory concerns with another drug of the same class (a numerical imbalance for bone fractures in patients with renal impairment). The search included 59 PTs of fractures. In SAF-5 (all patients), the frequency was 1.6% in the placebo group, 1.6% in the 10 mg empagliflozin group, 1.1% in the 25 mg empagliflozin group, and 1.5% in the 'all comparators' group. Calcium, phosphate, and alkaline phosphatase were assessed in all trials; 25-OH-vitamin D, intact parathyroid hormone, and urine N-terminal telopeptide (NTx) were assessed only in trials 1245.20, 1245.28, 1245.33, and 1245.38. No clinically meaningful changes in the median values were observed for vitamin D, intact parathyroid hormone, calcium, phosphate, and alkaline phosphatase. Urine NTx to creatinine ratio increased slightly in the empagliflozin groups, whereas it decreased slightly in the comparator groups. In trial 1245.28, for a small subgroup of patients (48 patients in the 25 mg empagliflozin group and 38 patients in the glimepiride group), bone mineral density was assessed based on T-scores of femoral neck or lumbar spine. No clinically meaningful change was observed in either the empagliflozin 25 mg or the glimepiride group after 52 weeks of treatment.

Malignancy

Events were analysed including either all malignancies (independent of onset date), or only events with an onset later than 6 months of exposure. For both analyses, the frequencies of malignancy were very low and similar for all treatment groups, for both absolute frequencies and exposure-adjusted incidence rates. In SAF-5 (all patients), some imbalances between treatment

groups occurred on PT level, but the frequency of patients with malignancies (onset later than 6 months) was 0.5% in the placebo group, 0.6% in the 10 mg empagliflozin group, 0.5% in the 25 mg empagliflozin group, and 0.5% in the 'all comparator' group.

The Applicant was requested to discuss all the observed cases for malignant melanoma, renal cancer and bladder cancer in more detail. Based on the answers it is concluded that a urinary tract carcinogenic risk cannot be ruled out and thus should be further monitored and studied in view of the observation in male mice in the pre-clinical studies (i.e. it cannot be excluded that the 4-OH CTA metabolite is absent in humans as it hasn't been quantified directly). Therefore, urinary tract malignancies monitoring through routine PhVig activities for an important potential risk in the RMP is considered appropriate. For malignant melanoma the imbalance in the number of cases remains a concern. However, in the absence of a mechanistic rationale and non-clinical findings for malignant melanoma, routine PhVig activities in the RMP is considered appropriate because currently there is a lack of long term data.

Laboratory findings

For most safety laboratory parameters, the analyses showed no clear trends that were considered clinically meaningful. Across most trials and poolings, small increases in lipid parameters were seen in all treatment groups. The increase was more pronounced for the empagliflozin groups than for the placebo and comparator groups for total cholesterol, HDL cholesterol, and LDL cholesterol. The placebo-corrected mean change from baseline after 24 weeks of treatment was between 0.06 mmol/L and 0.09 mmol/L for both LDL and HDL cholesterol (SAF-3, pivotal trials with extensions). For the LDL/HDL ratio and for triglycerides, no clinically meaningful differences were found between treatment groups.

In line with the efficacy analysis, the safety analysis of the change in diastolic and systolic blood pressure from baseline to last value on treatment showed decreases in the empagliflozin group and no change in the placebo and the comparator groups, across all SAFs and trials. The median pulse rate at the end of treatment showed no change from baseline for all treatment groups across all SAFs and trials.

Safety in special populations

Age

Only subjects at least 18 years of age were enrolled in all clinical trials. Although there had not been an age restriction for elderly patients, only 29 patients older than 85 years were treated in clinical trials. Therefore this age category was included in the ≥75 years category for subgroup analyses. The following age subgroups were assessed for SAF-5 (all patients): 2055 patients <50 years, 6857 patients from 50 to <65 years, 3404 patients from 65 to <75 years, and 760 patients 75 years or older.

Generally, the frequency of adverse events (all types) increased with age. For most types of adverse events, the frequencies were comparable in the empagliflozin and the comparators groups, for each age category. Exceptions were as follows. The frequency of genital infections (BIcMQ) was higher in the empagliflozin groups for all age categories. The frequency of urinary

tract infection (BIcMQ) was higher in the empagliflozin groups for the age categories 65 to <75 years (SAF-5: placebo: 73 patients, 7.5%; empagliflozin 10 mg: 87 patients, 8.9%; empagliflozin 25 mg: 130 patients, 10.7%) and for the age group 75 years and older (SAF-5: placebo: 25 patients, 10.5%; empagliflozin 10 mg: 34 patients; 15.7%; empagliflozin 25 mg: 41 patients; 15.1%). The frequency of volume depletion was higher in the empagliflozin 25 mg group for the age categories 75 years and older (SAF 5: placebo: 5 patients, 2.1%; empagliflozin 10 mg: 5 patients; 2.3%; empagliflozin 25 mg: 12 patients; 4.4%). The frequency of decreased renal function was slightly higher in the empagliflozin 25 mg group for the age categories 75 years and older. The frequency of serious adverse events was lower in the empagliflozin groups for the age categories 65 years and older.

A post-hoc analysis was conducted to investigate whether the observed imbalances in adverse event frequencies for volume depletion and urinary tract infection in patients ≥75 years of age were associated with decreased renal function. The analysis was performed in the largest pooling (SAF-5, all patients). The higher frequency of volume depletion in the empagliflozin groups compared with the placebo group was still observed in all subcategories, independent of renal function category. The frequency of urinary tract infections in patients ≥75 years and treated with empagliflozin seems to be at least partially associated with declining renal function: in patients with baseline eGFR ≥45 or ≥60 mL/min/1.73 m2, the frequency of urinary tract infections tended to be comparable between the empagliflozin and the placebo groups, whereas in the matching lower eGFR categories, frequencies were increased in the empagliflozin groups compared with the placebo group.

Gender, BMI, race ethnicity and region

There were no important effects of gender, BMI, race ethnicity and region on the adverse events with empagliflozin.

Renal impairment

The frequency of patients with any adverse events, serious adverse events, and adverse events leading to discontinuation of trial medication increased with the degree of renal impairment. However, the frequencies were similar between the empagliflozin and comparator treatment groups of each renal impairment category. For decreased renal function (SMQ) genital infection and urinary tract infection (BIcMQ), frequencies increased with the degree of renal impairment, and were higher in empagliflozin treatment groups than in comparator groups in the categories of patients with moderate renal impairment.

The estimated GFR and the urine-albumin-to-creatinine ratio were analysed by renal impairment subgroups. The mean eGFR change from baseline to last value on treatment was small and similar for all treatment groups among patients with eGFR ≥60 mL/min/1.73 m2. For patients with moderate or severe renal impairment, the mean and median eGFR decreased in the empagliflozin groups, while it increased in the comparator groups. The decrease of eGFR after empagliflozin treatment was also observed in the dedicated renal impairment trial (1245.36); however, 3 weeks after the end of treatment, eGFR returned to baseline levels in patients with mild, moderate, or severe renal impairment. This is similar to other SGLT2 inhibitors.

Patients with HbA1c above 10% treated with open-label empagliflozin

In the open-label empagliflozin 25 mg group, 63.0% of patients reported at least 1 adverse event (double-blind 25 mg empagliflozin in SAF-2: 59.7%), 3.5% reported serious adverse events (double-blind 25 mg empagliflozin in SAF-2: 2.6%), 3.5% adverse events leading to discontinuation of trial medication (double-blind 25 mg empagliflozin in SAF-2: 2.3%), 1.9% events of severe intensity (double-blind 25 mg empagliflozin in SAF-2: 3.0%), and 16% investigator-defined drug-related adverse events (double-blind 25 mg empagliflozin in SAF-2: 16.0%). No death was reported in the open-label empagliflozin 25 mg group.

The frequencies of patients with adverse events of special interest were generally very low in the open-label empagliflozin 25 mg group. Nine patients (3.5%) had confirmed hypoglycaemic events (plasma glucose value of ≤70 mg/dL or where assistance was required). The frequency of urinary tract infections (BIcMQ) was 4.3%. Four patients (1.6%) were reported with genital infections (BIcMQ). Two patients were reported with volume depletion (BIcMQ) and 3 patients with bone fractures (BIcMQ). Two patients were reported with decreased renal function (SMQ), and 2 with hepatic injury (SMQ). One patient was reported with ALT or AST ≥5x ULN.

2.6.1. Discussion on clinical safety

Trial data were pooled to adequately analyse the different aspects of the safety profile of empagliflozin. The most relevant safety pooling for the benefit-risk assessment of empagliflozin is SAF-3 as this pooling corresponds to the pivotal trials with extensions (2957 patients in total). However, rare events and subgroups were assessed based on the largest available pooling, which included all 12873 patients with type 2 diabetes mellitus treated in trials with empagliflozin (SAF-5). The overall exposure to empagliflozin (10 or 25 mg) was 1546 patient years (median treatment duration 369 days) in SAF-3 and 7828 patient years (median treatment duration 364 days) in SAF-5.

The frequencies of premature discontinuation of trial medication were higher in the placebo group than in the empagliflozin groups (SAF-3: placebo: 17.1%; empagliflozin 10 mg: 10.8%; empagliflozin 25 mg: 12.8%). The overall frequency of treatment-emergent adverse events was comparable between treatment groups (SAF-3: placebo: 74.1%; empagliflozin 10 mg: 71.8%; empagliflozin 25 mg: 70.1%). Investigator-assessed drug-related events were more frequent in the empagliflozin treatment groups than in the placebo group, whereas adverse events of severe intensity were more frequent in the placebo group. The frequencies of patients with serious adverse events (including fatal events) in the empagliflozin groups were lower than in the placebo group in the pivotal trials with extensions (SAF-3: placebo: 7.4%; empagliflozin 10 mg: 7.1%; empagliflozin 25 mg: 5.8%).

The most frequent events were nasopharyngitis (with similar frequencies for all groups), urinary tract infection (with similar frequencies for all groups), hyperglycaemia (with higher frequencies in the comparator groups than in the empagliflozin groups), and hypoglycaemia (with higher frequencies in the empagliflozin groups than in the comparator groups).

Hypoglycaemia

As could be expected, there was more hyperglycaemia and less hypoglycaemia with placebo compared to empagliflozin. There was an increase in the number of hypoglycaemic episodes with

empagliflozin in combination with MET+SU. In patients using other oral antihyperglycaemic drugs or insulin as background therapy, empagliflozin was not associated with an increased risk of hypoglycaemia.

Cardiovascular risk

There were small increases in LDL cholesterol with empagliflozin. However, HDL levels were also somewhat increased. In the cardiovascular pooled analyses, empagliflozin is compared to placebo. Although the follow-up is short and the numbers are small, this comparison tends to be in favour of empagliflozin. The incidence rate was also lower for the all empagliflozin group compared to the placebo group.

Urinary tract infections and genital infections

Urinary tract infections and genital infections were classified as adverse events of special interest. In accordance, these infections were identified as possible risks in the phase III protocols and respective patient information leaflets. However, infections did not have to be specifically monitored or followed up on the case report form. As these infections were not monitored specifically, the presented results may be unreliable. A wide list of PTs was analysed. Results show that there was an increased risk of genital infections. On average, there was no increased risk of urinary tract infections. However, in patients with a history of urinary tract infections, empagliflozin was associated with a higher risk of urinary tract infections (with history: 'all empa': 26.9%, 'all comparators': 24.2%; patients without history: 'all empa': 7.8%, 'all comparators': 7.7%).

Hepatic injuries

Although it was not expected that empagliflozin would be associated with hepatic injuries, it became clear during the registration process, that the number of patients with serious hepatic adverse events is remarkably higher in the empagliflozin groups compared to placebo and comparators. 22 patients are reported with serious liver enzyme elevation during or after treatment. Of these 22 patients 19 were reported during or after treatment with empagliflozin, whereas no cases were reported during treatment with placebo and only 2 cases were reported after treatment with placebo. One case was reported during treatment with glimepiride. In all but one of these cases the independent committee of hepatic experts judged that the causal relationship with the treatment was not probable. The occurrence of serious liver enzyme elevations was low and there were no imbalances unfavourable for empagliflozin in less severe signs of liver impairment.

The frequency of patients with elevated liver enzymes during the treatment period was not importantly influenced by history of liver or pancreatic disease at baseline or not. This means that the risk of liver injury cannot be diminished by limiting the use of empagliflozin to individuals without a history of liver or pancreatic disease.

Bone fractures

Bone fractures were of special interest, but not identified as a possible risk. The reported rates of bone fracture were very low and similar for all treatment groups. Changes in BMD were not found. However, treatment duration was too short (1 year) and the numbers of patients very small (48 treated with empagliflozin). In addition, urine NTx to creatinine ratio increased slightly in the empagliflozin groups, whereas it decreased slightly in the comparator groups. Harmful effects of empagliflozin cannot be excluded. In the PRAC-rapport the necessity for a PASS will be

discussed. In case of PASS, it is adviced to include bone fracture incidence in the PASS. For comparison, also with Dapagliflozin BMD measurements were asked in a subset of patients in the CV outcome study in order to obtain more data on bone metabolism.

Malignancies

There was no clear pattern with respect to the occurrence of malignancies. With empagliflozin, there were more cases of bladder cancer compared to comparators (empagliflozin 2 cases, comparators 0 cases), but fewer cases of breast cancer (empagliflozin 1 case, comparators 2 cases). It is likely that these differences do not represent a causal association, but are due to numerical imbalances. The urinary tract carcinogenic risk cannot be ruled out and should be further monitored and studied in view of the finding in male mice in the preclinical studies and conclusive evidence that the involved 4-OH CTA metabolite is absent in humans. This can be done with additional PhVig activities in the RMP.

Kidney

There were no relevant changes in creatinine levels. Overall, frequencies of decreased renal function and volume depletion reported as adverse events were similar. In animals, renal calcifications were observed. The risk of kidney stones in humans is unknown. The Applicant should analyse the occurrence of kidney stones in the development programme.

Subgroups

There were no important effects of gender, BMI, race ethnicity and region on the adverse events with empagliflozin.

Exposure to empagliflozin increased with the degree of renal impairment. Patients with different degrees of renal impairment were analysed separately. The frequency of patients with any adverse events, serious adverse events, and adverse events leading to discontinuation of trial medication increased with the degree of renal impairment. Importantly, empagliflozin treatment was associated with a higher frequency of decreased renal function, genital infection and urinary tract infection in patients with moderate renal impairment. Therefore, empagliflozin cannot be recommended to patients with moderate renal impairment. In addition, in the subgroup of patients using diuretics, frequency for volume depletion was slightly higher for patients using empagliflozin compared to comparators (patients with diuretics use at baseline: placebo: 2.2%, empagliflozin 10 mg: 2.5%, empagliflozin 25 mg: 2.7%; 'all comparators': 2.2%). The same was true for patients taking loop diuretics at baseline (patients with loop diuretics use at baseline: placebo: 2.9%, empagliflozin 10 mg: 4.9%, empagliflozin 25 mg: 3.0%; 'all comparators': 2.8%). Therefore, caution should be exercised in patients on diuretics. This should be mentioned in the SmPC.

Different age groups were analysed separately. There was a higher frequency of urinary tract infections, volume depletion and decreased renal function in patients ≥75 years. In elderly patients, the frequency of urinary tract infection was higher in the empagliflozin groups especially for the age group 75 years and older (SAF-5: placebo: 25 patients, 10.5%; empagliflozin 10 mg: 34 patients; 15.7%; empagliflozin 25 mg: 41 patients; 15.1%). However, the higher frequency of urinary tract infection in patients >75 years with empagliflozin may be explained by declining renal function: in patients >75 years with baseline eGFR ≥45 or ≥60 mL/min/1.73 m2, the frequency of urinary tract infections tended to be comparable between the empagliflozin and the placebo groups, whereas in the matching lower eGFR categories, frequencies were increased in

the empagliflozin groups compared with the placebo group. These data suggest that renal function is a determinant of urinary tract infections in patients ≥75 years. The increased risk of volume depletion in patients ≥75 years with empagliflozin is an important issue (placebo: 5 patients, 2.1%; empagliflozin 10 mg: 5 patients; 2.3%; empagliflozin 25 mg: 12 patients; 4.4%). Subgroup analyses demonstrated that this higher frequency was independent of renal function category. The frequency of decreased renal function was slightly higher in the empagliflozin 25 mg group for the age categories 75 years and older (4 patients (1.7%) in the placebo group vs. 6 patients (2.2%) for empagliflozin 25 mg). Taken together, caution should be exercised in elderly patients. This is adequately reflected in the product information.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Although genital and urinary infections were not monitored specifically, the presented results show that there was an increased risk of genital infections with empagliflozin.

In patients with moderate renal impairment, empagliflozin treatment was associated with a higher frequency of decreased renal function, genital infection and urinary tract infection. Therefore, empagliflozin cannot be recommended in patients with moderate renal impairment.

There was a higher frequency of urinary tract infections, volume depletion and decreased renal function in patients ≥75 years. Subgroup analyses demonstrated that this higher frequency of volume depletion was independent of renal function category. Empagliflozin cannot be recommended in patients >75 years.

There was an increase in the number of hypoglycaemic episodes with empagliflozin in combination with MET+SU. This risk should be clearly mentioned in the SmPC.

Although it was not expected that empagliflozin would be associated with hepatic injuries, the number of patients with serious hepatic adverse events was remarkably higher in the empagliflozin groups compared to placebo and comparators. In all but one of these cases the independent committee of hepatic experts judged that the causal relationship with the treatment was not probable. The occurrence of serious liver enzyme elevations was low and there were no imbalances unfavourable for empagliflozin in less severe signs of liver impairment.

No effects on bone mineral density and bone fractures were found. However, treatment duration was too short and the numbers of patients very small. Harmful effects of empagliflozin cannot be excluded.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received a PRAC Advice on the submitted Risk Management Plan in which there were outstanding issues regarding the proposed safety specification, pharmacovigilance plan, as well as the proposed risk minimisation measures.

The CHMP endorsed this advice with changes.

These changes concerned the following elements of the Risk Management Plan:

In the safety specification, the suggested important potential risk of 'Malignancy (non-urinary tract) should be removed. Instead, in the section 'missing information' of the safety specification, it should be added that there is missing information regarding the long term risk of melanoma.

The CHMP justified these changes as follows:

The term 'malignancy, non-urinary tract' was based on the finding of 6 melanoma cases in the clinical trials and there was an imbalance in frequency between the exposure groups. One of the melanoma cases was pre-existing.

There is no known plausible mechanism of action as to why empagliflozin might increase the risk of melanoma; therefore this was considered a weak signal.

CHMP agreed with PRAC that it will be useful to monitor this outcome in the post-marketing phase, however, because of the weakness of the signal the risk needs to be downgraded to 'missing information' and because the signal only applied to melanoma and (apart from urinary tract malignancies) no other malignancies, using the term 'malignancies' was considered to be too broad. Instead, the description needs to be more specific to clarify the risk being managed is that of melanoma and does not include other cancers such as breast cancer.

The MAA has submitted an updated RMP, version 1.4 in which all outstanding issues from the PRAC Advice as well as the outcome of the CHMP discussion were incorporated. This RMP was considered acceptable. It contains the following Safety specification:

Summary of safety concerns

Important identified risks	Urinary tract infection
	Genital infection
	Volume depletion
	Hypoglycaemia (with insulin and/or sulphonylurea)
Important potential risks	Urinary tract carcinogenicity
	Renal impairment
	Liver injury
	Off-label use (e.g. for weight loss in non-T2DM patients)
	Bone fracture
Missing information	Paediatric patients
	Elderly patients
	Pregnancy/breast-feeding
	Clinical impact of dyslipidaemia
	Long-term safety (particularly cardiovascular)
	Concomitant use with GLP-1 analogues
	Use in patients with severe hepatic impairment
	Missing long-term safety information on melanoma

The CHMP agreed.

SUMMARY OF THE PHARMACOVIGILANCE PLAN

Table 18 Ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan

Study/activity[1]	Objectives	Safety concerns addressed	Status[2]	Date for submission of interim or final reports[3]
Long-term CV safety study 1245.25; category 3	To evaluate long-term CV safety of empagliflozin in patients with T2DM and increased CV risk	Long-term safety (particularly CV), dyslipidaemia, concomitant use of GLP-1 analogues, urinary tract carcinogenicity, bone fracture, missing long-term safety information on melanoma	Started	Event driven, final CTR, Q4 2015
PASS (1245.96) to assess the risk of renal and liver injury, urinary tract and genital infection; category 3	A PASS will evaluate the risk of urinary tract and genital infection, acute renal and hepatic injury, resulting in hospitalisations, in empagliflozin-treated patients, compared to users of other antidiabetic treatment.	Urinary tract infection, genital infection Renal impairment, liver injury	Planned	Will depend on patient uptake; estimates to be determined in the final protocol
PASS (1245.97) to assess the risk of urinary tract malignancies, preceded by feasibility assessment; category 3	To evaluate the risk of renal and bladder cancer in empagliflozin-treated patients, compared to users of other antidiabetic treatment.	Urinary tract carcinogenicity	Planned	Will be determined in the final protocol

[1] Type, title and category (1-3).
[2] Planned or started.
[3] Planned or actual.

The CHMP, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

PV.Table 18 Summary of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Urinary tract infection	Routine pharmacovigilance activities Appropriate labelling in SmPC sections 4.4 Special warnings and precautions for use, 4.8 Undesirable effects	None
Genital infection	Routine pharmacovigilance activities Appropriate labelling in SmPC section 4.8 Undesirable effects	None
Volume depletion	Routine pharmacovigilance activities Appropriate labelling in SmPC sections 4.4. Special warnings and precautions for use, 4.8 Undesirable effects	None
Hypoglycaemia (with insulin and/or SU)	Routine pharmacovigilance activities Appropriate labelling in SmPC sections 4.2 Posology and method of administration, 4.8 Undesirable effects	None
Important potential risks		
Urinary tract carcinogenicity	Routine pharmacovigilance activities	None
Renal impairment	Routine pharmacovigilance activities Appropriate labelling in SmPC sections 4.2 Posology and method of administration, 4.4. Special warnings and precautions for use	None
Liver injury	Routine pharmacovigilance activities Appropriate labelling in SmPCs section 4.2 Posology and method of administration, 4.4. Special warnings and precautions for use	None
Off-label use (e.g. for weight loss in non-T2DM patients)	Routine pharmacovigilance activities	None
Bone fracture	Routine pharmacovigilance activities	None

PV.Table 18 (cont'd) Summary of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information		
Paediatric patients	Routine pharmacovigilance activities Appropriate labelling in SmPC sections 4.2 Posology and methods of administration.	None
Elderly patients	Routine pharmacovigilance activities Appropriate labelling in SmPC sections 4.2 Posology and methods of administration, 4.4 Special warnings and precautions for use.	None
Pregnancy/breast-feeding	Routine pharmacovigilance activities Appropriate labelling in SmPC section 4.6 Pregnancy, fertility and lactation	None
Clinical impact of dyslipidaemia	Routine pharmacovigilance activities	None
Long-term safety (particularly cardiovascular)	Routine pharmacovigilance activities	None
Concomitant use with GLP-1 analogues	Routine pharmacovigilance activities	None
Use in patients with severe hepatic impairment	Routine pharmacovigilance activities Appropriate labelling in SmPC section 4.2 Posology and methods of administration, 4.4. Special warnings and precautions for use	None
Missing long-term safety information on melanoma	Routine pharmacovigilance activities	None

The CHMP, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Empagliflozin is an orally administered, selective inhibitor of the sodium-dependent glucose co-transporter-2 (SGLT-2) in the kidney. It is intended for use in patients with type 2 diabetes mellitus.

A total of 11250 randomised and treated patients are included in the evaluation of efficacy presented. Of these, 3021 patients were randomised to empagliflozin 10 mg and 3994 patients were randomised to empagliflozin 25 mg. Another 3081 patients were randomised to receive placebo and 1154 patients were randomised to an active comparator. At Day 120 an additional (add-on to insulin) study was submitted. Study 1245.49 enrolled 563 subjects of whom 186 received empagliflozin 10 mg and 189 empagliflozin 25 mg. The primary end point in most trials was a change in HbA1c.

Monotherapy (study 1245.20): After 24 weeks, compared to placebo, empagliflozin monotherapy was associated with a clinically relevant reduction in HbA1c of -0.74% (10 mg) and -0.85% (25 mg). These reductions were similar compared to the effect of sitagliptin 100 mg (-0.73%). A formal monotherapy study comparing empagliflozin to metformin has not been performed. However, dose finding study 1245.9 included empagliflozin and metformin, showing that the effect of metformin on HbA1c was somewhat larger (-0.85%) compared to empagliflozin 25 mg (-0.72%).

Add-on to other oral glucose-lowering drugs (study 1245.31 and study 1245.19): Compared to placebo, empagliflozin as add on to metformin was associated with a clinically relevant reduction in HbA1c of -0.57% (10 mg) and -0.64% (25 mg). In addition, compared to placebo, empagliflozin as add on to metformin plus SU was also associated with a clinically relevant reduction in HbA1c of -0.64% (10 mg) and -0.59% (25 mg). Compared to placebo, empagliflozin as add on to pioglitazone (with and without metformin) was associated with a clinically relevant reduction in HbA1c of -0.48% (10 mg) and -0.61% (25 mg).

Add-on to basal insulin (study 1245.33): Compared to placebo without changes in insulin dose, empagliflozin as add on to insulin was associated with a clinically relevant reduction in HbA1c of -0.56% (10 mg) and -0.70% (25 mg) at 18 weeks. After these 18 weeks, insulin dose adjustments were allowed. The adjusted mean differences from placebo in insulin dose at Week 78 were -6.66 IU in the empagliflozin 10 mg group and -5.92 IU in the empagliflozin 25 mg group. Compared to placebo after 78 weeks, empagliflozin as add on to insulin was associated with a clinically relevant reduction in HbA1c of -0.46% (10 mg) and -0.62% (25 mg). It should be noted that these changes in insulin dose were small and of doubtful clinical relevance.

Add-on to multiple daily injection insulin therapy (Study 1245.49): After 18 weeks, change in HbA1c was -0.44 for 10 mg empagliflozin and -0.52 for 25 mg empagliflozin, compared to placebo. After 52 weeks, the adjusted mean changes in insulin dose from baseline compared with placebo were -8.83 IU/day for empagliflozin 10 mg and -11.22 IU/day for empagliflozin 25 mg. The placebo-adjusted mean changes in HbA1c values at 52 weeks were -0.38% for 10 mg and -0.46% for 25 mg.

Patients with hypertension (study 1245.48): In this study, various antidiabetic drugs were used as background medication. Compared to placebo, there was a relevant decrease in HbA1c (-0.62% and -0.65% for empagliflozin 10 and 25 mg, respectively).

Effects on body weight: In the pivotal trials, empagliflozin was associated with a decrease in body weight. For the pooled data of the pivotal trials, the treatment difference to placebo at 24 weeks was 1.8 kg for the empagliflozin 10 mg group and 2.0 kg for the empagliflozin 25 mg group. In the active controlled trial with glimepiride, treatment with glimepiride led to a 1.6 kg increase in mean body weight after 52 weeks, whereas mean body weight decreased by 3.2 kg in the empagliflozin 25 mg group. The resulting adjusted mean difference between treatment groups was 4.8 kg. Body weight was an exploratory endpoint in the other trials. In each trial, empagliflozin provided reductions in body weight compared with placebo. The results were in a similar range as for the pivotal trials.

Effects on blood pressure: In the pivotal studies, in comparison to placebo, empagliflozin was associated with a lower systolic (-2.1 to -4.9 mmHg) and diastolic blood pressure systolic (-0.5 to -2.5 mmHg). In the active controlled trial with glimepiride, after 52 weeks, the adjusted mean difference in to glimepiride was -5.8 mmHg for SBP and -2.8 mmHg for DBP. In the study in patients with hypertension (study 1245.48), blood pressure was also lower with empagliflozin.

Uncertainty in the knowledge about the beneficial effects

In the dose findings studies study (1245.9, study 1245.10), the 25 mg dose of empagliflozin provided better efficacy than the 10 mg dose. In each of the pivotal phase III trials, except for 1245.23 (met+SU), the reduction in HbA1c from baseline at 24 weeks was greater for empagliflozin 25 mg than for empagliflozin 10 mg. The pooled data of the pivotal trials showed that the adjusted mean change from baseline in HbA1c after 24 weeks of treatment was -0.70% for empagliflozin 10 mg and 0.76% for empagliflozin 25 mg. It could be useful to start treatment with this lower dose and then increase the dose if necessary. Therefore it was questioned why the Applicant abandoned the 10 mg dose. The Applicant decided to re-introduce the 10 mg dose as a starting dose. In the submitted pharmacology studies, only in one study (Trial 1245.79) a 10 mg formulation is administered as a single dose to healthy volunteers under fasting conditions. In this study bioequivalence is proven.

The company requests an indication for empagliflozin monotherapy in patients for whom metformin is considered inappropriate. This can be due to intolerance (gastrointestinal complaints) or contraindications. Patients with gastrointestinal complaints with metformin were not specifically investigated. However, it is not likely that gastrointestinal complaints due to metformin influence the efficacy of empagliflozin. The most important contraindications for metformin include renal impairment (GFR<60 ml/min) and heart failure. With respect to heart failure, there is no experience in clinical studies with empagliflozin in NYHA class III-IV. Patients with renal insufficiency were investigated in a specific trial *(study 1245.36).* Patients with moderate renal impairment were subdivided in patients with GFR 45-60 and 30-45 ml/min. The adjusted mean treatment differences for empagliflozin 25 mg compared with placebo were -0.46 and -0.39%, respectively. In the pivotal studies, the effect of empagliflozin on HbA1c in individuals with GFR 45-60 ml/min was of borderline significance (-0.33% for empagliflozin 25 mg, n=50 and -0.48% for empagliflozin 10 mg, n=51). Thus, similar to other SGLT-2 inhibitors, treatment effects diminish with decreasing renal function.

Subgroup analyses of the pivotal trials demonstrate that the treatment effect of empagliflozin on HbA1C in patients older than 75 years is only -0.21 and -0.33%. However, in the subgroup of elderly patients >75 years and renal function 45-60 ml/min efficacy in terms of HbA1C was not acceptable (-0.37%).

The effects of empagliflozin were compared to SU in a non-inferiority study. The decrease in HbA1c was numerically greater with empagliflozin compared to glimepiride (-0.73% vs. -0.66%). Only 60% of the patients in the glimepiride group were taking less than the maximum allowed dose of 4 mg, whereas all patient in the empagliflozin group were treated with the maximum dose of 25 mg. However, this is also observed in clinical practice. It may be difficult to uptitrate glimepiride due to higher risk of hypoglycaemia. Efficacy of empagliflozin was numerically larger than that of glimepiride and statistical non-inferiority was established. Therefore, a formal non-inferiority claim is acceptable. There were small increases in LDL cholesterol with empagliflozin, similar as what has been seen with other SGLT-2 inhibitors. However, HDL levels were also somewhat increased. More data will be obtained when the data from the CV outcome study are obtained. These data should be provided in due time.

In several studies, mean daily glucose, body composition and meal tolerance tests were performed in subgroups. These data are of interest, but it is not known whether or not the effects are of clinical relevance.

Risks

Unfavourable effects

Trial data were pooled to adequately analyse the different aspects of the safety profile of empagliflozin. The most relevant safety pooling for the benefit-risk assessment of empagliflozin is SAF-3 as this pooling corresponds to the pivotal trials with extensions (2957 patients in total). However, rare events and subgroups were assessed based on the largest available pooling, which included all 12873 patients with type 2 diabetes mellitus treated in trials with empagliflozin (SAF-5). The overall exposure to empagliflozin (10 or 25 mg) was 1546 patient years (median treatment duration 369 days) in SAF-3 and 7828 patient years (median treatment duration 364 days) in SAF-5.

The frequencies of premature discontinuation of trial medication were higher in the placebo group than in the empagliflozin groups (SAF-3: placebo: 17.1%; empagliflozin 10 mg: 10.8%; empagliflozin 25 mg: 12.8%). The overall frequency of treatment-emergent adverse events was comparable between treatment groups (SAF-3: placebo: 74.1%; empagliflozin 10 mg: 71.8%; empagliflozin 25 mg: 70.1%). Investigator-assessed drug-related events were more frequent in the empagliflozin treatment groups than in the placebo group, whereas adverse events of severe intensity were more frequent in the placebo group. The frequencies of patients with serious adverse events (including fatal events) in the empagliflozin groups were lower than in the placebo group in the pivotal trials with extensions (SAF-3: placebo: 7.4%; empagliflozin 10 mg: 7.1%; empagliflozin 25 mg: 5.8%). The most frequent events were nasopharyngitis (with similar frequencies for all groups), urinary tract infection (with similar frequencies for all groups), hyperglycaemia (with higher frequencies in the comparator groups than in the empagliflozin groups), and hypoglycaemia (with higher frequencies in the empagliflozin groups than in the comparator groups.

As could be expected, there was more hyperglycaemia and less hypoglycaemia with placebo compared to empagliflozin. There was an increase in the number of hypoglycaemic episodes with empagliflozin in combination with MET+SU. In patients using other oral antihyperglycaemic drugs or insulin as background therapy, empagliflozin was not associated with an increased risk of hypoglycaemia.

There were no relevant changes in creatinine levels. Overall, frequencies of decreased renal function and volume depletion reported as adverse events were similar.

There were no important effects of gender, BMI, race ethnicity and region on the adverse events with empagliflozin.

Urinary tract infections and genital infections were classified as adverse events of special interest due to its mechanism of action. In accordance, these infections were identified as possible risks in the phase III protocols and respective patient information leaflets. However, infections did not have to be specifically monitored or followed up on the case report form. Therefore, the presented results may be unreliable. A wide list of PTs was analysed. Results show that there was an increased risk of genital infections. The Applicant has included genital infections as an important identified risk in the updated RMP. As a proactive step to ensure patient safety, the Applicant proposes a PASS to evaluate the risk of genital infection in empagliflozin-treated patients. On average, there was no increased risk of urinary tract infections. However, in patients with a history of urinary tract infections, empagliflozin was associated with a higher risk of urinary tract infections (with history: 'all empa': 26.9%, 'all comparators': 24.2%; patients without history: 'all empa': 7.8%, 'all comparators': 7.7%). The time of onset of UTI in the empagliflozin groups is shorter than in the placebo group during the first 80 days, most likely due to symptomatic UTIs. The Applicant has included urinary tract infections as an important identified risk in the RMP. As a proactive step to ensure patient safety, the Applicant proposes a PASS to evaluate the risk of urinary tract infection in empagliflozin-treated patients.

As empagliflozin is metabolised by Cytochrome P450 enzymes to a very limited extent but instead mainly by glucuronidation, P450-mediated pharmacokinetic interactions with other medicinal products are not expected and known and intrinsic factors like age, gender and race do not affect the pharmacokinetics of empagliflozin. Thus the product can be safely used from a pharmacokinetic point of view.

Uncertainty in the knowledge about the unfavourable effects

Pharmacology related renal stress as evident from the data provided by the Applicant is not species specific and could be relevant for humans as well. It is therefore important that renal function, especially where related to renal tubular integrity, is followed up in the RMP.

In the mouse carcinogenicity study, renal tumours were observed. The mechanism behind these tumours was clarified and a satisfactory response to the List of Outstanding Issues was received. The formation of the cytotoxic male mouse renal metabolite 4-OH-CTA is a key event in the proposed mechanism. Yet any potential formation of this metabolite in humans has not been excluded. There was no clear pattern with respect to the occurrence of malignancies. With empagliflozin, there were more cases of bladder cancer compared to comparators (empagliflozin 2 cases, comparators 0 cases), but fewer cases of breast cancer (empagliflozin 1 case, comparators 2 cases). It is likely that these differences do not represent a causal association, but

are due to numerical imbalances. Nevertheless, long term effects of empagliflozin on the risk of malignancies cannot be excluded. The Applicant was requested to discuss all the observed cases for malignant melanoma, renal cancer and bladder cancer in more detail. The urinary tract carcinogenic risk cannot be ruled out and should be further monitored and studied in view of the finding in male mice in the preclinical studies and conclusive evidence that the involved 4-OH CTA metabolite is absent in humans. This can be done with additional PhVig activities in the RMP.

For malignant melanoma the imbalance in the number of cases remains a concern. However, in the absence of a mechanistic rationale and non-clinical findings for malignant melanoma, routine PhVig activities in the RMP is considered appropriate because there is currently a lack long term data.

Variable hepatic effects seen in animal studies were discussed to clarify the clinical relevance, especially in relation with the hepatic findings in patients. It was concluded that the hepatic findings in animals do not reflect the profile of a clear hepatotoxic compound. However, some signals were found including mild elevations of AST and ALT, incidental proliferation or hypertrophy of Kupffer cells, and some incidences of hepatocellular necrosis. In addition vacuolation of hepatocytes or sinusoidal cells was seen, which may reflect increased lipid mobilisation. In patients with severe hepatic impairment the exposure to empagliflozin is significant increased. As no further in depth toxicological investigations have been undertaken to determine the precise nature of the vacuolation or the cause of AST/ALT elevations and sporadic incidence of necrosis, it is premature to conclude that there would be no risk for adverse liver events in patients. It is therefore agreed that liver safety is followed up in long-term clinical studies and included as an important potential risk in the RMP.

Other non-clinical aspects for which there is remaining uncertainty on the clinical relevance are ophthalmoscopic findings and the background for Leydig tumors.

The number of patients with serious hepatic adverse events was remarkably higher in the empagliflozin groups compared to placebo and comparators. In all but one of these cases the independent committee of hepatic experts judged that the causal relationship with the treatment was not probable. Nevertheless, the number of cases with empagliflozin was remarkably high. On the other hand, there were no imbalances unfavourable for empagliflozin in less severe signs of liver impairment. The frequency of patients with elevated liver enzymes during the treatment period was not importantly influenced by history of liver or pancreatic disease at baseline or not. This means that the risk of liver injury cannot be diminished by limiting the use of empagliflozin to individuals without a history of liver or pancreatic disease. Regular follow-up of liver enzymes to prevent hepatic injury was discussed by the Applicant. Empagliflozin did not increase the frequency of patients with elevated ALT and/or AST among all patients and among several subgroups. The occurrence of high-level elevations was low, and during the empagliflozin development program there were no reports of drug induced hepatotoxicity such as fatalities or liver transplantation. Therefore, regular follow-up of liver enzymes will add unnecessary burdens to clinicians and patients without added benefit.

In clinical studies, exposure to empagliflozin increased with the degree of renal impairment. Patients with different degrees of renal impairment were analysed separately. The frequency of patients with any adverse events, serious adverse events, and adverse events leading to discontinuation of trial medication increased with the degree of renal impairment. Importantly,

empagliflozin treatment was associated with a higher frequency of decreased renal function, genital infection and urinary tract infection in patients with moderate renal impairment.

In the subgroup of patients using diuretics, frequency for volume depletion was slightly higher for patients using empagliflozin compared to comparators (patients with diuretics use at baseline: placebo: 2.2%, empagliflozin 10 mg: 2.5%, empagliflozin 25 mg: 2.7%; 'all comparators': 2.2%). The same was true for patients taking loop diuretics at baseline (patients with loop diuretics use at baseline: placebo: 2.9%, empagliflozin 10 mg: 4.9%, empagliflozin 25 mg: 3.0%; 'all comparators': 2.8%). Therefore, caution should be exercised in patients on diuretics. This should be mentioned in the SmPC.

Different age groups were analysed separately. There was a higher frequency of urinary tract infections, volume depletion and decreased renal function in patients ≥75 years. In elderly patients, the frequency of urinary tract infection was higher in the empagliflozin groups especially for the age group 75 years and older (SAF-5: placebo: 25 patients, 10.5%; empagliflozin 10 mg: 34 patients; 15.7%; empagliflozin 25 mg: 41 patients; 15.1%). However, the higher frequency of urinary tract infection in patients >75 years with empagliflozin may be explained by declining renal function: in patients >75 years with baseline eGFR ≥45 or ≥60 mL/min/1.73 m2, the frequency of urinary tract infections tended to be comparable between the empagliflozin and the placebo groups, whereas in the matching lower eGFR categories, frequencies were increased in the empagliflozin groups compared with the placebo group. These data suggest that renal function is a determinant of urinary tract infections in patients ≥75 years. The increased risk of volume depletion in patients ≥75 years with empagliflozin is an important issue (placebo: 5 patients, 2.1%; empagliflozin 10 mg: 5 patients; 2.3%; empagliflozin 25 mg: 12 patients; 4.4%). Subgroup analyses demonstrated that this higher frequency was independent of renal function category. The frequency of decreased renal function was slightly higher in the empagliflozin 25 mg group for the age categories 75 years and older (4 patients (1.7%) in the placebo group vs. 6 patients (2.2%) for empagliflozin 25 mg). Taken together, caution should be exercised in elderly patients. This should be mentioned in the SmPC.

Bone fractures were of special interest, but not identified as a possible risk. The reported rates of bone fracture were very low and similar for all treatment groups. Changes in BMD were not found. However, treatment duration was too short (1 year) and the number of patients very small (48 treated with empagliflozin). In addition, urine NTx to creatinine ratio increased slightly in the empagliflozin groups, whereas it decreased slightly in the comparator groups. Harmful effects of empagliflozin cannot be excluded. In the PRAC-rapport the necessity for a PASS will be discussed. In case of PASS, it is advised to include bone fracture incidence in the PASS. For comparison, also with Dapagliflozin BMD measurements were asked in a subset of patients in the CV outcome study in order to obtain more data on bone metabolism.

In animals, renal calcifications were observed. There was not an increased risk of kidney stones with empagliflozin in the development programme.

Benefit-risk balance

Importance of favourable and unfavourable effects

The observed effects of empagliflozin on HbA1c, body weight and blood pressure could be beneficial for patients as they may translate into reductions in macrovascular and microvascular disease in the long term. Long-term effects have not been investigated. The results of the CV outcome study are awaited.

There were small increases in LDL cholesterol with empagliflozin. However, HDL levels were also somewhat increased.

Although the 25 mg performed better, the lower dose also showed clinically significant changes in HbA1c. It could be useful to start treatment with this lower dose and then increase the dose if necessary, also because serious side effects appear dose-dependent, in particular in high-risk patients, in particular the elderly. Therefore it was questioned why the Applicant abandoned the 10 mg dose. Subsequently, the Applicant decided to re-introduce the 10 mg dose as a starting dose. This 10 mg is acceptable from a clinical point of view and supported by earlier policy of CHMP regarding another SGLT2 inhibitor.

The company requested an indication for empagliflozin monotherapy in patients for whom metformin is considered inappropriate. This can be due to intolerance (gastrointestinal complaints) or contraindications. The most important contraindications for metformin include renal impairment (GFR<60 ml/min) and heart failure. Patients with gastrointestinal complaints with metformin were not specifically investigated. However, it is not likely that gastrointestinal complaints due to metformin influence the efficacy and safety of empagliflozin. This indication has also been accepted for dapagliflozin. Patients with heart failure NYHA III and IV were not investigated in any of the trials. In patients with GFR 45-60 ml/min, efficacy was of borderline significance and the risk of adverse events tended to be higher. Therefore, empagliflozin cannot be recommended in these patients. In general, the benefit-risk ratio for empagliflozin was negative for patients with a GFR below 60 ml/min. However, several commonly used classes of antihyperglycemic agents are contraindicated in patients with a GFR below 60 ml/min, and a subgroup of patients may benefit from treatment with empagliflozin. Therefore, as an alternative, initiation of treatment with empagliflozin may only be allowed in patients with an eGFR of ≥60 mL/min/1.73m2 but continuation of empagliflozin therapy may be allowed until the eGFR decreases to <45 mL/min, at which time empagliflozin therapy would be discontinued.

In general, the safety profile of empagliflozin is that of a SGLT 2 inhibitor. Overall, no major differences were observed between the 10 and 25 mg dose, but number of AEs may be higher for the higher dose in some high risk patients, like patients ≥75 years. There was an increased risk of genital infections in patients using empagliflozin. Genital infections were usually not serious, but can be very uncomfortable. The Applicant has included genital infections as an important identified risk in the updated RMP. As a proactive step to ensure patient safety, the Applicant proposes a PASS to evaluate the risk of genital infection in empagliflozin-treated patients. The higher risk of urinary tract infections in patients with a history of urinary tract infections is very important, as urinary tract infections may be very serious. The Applicant has included urinary infections as an important identified risk in the RMP. As a proactive step to ensure patient safety, the Applicant proposes a PASS to evaluate the risk of urinary tract infection in empagliflozin-treated patients. There were no relevant changes in creatinine levels.

Overall, frequencies of decreased renal function and volume depletion reported as adverse events were similar. However, due to the higher risk of volume depletion, caution should be exercised in patients on diuretics.

In elderly patients (>75 yrs) with renal function > 60 ml/min, efficacy was acceptable. However, there was an increased risk of urinary tract infections, volume depletion and decreased renal function. Thus, care should be taken.

With empagliflozin there was a low risk of hypoglycaemia, except in patients using empagliflozin in combination with MET+SU. In these patients empagliflozin should be used with caution.

The increased risk of serious hepatic adverse events is important; therefore, the inclusion of hepatic injury as an important potential risk in the updated RMP is warranted.

There was an imbalance in malignancies, and long term effects of empagliflozin on the risk of malignancies cannot be excluded. The urinary tract carcinogenic risk cannot be ruled out and should be further monitored and studied in view of the finding in male mice in the preclinical studies and conclusive evidence that the involved 4-OH CTA metabolite is absent in humans. This can be done with additional PhVig activities in the RMP.

In the absence of a mechanistic rationale and non-clinical findings for malignant melanoma, routine PhVig activities for an important potential risk in the RMP are considered appropriate.

Harmful effects of empagliflozin on bone cannot be excluded. This issue should be addressed in the RMP as a potential risk.

Benefit-risk balance

Discussion on the benefit-risk balance

Although it has clearly been shown that empagliflozin has the B/R profile of a SGLT-2 inhibitor, several issues remain. These issues concern the use in patients with a GFR<60 ml/min and the risk of serious liver injury. The issue with renal function may be solved by restricting the use of empagliflozin to patients with an eGFR of ≥60 mL/min/1.73m2 but continuation of empagliflozin therapy may be allowed until the eGFR decreases to <45 mL/min, at which time empagliflozin therapy would be discontinued. This has been reflected in sections 4.2 and 4.4 of the SmPC.

The increased risk of serious hepatic adverse events is important; therefore the inclusion of hepatic injury as an important potential risk in the updated RMP is warranted.

In general, the benefit-risk balance of empagliflozin in type 2 diabetes mellitus is acceptable but its use in patients with moderate renal failure cannot be recommended.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Jardiance in the treatment of

type 2 diabetes mellitus to improve glycaemic control in adults as:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy

In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that empagliflozin is qualified as a new active substance.