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Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for empagliflozin

Proprietary Product Name: Jardiance

Sponsor: Boehringer Ingelheim Pty Ltd

First round CER: 16 October 2013

Second round CER: 31 January 2014

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
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List of abbreviations

Abbreviation	Meaning
1,5-AG	1,5-anhydroglucitol
ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
AUEC	Area under the effect time curve
BI	Boehringer Ingelheim
BIcMQ	BI-customised MedDRA query
BID	Twice a day
BMI	Body mass index
CCDS	Company Core Data Sheet
CEC	Clinical Event Committee
CI	Confidence interval
CTR	Clinical trial report
DBP	Diastolic blood pressure
DILI	Drug induced liver injury
DMC	Data monitoring committee
DPP-4	Dipeptidyl-peptidase 4
ECG	Electrocardiogram
EFF	Efficacy trial pooling
eGFR	(Estimated) glomerular filtration rate
EMA	European Medicines Agency

Abbreviation	Meaning
Empa	Empagliflozin
FAS	Full analysis set
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FF	Final formulation
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GMR	Geometric mean ratio
HbA1c	Glycosylated haemoglobin
HDL	High-density lipoprotein
HOMA-IR	Homeostasis model assessment index to assess insulin resistance
HOMA-IS	Homeostasis model assessment index to assess insulin secretion
HYPO	Hypoglycaemia
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
LDL	Low-density lipoprotein
LLN	Lower limit of normal
LOCF	Last observation carried forward
MACE	Major adverse cardiovascular events
MDG	Mean daily glucose
MedDRA	Medical dictionary for drug regulatory activities
Met	Metformin
MMRM	Mixed model repeated measures
NDA	New Drug Application
OC	Observed cases

Abbreviation	Meaning
OC-IR	Observed cases including values after rescue medication
OD	Once daily
OGTT	Oral glucose tolerance test
OLS	Open label set
PD	Pharmacodynamics
Pio	Pioglitazone
PIP	Paediatric Investigational Plan
PK	Pharmacokinetics
PPS	Per-protocol set
PT	Preferred term
QD	Every day/Once daily
RMP	Risk Management Plan
SAF	Safety trial pooling
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SD	Standard deviation
SE	Standard error
SGLT	Sodium-dependent glucose co-transporter
SMQ	Standardised MedDRA query
SOC	System organ class
SU	Sulphonylurea
TF	Trial formulation
TS	Treated set
UGE	Urinary glucose excretion

Abbreviation	Meaning
ULN	Upper limit of normal
UTI	Urinary tract infections

1. Introduction

This is a Category 1 application to seek the registration of empagliflozin (also referred to as BI 10773 in this report) onto the Australian Register of Therapeutic Goods (ARTG). It is a Type A - New Chemical Entity submission.

The proposed indication is:

'[Jardiance] is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.'

2. Clinical rationale

Type 2 diabetes mellitus (T2DM) is characterised by insulin resistance and impaired insulin secretion. Diabetes is also associated with microvascular complications and elevated cardiovascular risk. The estimated worldwide prevalence of diabetes is 366 million with an increase of 50 % expected within the next 20 years. The majority of these patients will be expected to have T2DM. The current treatment algorithm for T2DM involves lifestyle interventions such as diet and exercise, as well as the administration of oral or injectable anti-diabetic drugs. Although initially effective, currently available oral antidiabetic agents often fail to maintain long term glycaemic control or are associated with side effects that may limit their use. Hence, there is a need for new therapeutic options for patients with T2DM to provide sustained improvements in glycaemic control and to contribute in reducing cardiovascular risk factors such as increased body weight and hypertension.

The kidney has a role in the regulation of blood glucose levels and can therefore serve as a target for new anti-diabetic drugs. SGLT2 is mainly expressed in the renal proximal tubules and accounts for approximately 90 % of renal glucose re-absorption. Inhibition of SGLT2 decreases the renal re-absorption of glucose, thereby promoting glucose excretion in the urine resulting in reduction in blood glucose levels. Due to their insulin-independent mechanism of action, SGLT2 inhibitors have a low risk of hypoglycaemia. Further benefits of SGLT2 inhibition may include weight reduction due to the calorie loss associated with increased glucose excretion and a decrease in blood pressure that is possibly due to a mild diuretic effect.

2.1. Guidance

Regulatory guidelines for the development of diabetes drugs were followed in designing and adapting the clinical development programme for empagliflozin. These included:

- European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP): Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus (draft) (20 January 2010, CPMP/EWP/1080/00 Rev. 1). 2010.
- EMA. Committee for Medicinal Products for Human Use (CHMP): Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (14 May 2012, CPMP/EWP/1080/00 Rev. 1). 2012.

- U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER): Guidance for industry: diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention (draft guidance, February 2008). Rockville: 2008.
- US FDA. (CDER): Guidance for industry: diabetes mellitus - evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes (December 2008). Silver Spring. 2008.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical programme supporting this registration comprises of: 30 Phase I trials, 5 dose finding Phase II trials and 13 Phase IIb/III trials. A total of 11,250 randomised and treated patients are included in the evaluation of efficacy. 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.

The submission contained the following clinical information:

- Module 1: Application letter, application form, draft Australian PI and Consumer Medicines Information (CMI).
- Module 2: Clinical overview, summary of clinical efficacy, summary of clinical safety and literature references.
- Module 5
 - 30 clinical pharmacology studies;
 - population pharmacokinetic analyses (U12-2525);
 - 4 pivotal efficacy/safety studies: monotherapy trial 1245.20; add-on to metformin therapy (trial 1245.23, met); add-on to metformin + sulfonylurea therapy (trial 1245.23, met+SU)¹ and add-on to pioglitazone therapy ± metformin therapy (trial 1245.19);
 - 2 main dose finding Phase IIb studies (1245.9 and 1245.10);
 - 6 additional studies are provided to support the long term efficacy and safety profile of empagliflozin in T2DM patients:
 - Study 1245.33 (Add-on to basal insulin);
 - Study 1245.36 (in T2DM patients with renal impairment);
 - Study 1245.48 (in T2DM patients with hypertension and three ongoing studies (only interim reports up to 52 weeks) to support the long term efficacy and safety of empagliflozin in T2DM patients;
 - Trial 1245.31: long term extension of the 4 pivotal studies ((Studies 1245.20, 1245.23 (met), 1245.23 (met+SU), 1245.19));
 - Trial 1245.28: empagliflozin (25mg) compared with glimepiride (1mg to 4 mg) as add-on therapy to metformin over 52 and 104 weeks, with a further 104 week extension period;
 - Trial 1245.25: large cardiovascular outcome trial (for up to 8 years) comparing empagliflozin with placebo in patients with high cardiovascular risk.

¹ Trials 1245.23 (met) and 1245.23 (met+SU) were conducted under a single trial number (1245.23), however for the purpose of data analyses, these trials were considered as 2 independent trials.

- Other, e.g. pooled analyses, meta-analyses, Integrated Summary of Efficacy, Integrated Summary of Safety, etc.

3.2. Paediatric data

This submission did not include paediatric data.

The requirement to submit a paediatric investigation plan (PIP) has been waived by the European Medicines Agency (EMA) for children below 10 years and a deferral for children and adolescents (aged 10 to < 18 years) was agreed by EMA (Decision P/33/2011). An application for modification of the agreed PIP was submitted by Boehringer Ingelheim to EMA on 13 September 2012 and has been accepted by EMA. The waiver for children less than 10 years of age was on the basis that type 2 diabetes mellitus does not occur in this specific paediatric subset.

3.3. Good clinical practice

All clinical trials followed the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP), conformed to the Declaration of Helsinki and were conducted in accordance with Boehringer Ingelheim standard operating procedures. All clinical trial protocols were approved by institutional review boards or independent ethics committees. Written informed consent was obtained from all patients as per GCP requirement.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 below shows the studies relating to each PK topic.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK Single dose	1245.1
		1245.8
		1245.5
	Multi-dose	None
	Bioequivalence † Single dose	1245.51
		1275.3
1276.5		
Multi-dose	1276.9	
Food effect	1245.3 1245.79	
PK in special populations	Target population §	
	Single / multiple dosing Multi-dose PK-PD study	1245.2 1245.4
	Hepatic impairment	1245.13

PK topic	Subtopic	Study ID
	Renal impairment	1245.12
	Neonates/infants/children/ adolescents	None
	Elderly	None
	Other special population PK-PD study in Chinese T2DM patients PK-PD study in Japanese T2DM patients	1245.44 1245.15
Genetic/gender related PK	Males versus females	None
	Other genetic variable	None
PK interactions	Metformin	1245.6
	Glimepiride	1245.7
	Pioglitazone	1245.17
	Warfarin	1245.18
	Sitagliptin	1245.27
	Linagliptin	1245.30
	Digoxin	1245.40
	Ethinylestradiol and levonorgestrel	1245.41
	Hydrochlorothiazide	1245.42
	Verapamil	1245.43
	Ramipril	1245.45
	Pioglitazone with various doses of BI 10773	1245.50
	Gemfibrozil	1245.58
	Simvastatin	1245.63
Rifampicin and Probenecid	1245.83	
Population PK analyses	Healthy subjects	None
	Target population	U12-2525-01

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the PK studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Absorption

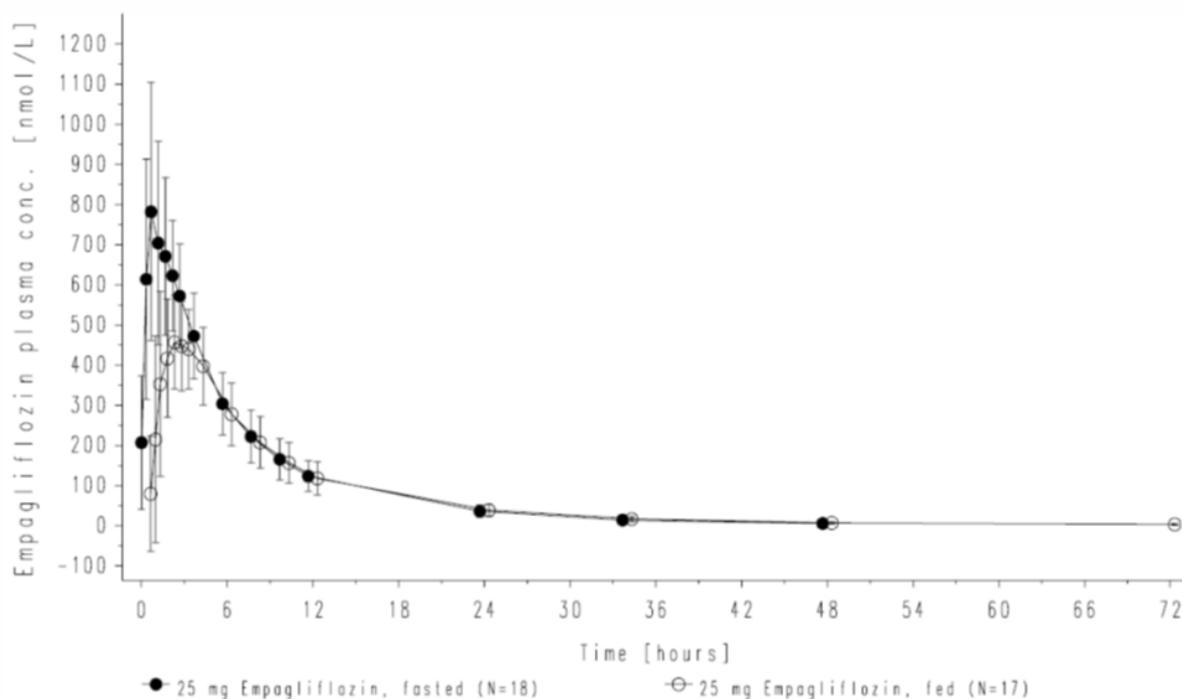
4.2.1.1.1. Sites and mechanisms of absorption

In the first human study (1245.1) involving 72 healthy male volunteers, single oral doses of 0.5 to 800 mg BI 10773 (empagliflozin) were rapidly absorbed, reaching peak levels in 1.5 to 2.5 h. Plasma concentration time profiles showed a biphasic decline, that is a rapid distribution phase and a slower elimination phase. The mean terminal elimination half-life ranged from 8.57 to 13.1 h. Increases in BI 10773 exposure (AUC and C_{max}) were approximately proportional with dose from 0.5 to 800 mg. Oral clearance was moderate (221 to 429 mL/min). Oral administration of glucose had no relevant effect on the pharmacokinetics of BI 10773. The amount of drug excreted unchanged in the urine ranged from 11.0% to 18.7% of the administered dose of BI 10773.

Table 2: Summary of mean (% CV) PK parameters of BI 10773

Parameter	units	0.5 mg	2.5 mg	10 mg	25 mg	50 mg	50 mg / OGTT	100 mg	200 mg	400 mg	800 mg
C _{max}	[nmol/L]	9.33 (40.0)	53.2 (11.7)	226 (20.4)	505 (25.9)	1110 (24.6)	951 (31.5)	2500 (26.7)	3490 (23.4)	6060 (28.4)	7950 (22.8)
t _{max}	[h]	1.68 (45.3)	1.83 (37.4)	1.42 (27.2)	2.19 (34.1)	1.75 (47.5)	2.49 (78.9)	1.55 (60.8)	1.83 (37.0)	2.30 (47.8)	1.46 (35.9)
t _{1/2}	[h]	5.57 (12.4)	8.57 (6.86)	13.1 (30.9)	10.2 (20.9)	10.3 (18.0)	8.83 (20.9)	10.6 (23.5)	11.1 (23.7)	11.2 (32.4)	11.2 (14.5)
AUC _{0-tz}	[nmol·h/L]	50.0 (29.2)	377 (10.1)	1690 (21.8)	3790 (21.8)	8530 (19.9)	7070 (12.7)	16400 (14.5)	30900 (19.9)	46300 (21.5)	69600 (13.7)
AUC _{0-∞}	[nmol·h/L]	61.2 (28.1)	396 (11.0)	1730 (21.8)	3830 (21.5)	8580 (19.6)	8090 (15.3)	16500 (14.5)	31200 (20.1)	46600 (21.8)	70200 (13.6)
%AUC _{tz-∞}	[%]	18.4 (19.0)	4.55 (20.7)	1.94 (17.5)	1.18 (39.6)	0.613 (104)	12.3 (37.1)	0.436 (69.3)	0.855 (47.0)	0.695 (85.7)	0.909 (57.1)
λ _z	[1/h]	0.126 (12.4)	0.0812 (6.51)	0.0576 (30.8)	0.0707 (20.5)	0.069 (16.7)	0.0812 (20.6)	0.0689 (25.4)	0.0668 (32.6)	0.068 (33.1)	0.0629 (15.5)
MRT _{po}	[h]	8.10 (9.89)	10.0 (9.49)	11.7 (15.0)	11.2 (18.5)	11.1 (17.0)	11.2 (20.0)	9.91 (9.47)	11.4 (16.3)	11.0 (15.6)	12.7 (20.3)
CL/F	[mL/min]	317 (20.8)	236 (11.2)	224 (24.3)	252 (23.7)	221 (16.5)	233 (15.9)	228 (16.7)	245 (20.1)	332 (26.0)	429 (15.6)
V _z /F	[L]	153 (25.7)	174 (8.29)	241 (17.4)	218 (24.4)	199 (31.2)	175 (14.3)	209 (30.4)	229 (23.4)	308 (24.0)	421 (27.3)
Ae ₀₋₇₂	[nmol]	168 (28.9)	964 (14.8)	4130 (13.2)	8330 (16.0)	15900 (3.99)	14700 (20.1)	39900 (23.5)	82800 (18.5)	134000 (15.2)	196000 (21.8)
fe ₀₋₇₂	[%]	15.2 (28.9)	17.4 (14.8)	18.6 (13.2)	15.0 (16.0)	14.4 (3.99)	13.3 (20.1)	18.0 (23.5)	18.7 (18.5)	15.1 (15.2)	11.0 (21.8)
CL _{R,0-72}	[mL/min]	51.3 (22.4)	41.3 (22.2)	41.1 (10.1)	37.7 (24.9)	32.1 (22.7)	35.5 (25.1)	40.7 (22.3)	45.6 (20.0)	49.5 (19.8)	47.3 (21.2)

In study 1245.79, following single oral administration of proposed dose of 25 mg empagliflozin under fasted conditions, empagliflozin was rapidly absorbed with a median t_{max} of 1.00 h. Thereafter, plasma levels declined in a biphasic fashion with a rapid distribution phase and a slower elimination phase (Figure 1).

Figure 1: Plasma levels of empagliflozin after a single oral administration

4.2.1.2. Bioavailability

4.2.1.2.1. Absolute bioavailability

Not evaluated.

Comments: The sponsors have provided justification for no absolute bioavailability studies in Module 1.11. Absolute bioavailability (BA) of empagliflozin in humans was not assessed during clinical development for the treatment of T2DM. By taking into account criteria listed in Section 4 of Appendix 15 of the Australian Regulatory Guidelines for Prescription Medicine, absolute BA data for empagliflozin was not considered necessary based on the following reasons:

- Empagliflozin is highly soluble at the proposed therapeutic dose strength (25 mg once daily).
- Solubility of empagliflozin is almost pH-independent since it does not have any ionisable centres
- Empagliflozin film coated tablet is an immediate release dosage form showing comparable dissolution profiles across the physiological range (pH 1, 4.5 and 6.8)
- No relevant differences were observed between the various immediate release tablet formulations evaluated during the development of empagliflozin
- Empagliflozin demonstrated linear pharmacokinetics over the entire dose range (0.5 to 800 mg) evaluated in clinical trials and the variability was low
- Empagliflozin was well tolerated over the entire dose range evaluated in clinical trials
- There were no clinically relevant changes in empagliflozin exposure that could be attributed to the various intrinsic or extrinsic factors evaluated including effect of food, hepatic impairment, renal impairment, and concomitant medication.

The reasons provided by the sponsors appear to be reasonable.

4.2.1.2.2. Bioavailability relative to an oral solution or micronised suspension

Not evaluated.

4.2.1.2.3. *Bioequivalence of clinical trial and market formulations*

The Phase I, open label, randomised, single dose, two way cross-over trial 1245.51 evaluated the relative bioavailability of empagliflozin when administered as 25 mg empagliflozin Final Formulation (FF) compared with 25 mg empagliflozin Trial Formulation II (TF-II). Following single oral administration of 25 mg BI 10773 TF-II, BI 10773 was rapidly absorbed, reaching mean peak plasma concentrations at 1.63 h. Thereafter, plasma levels declined in a biphasic fashion with a rapid distribution phase and a slower elimination phase. The mean $AUC_{0-\infty}$ was 5090 nmol·h/L and the mean C_{max} was 764 nmol/L. Following single oral administration of 25 mg BI 10773 FF, no relevant differences in the rate (C_{max}) and extent ($AUC_{0-\infty}$) of absorption of BI 10773 were observed compared with BI 10773 XX TFII. Mean peak plasma levels of BI 10773 were reached at 1.64 h, the mean $AUC_{0-\infty}$ was 5200 nmol·h/L, and the mean C_{max} was 764 nmol/L. The geometric mean ratios (90% confidence intervals) of $AUC_{0-\infty}$ and C_{max} were 101.67% (98.10, 105.37) and 99.46% (90.18, 109.68), respectively. Intra-individual variability (% gCV) was 6.7% for $AUC_{0-\infty}$ and 18.7% for C_{max} .

Comments: In vitro dissolution profiles depict immediate release characteristics and were similar for TF-II and FF empagliflozin formulations. Bioequivalence between the proposed commercial formulation (FF) and the TF-II formulation used in earlier clinical trials was demonstrated unequivocally. The 90% confidence intervals for the geometric mean ratios of both $AUC_{0-\infty}$ and C_{max} were within the standard bioequivalence criteria of 80% to 125%.

4.2.1.2.4. *Bioequivalence of different dosage forms and strengths*

In study 1275.3 the 90% confidence intervals for AUC and C_{max} of BI 10773 and linagliptin were within the standard acceptance range for bioequivalence of 80 to 125% when the 25 mg BI 10773 / 5 mg linagliptin fixed dose combination (FDC) A1 tablet was compared with the individual tablets of BI 10773 and linagliptin administered together. Thus, the FDC A1 tablet and the individual tablets can be considered bioequivalent. There was also no difference with regard to AUC and C_{max} between the FDC tablet with normal dissolution (FDC A1) and a slow dissolving formulation (FDC A3). Administration of the FDC A1 tablet in the fed state reduced the peak exposure of BI 10773 and linagliptin but did not influence the total exposure; in the fed state, AUC was reduced by 15% for BI 10773 and by 9% for linagliptin, and C_{max} was reduced by 39% for BI 10773 and by 32% for linagliptin compared with the same tablet taken while fasted.

In study 1276.5 the relative bioavailabilities of both BI 10773 and metformin were similar when 12.5 mg BI 10773 and 1000 mg metformin were administered as the FDC tablet compared to individual components co-administered in healthy male and female volunteers. Food had no effect with respect to the bioequivalence boundaries of 80 to 125% on $AUC_{0-\infty}$ of both BI 10773 and metformin, but peak levels (C_{max}) of both drugs were lower when the FDC tablet was administered with food compared to the fasted condition.

4.2.1.2.5. *Bioequivalence to relevant registered products*

Not applicable.

4.2.1.2.6. *Influence of food*

The effect of food was investigated in an exploratory manner in trial 1245.3 with a 50 mg dose of TF-I and confirmed later with a 25 mg FF tablet in trial 1245.79. In study 1245.79, administration of empagliflozin with food resulted in a small decrease in empagliflozin exposure, with $AUC_{0-\infty}$ being 16% lower and C_{max} being 37% lower under fed than under fasted conditions. The 90% confidence intervals were not within the accepted 80 to 125% limits for C_{max} .

Comments: The observed effect of food on empagliflozin PK was not considered clinically relevant and empagliflozin may be administered with or without food.

4.2.1.2.7. Dose proportionality

In the Phase I study 1245.79 involving 18 healthy volunteers, the gMean values of $AUC_{0-\infty}$ and C_{max} increased slightly less than dose proportionally between 10 mg and 25 mg empagliflozin and the slope β of the regression line was slightly less than 1 (0.94 and 0.91, respectively). The 95% CIs for the slope of C_{max} included 1 and the corresponding intervals of $AUC_{0-\infty}$ did not include 1. However, the point estimate and the corresponding 95% CIs were close to 1 for both parameters and therefore it can be concluded that empagliflozin exposure increased roughly dose proportionally between 10 mg and 25 mg empagliflozin.

In Phase I study 1245.2 in T2DM patients after multiple doses of BI 10773, slope β was not significantly different from unity for both $AUC_{\tau,ss}$ (95% CI: 0.8754, 1.0913) and $C_{max,ss}$ (95% CI: 0.8179, 1.0454), indicating that BI 10773 exposure was proportional to dose at steady state from 2.5 to 100 mg BI 10773 q.d.

In study 1245.4 after single doses of BI 10773 (Day 1), slope b was not significantly different from unity for both AUC_{0-24} (95% confidence interval: 0.9581, 1.0582) and $C_{max,ss}$ (95% CI 0.8691, 1.0073) with similar results observed after multiple doses of BI 10773 (Day 28), slope b was not significantly different from unity for both $AUC_{\tau,ss}$ (95% CI: 0.9384, 1.0461) and $C_{max,ss}$ (95% CI: 0.8839, 1.0140), indicating that BI 10773 exposure was proportional to dose at steady state from 10 to 100 mg BI 10773 q.d.

In study 1245.5 involving 48 healthy Japanese subjects, slope β was not significantly different from unity for $AUC_{0-\infty}$ (95% CI: (0.9293, 1.0176)), AUC_{0-tz} (95% CI: (0.9424, 1.0328)), C_{max} (95% CI: (0.8836, 1.0016)), and Ae_{0-72} (95% CI: (0.9604, 1.0354)), indicating that BI 10773 exposure was dose proportional from 1 to 100 mg BI 10773.

In study 1245.15 involving Japanese T2DM patients, BI 10773 exposure was proportional to dose after the first and multiple drug administrations over the dose range from 1 mg to 25 mg of BI 10773 once daily; after multiple administration of BI 10773 (Day 28), 95% CI of slope β included 1 for both $AUC_{\tau,ss}$ (95% CI: 0.9384, 1.0063) and $C_{max,ss}$ (95% CI: 0.8852, 1.0029).

4.2.1.2.8. Bioavailability during multiple dosing

In the PK-PD study 1245.2 in T2DM patients, the PKs of BI 10773 were similar after administration of a single dose on Day 1 and multiple doses at steady-state on Day 9. BI 10773 was rapidly absorbed after oral administration, reaching peak levels between 1 and 2.5 h after dosing. Plasma concentration time profiles showed a biphasic decline, i.e. a rapid distribution phase and a slower elimination phase. The mean terminal elimination half-life was similar after a single dose and at steady state and ranged from 10 to 19 h. Increases in BI 10773 exposure (AUC and C_{max}) were approximately proportional with dose from 2.5 to 100 mg BI 10773 q.d. Oral clearance was moderate (162 to 201 mL/min on Day 1 and 173 to 206 mL/min on Day 9). The amount of parent excreted unchanged in the urine ranged from 12% to 19% of the administered dose at steady state. The similarities in single dose and steady state parameters suggest linear PK with respect to time. The mean linearity index ranged from 0.978 to 1.05. Consistent with the half-life, up to 23% accumulation was observed at steady state.

Similar results were observed in the PK-PD study 1245.4 as the PKs of BI 10773 were similar after administration of a single dose on Day 1 and multiple doses at steady state on Day 28. The similarities in single dose and steady state parameters suggest linear PKs with respect to time. The mean linearity index ranged from 1.04 to 1.10. Consistent with the half-life, up to 22% accumulation was observed at steady state.

4.2.1.2.9. Effect of administration timing

In study 1276.9 relative bioavailability of BI 10773 was estimated following oral administration of 5 mg BI 10773 b.i.d. compared to 10 mg BI 10773 q.d. in 16 healthy volunteers. The $AUC_{0-24,ss}$ geometric mean ratio (5 mg bid/10 mg q.d.) was 99.36%, and the 90% CI of 94.29%, 104.71% was within the standard bioequivalence boundary of 80 to 125%, indicating that there was no significant difference between the once and twice daily dosage regimens with regard to BI

10773 exposure. Intra-individual variability was low. BI 10773 exposure in the 5 mg b.i.d. regimen was slightly lower with the evening dose ($AUC_{0-12,ss}$: 867 nmol·h/L; C_{max} : 120 nmol/L) than with the morning dose ($AUC_{0-12,ss}$: 1010 nmol·h/L; C_{max} : 193 nmol/L). The cumulative amount of glucose (UGE0-24) excreted in urine was slightly higher with 5 mg bid (52.1 g) than with the 10 mg qd (43.9 g) regimen.

Comments: Overall, bioequivalence was demonstrated between once daily (10mg OD) and twice daily (5mg b.i.d.) dosing regimens of BI10773. The interpretation of urinary glucose excretion was limited as the study was carried out in healthy volunteers and also there were no stringent restrictions on calorie intake. However, effect of morning versus evening dosing was not evaluated. In most of the Phase II and III clinical trials, empagliflozin was administered in the morning.

4.2.1.3. *Distribution*

4.2.1.3.1. *Volume of distribution*

The typical apparent steady state volume of distribution was 73.8 L.

4.2.1.3.2. *Plasma protein binding*

Empagliflozin binding to mouse, rat, dog, and human plasma was determined in vitro by equilibrium dialysis using radiolabeled drug. The plasma protein binding (mean \pm SD) of empagliflozin in mouse, rat, dog, and human plasma was 88.1 ± 0.5 , 90.5 ± 0.6 , 88.8 ± 0.6 , and 83.7 ± 1.2 , respectively. There were no major differences in protein binding of empagliflozin in human plasma compared to animals in vitro. The plasma protein binding of empagliflozin in vivo in healthy volunteers and patients with T2DM was similar to in vitro findings. The plasma protein binding of empagliflozin in healthy volunteers was determined in the human absorption, distribution, metabolism and excretion (ADME) study and it ranged from 80.3% to 86.2% (study 1245.8). In patients with T2DM, the plasma protein binding was 85.1% (trial 1245.12). Disease conditions such as renal impairment have been shown to alter protein binding of drugs [R10-2511]. However, the plasma protein binding of empagliflozin was not affected by renal impairment; it ranged from 81.0% to 83.9% in subjects with various degrees of renal impairment. The protein binding was also not affected by hepatic impairment; with mean values ranging from 83.4% to 85.2% in subjects with various degrees of liver impairment (study 1245.13). These results indicate that the protein binding of empagliflozin in the target population is similar to healthy subjects and in vitro findings. Moreover, disease conditions that affect renal or hepatic function did not have any relevant effect on the binding of empagliflozin to plasma proteins.

Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, the red blood cell (RBC) partitioning was approximately 36.8% and plasma protein binding was 86.2%.

4.2.1.3.3. *Erythrocyte distribution*

The concentration dependence of RBC partitioning of empagliflozin was determined in vitro in rat, dog and human blood. Mean ratios of radioactivity concentration in RBC compared to the concentration in plasma (C_{bc}/C_p) were 29.6%, 25.3%, and 30.1% in rat, dog, and human blood, respectively, at the 1 μ g Eq/mL concentration. The RBC partitioning was similar (24.3% to 34.3%) with 10 μ g Eq/mL concentration, indicating that RBC partitioning of drug related radioactivity was not dependent on empagliflozin concentration. RBC partitioning of empagliflozin determined ex vivo in animals was consistent with in vitro results; 25% to 28% and 16% to 44% in mice and rats, respectively. RBC partitioning in humans was determined ex vivo as part of the human ADME study (study 1245.8). In humans, ex vivo RBC partitioning of drug related radioactivity was similar to in vitro findings; mean ratios at 2, 6, and 12 h post-dose were 28.6%, 30.2%, and 36.8%, respectively. The extent of partitioning in humans was also similar to that observed in animals.

4.2.1.4. Metabolism

4.2.1.4.1. Interconversion between enantiomers

Empagliflozin contains six chiral centres; however, the chirality of each of these chiral centres is fixed and cannot be inverted. The stereochemical stability of empagliflozin has been demonstrated during long term, accelerated and stress stability studies. Due to its C-glycoside structure, empagliflozin is expected to be stereochemically stable in vivo. Following oral administration of empagliflozin to animals and humans, no metabolism was found to occur on any of the five chiral carbons within the glucose moiety, nor was metabolism of empagliflozin detected at the sixth chiral centre, that is, the 3-position of the tetrahydrofuran ring. Since the chemical structure of empagliflozin does not allow for racemization or chiral inversion without oxidative metabolism of the glucose or tetrahydrofuran moieties, empagliflozin was not expected to undergo chiral inversion via catalysis by relevant mammalian enzymes or at biologically relevant pH values. To confirm that chiral inversion of empagliflozin does not occur in vivo, analysis for the chirally inverted product (BI 10772) at the sixth chiral centre was evaluated using selected reserved human plasma samples from study 1245.83. BI 10772 was not detectable in all tested plasma samples (Lower Limit of Quantification was 2.24 nmol/L). These data confirm that chiral inversion of empagliflozin to BI 10772 does not occur in humans [U13-3020].

4.2.1.4.2. Sites of metabolism and mechanisms / enzyme systems involved

Empagliflozin is not metabolized by any human CYP450 enzymes, as determined using human liver microsomes. Additionally, empagliflozin is not an inducer of human hepatic CYP450 enzymes, as determined using cultured human hepatocytes. From incubations with a panel of 12 relevant human recombinant uridine diphosphate glycosyltransferase (UGT) enzymes, it was determined that UGT2B7, UGT1A3, UGT1A8, and UGT1A9 are responsible for the glucuronidation of empagliflozin [Module 2.6.4]. The elimination of empagliflozin in mice, rats and dogs was primarily facilitated by nonmetabolic mechanisms, as unchanged empagliflozin was the most abundant drug related component identified in urine, feces, bile and plasma following oral administration. In humans, unchanged empagliflozin was the most abundant drug related component in plasma (75.5 to 77.4% of total radioactivity). A total of six metabolites of empagliflozin were detected in plasma; but none were considered as major metabolites as the proportion of each metabolite was < 10% of total drug related exposure. As such, the most abundant metabolites of empagliflozin were 3 glucuronide conjugates (3.3 to 7.4% of plasma radioactivity). In vitro studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

4.2.1.4.3. Non-renal clearance

Empagliflozin biotransformation primarily involved glucuronidation, and to a lesser extent oxidation.

4.2.1.4.4. Metabolites identified in humans

4.2.1.4.4.1. Active metabolites

As the proportion of each metabolite was < 10% of total radioactivity, none of the metabolites were considered major. No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O, 3-O, and 6-O glucuronide). Systemic exposure of each metabolite was less than 10% of total drug related material. All 3 glucuronide conjugates have been shown to be inactive and are not expected to contribute significantly to overall efficacy.

4.2.1.4.5. Pharmacokinetics of metabolites

No major metabolites were detected in human plasma.

4.2.1.4.6. *Consequences of genetic polymorphism*

Not evaluated.

4.2.1.5. **Excretion**

4.2.1.5.1. *Routes and mechanisms of excretion*

The typical apparent terminal elimination half-life of empagliflozin was 12.4 h and typical apparent oral clearance was 10.6 L/h. Following administration of an oral [¹⁴C]-empagliflozin solution to healthy subjects, approximately 95.6% of the radioactivity was eliminated in faeces (41.2%) or urine (54.4%). The majority of drug related radioactivity recovered in faeces was unchanged parent drug and approximately 50% of the drug related radioactivity excreted in urine was unchanged parent (28.6%) (Study 1245.8).

4.2.1.5.2. *Mass balance studies*

In the ADME study 1245.8 the concentration time profiles of total radioactivity in blood and plasma were parallel with similar t_{max} (1 h and 0.938 h, respectively) and terminal elimination half-lives (t_{1/2}) (8.68 h and 9.15 h, respectively). The total radioactivity exposure in blood was lower compared to plasma, consistent with moderate RBC partitioning (28.6% to 36.8%) observed in vivo. Protein binding of total radioactivity ranged from 80.3% to 86.2%. The majority of drug related radioactivity in plasma was unchanged parent. The rate of absorption and disposition of total radioactivity and BI 10773 were similar. BI 10773 reached maximum plasma concentrations at a mean t_{max} of 0.875 h and the terminal t_{1/2} was 15.9 h. There were no major differences in the PK of total radioactivity and unchanged parent.

4.2.1.5.3. *Renal clearance*

In study 1245.2 in T2DM patients, BI 10773 was detected in urine in all BI 10773 dose groups (2.5 to 100 mg). After BI 10773 dosing, urinary excretion of BI 10773 increased with dose after administration of both a single dose on Day 1 and multiple doses on Day 9. The cumulative fractions of BI 10773 excreted in urine were similar in all dose groups. The total fractions of BI 10773 collected in urine (24 h) at doses of 2.5 to 100 mg ranged from 7.88 to 11.4% on Day 1 and from 12.2 to 18.7% on Day 9. Renal clearance of BI 10773 was similar in all dose groups on both Day 1 (CLR, 0-48h; 15.0 to 29.1 mL/min) and Day 9 (CLR, τ_{ss}; 23.5 to 34.4 mL/min).

4.2.1.6. ***Intra- and inter-individual variability of pharmacokinetics***

In the bioequivalence study 1245.51 intra-individual variability (% gCV) was 6.7% for AUC_{0-∞} and 18.7% for C_{max} following oral administration of the proposed 25mg marketing formulation.

4.2.2. **Pharmacokinetics in the target population**

1245.2 was a Phase II study which evaluated PKs, PDs and initial tolerability of empagliflozin 10mg, 25mg and 100mg OD for 28 days in 80 patients with Type 2 diabetes. Empagliflozin was rapidly absorbed, with peak plasma concentrations observed approximately 1.5 h after dosing. Thereafter, plasma levels declined in a biphasic fashion. Increases in empagliflozin exposure were dose proportional following multiple oral dosing. After multiple doses, trough concentrations remained constant after Day 6, indicating that steady state had been reached. The mean terminal elimination half-life at steady state ranged from 13.2 to 16.5 h. Consistent with this, up to 22% accumulation was observed at steady state. Oral clearance at steady state was similar to corresponding single dose values, suggesting linear PK with respect to time. Approximately 18% of administered drug was excreted as unchanged parent in urine.

Comments: The PK data from the above study 1245.2 in T2DM patients were compared with the data from the single rising dose study in healthy volunteers (trial 1245.1) although interpretation was limited by differences between the two trials, especially differences in body weights (mean weight of HV was 81 kg and of patients with T2DM was 95 kg). Empagliflozin exposure (AUC and C_{max}) was slightly higher in patients with T2DM compared to healthy volunteers. There were no major differences in t_{max} and t_{1/2} suggesting the rate of absorption

and disposition of empagliflozin were unaffected. Hence, empagliflozin exposure (AUC) in healthy volunteers appeared to be approximately 25% lower for doses less than 400 mg compared to T2DM patients. The majority of healthy volunteer trials were carried out to establish safety/tolerability, evaluate test formulations, and investigate potential DDIs with medicinal products. The highest dose (800 mg) studied in study 1245.1 was 32-fold greater than the therapeutic dose (25 mg) investigated in Phase III trials. In the majority of other Phase I trials conducted to evaluate test formulations and potential DDIs, either 25 mg or 50 mg empagliflozin dose was used based on the objective of individual trials. Since the exposure differences were marginal and empagliflozin shows linear PK in both healthy volunteers and patients with T2DM, the observed minor differences in empagliflozin exposure are not likely to confine the applicability of healthy volunteer trial results to the patient population. Overall, there were no clinically relevant differences in empagliflozin pharmacokinetics between healthy volunteers and patients with T2DM.

In Phase II study 1245.15 involving 100 Japanese T2DM patients, BI 10773 was rapidly absorbed after oral administration, reaching a peak at approximately 1.5 to 2 hours after drug administration. Plasma concentration time profiles showed a biphasic decline, that is, a rapid distribution phase and a slower elimination phase. The mean terminal elimination half-life after multiple drug administration ranged from 13.2 hours to 18.0 hours. Increases in BI 10773 exposure (AUC and C_{max}) were proportional to dose from 1 mg to 25 mg of BI 10773 once daily. Oral clearance (CL/F) was moderate and not apparently different between values after the first drug administration and those after multiple drug administration (150 to 162 mL/min [except for the BI 10773 5 mg group, in which an outlier was noted] on Day 1 and 135 to 149 mL/min on Day 28). In urine, 21.4% to 22.3% of the administered dose was excreted unchanged after multiple drug administration. The mean linearity index (LI) ranged from 1.08 to 1.32. Accumulation amounted to 4% to 51% in terms of AUC and C_{max} after multiple drug administration.

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

The Phase I, open label study 1245.13 evaluated the effect of mild, moderate and severe hepatic impairment on the PKs of empagliflozin following single oral dose of 50mg (2x25mg tablets) in 36 subjects. In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased approximately by 23%, 47%, and 75% and C_{max} by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function. The mean t_{1/2} of empagliflozin was not affected due to liver impairment (19.9 h in healthy subjects versus 17.1 to 18.1 h in subjects with liver impairment) and there was no major effect of liver impairment on protein binding of empagliflozin (85.2% in subjects with normal hepatic function versus 84.6%, 85.2% and 83.4% in subjects with mild, moderate and severe hepatic impairment, respectively). Apparent volume of distribution (V_z/F) and oral clearance (CL/F) decreased due to liver impairment. However, any potential changes in the bioavailability (F) of empagliflozin due to liver impairment could not be quantified in this study and as such the relevance of changes observed in case of CL/F and V_z/F is unknown. In subjects with normal liver function, the fraction of drug excreted unchanged in urine was 16.6%. There were no consistent trends in changes observed in plasma and urine levels of glucuronide conjugates of empagliflozin. Hepatic impairment did not affect renal clearance of empagliflozin. However, consistent with the trend observed in case of plasma levels, the fraction (% of dose) of unchanged drug excreted in urine increased slightly across liver impairment groups from 15.2% in subjects with mild liver impairment to 20.3% in subjects with severe liver impairment. These slight changes in renal excretion of unchanged parent did not affect urinary glucose excretion which was similar in subjects with liver impairment compared with normal hepatic function (UGE was 42.6 g in subjects with normal hepatic function versus 36.2, 38.4 and 40.2 g in subjects with mild, moderate and severe hepatic impairment, respectively). Empagliflozin exposure increased with hepatic impairment; however, increases were less than 2-fold.

Comments: Although empagliflozin exposure increased with degree of hepatic impairment, the increases were < 2 fold and this increase in exposure did not have any effect on the PD parameter of urinary glucose excretion (UGE). In earlier Phase I studies, it has been shown that urinary glucose excretion reaches a plateau at around 10 mg (Trial 1245.2 and 1245.4). In the current study, 50 mg BI 10773 was evaluated and, as expected, there were no major changes in urinary glucose excretion with an increase in BI 10773 exposure due to hepatic impairment compared to subjects with normal liver function. Hence, the clinical relevance of the increased exposure in hepatic impairment does not appear to be significant and no dosage adjustments may be required. Due to increased exposure of empagliflozin in patients with hepatic impairment, it should not be administered in these patients².

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

The Phase I study 1245.12 evaluated the effect of varying degrees of renal impairment on the PKs of empagliflozin following a single oral dose of 50mg. The extent of exposure ($AUC_{0-\infty}$) of BI 10773 increased with the degree of renal impairment. The $AUC_{0-\infty}$ of empagliflozin increased by approximately 18%, 20%, 66%, and 48% in subjects with mild, moderate, severe, and kidney failure/ESRD renal impairment, respectively, as compared with subjects with normal renal function. The C_{max} of empagliflozin was similar in patients with moderate renal impairment and patients with kidney failure/ESRD. Empagliflozin C_{max} was roughly 20% higher in mild and severe renal impaired patients. The upper limits of 90% confidence intervals for both $AUC_{0-\infty}$ and C_{max} were greater than 125% for all renal impairment groups compared to patients with normal kidney function. The mean terminal elimination half-life of BI 10773 increased slightly with the degree of renal impairment (20 h versus 28 h in patients with normal renal function and severe renal impairment, respectively). In addition, BI 10773 oral clearance and volume of distribution decreased with an increase in renal impairment. There were no major effects of renal impairment on protein binding of BI 10773. The moderate increase in systemic exposure of BI 10773 could be explained by the decrease in its renal clearance with renal impairment. The fraction of parent excreted in urine was 16.1%, 11.7%, 7.7%, 3.6%, and 0.3% in normal, mild, moderate, severe, and kidney failure/ESRD patients, respectively. A corresponding decrease in glucose excretion was observed with an increase in the degree of renal impairment. The cumulative amount of glucose excreted in urine was 97.6, 61.6, 55.7, 18.3, and 0.8 g in normal, mild, moderate, severe, and kidney failure/ESRD patients, respectively. The decrease in renal clearance of BI 10773 and glucose excretion correlated well with the decrease in glomerular filtration rate.

Comments: Despite the increased exposure, the glucuretic response to empagliflozin was progressively less with further impairment of renal function, consistent with this pharmacodynamic response being rate limited by the filtered load of glucose as determined by the glomerular filtration rate. The finding of increased drug exposure with impairment of renal function was confirmed by the PPK analysis. Hence, the finding in relation to renal function is of diminished importance in the sense that a degree of renal dysfunction which causes retention of the drug also significantly impairs its pharmacodynamic response. The impact of decreased glucose excretion on plasma glucose and HbA1c cannot be quantified, based on the limited data available, at this point and, as a result, the final dose adjustments for patients with renal impairment needs further study in Phase III trials (this has been done by the sponsors in study 1245.36 and is discussed in section 7 of this report).

4.2.3.3. Pharmacokinetics according to age

Refer below.

4.2.3.4. Pharmacokinetics related to genetic factors

Not evaluated.

² This issue was addressed in the sponsor's response to TGA questions

4.2.3.5. Pharmacokinetics (in other special population / according to other population characteristic)

4.2.3.5.1. Race

The PK of empagliflozin were evaluated in Caucasian and Japanese healthy volunteers as well as in Caucasian, Japanese, and Chinese patients with T2DM in Phase I studies. In Caucasian (study 1245.1) and Japanese (study 1245.5) healthy volunteers, PK of empagliflozin after single oral doses showed higher empagliflozin exposure in Japanese compared to Caucasians. The terminal elimination half-life and renal clearance of empagliflozin were similar. The observed differences in exposure between Caucasian and Japanese healthy volunteers could be attributed to the body weight differences. The mean body weight of Caucasians in the 1245.1 trial was 81.0 kg and of Japanese in the 1245.5 trial was 62.7 kg.

Empagliflozin PKs were further evaluated in Caucasian (study 1245.4), Japanese (study 1245.15), and Chinese (study 1245.44) patients with T2DM. Similar to the trend observed in healthy volunteers, empagliflozin exposure was higher in Japanese and Chinese compared to Caucasian patients. Again, mean body weights of Japanese (68.5 kg) and Chinese (68.8 kg) patients were lower compared to Caucasians (93.1 kg) which would explain the differences observed in drug exposure. Although terminal elimination half-life and renal clearance of empagliflozin were comparable between Japanese and Chinese subjects, empagliflozin exposure in Chinese was slightly higher than Japanese.

In study 1245.44 involving Chinese T2DM patients, empagliflozin was rapidly absorbed following oral administration. Exposure increased roughly proportional with an increase in dose from 10 mg to 25 mg. The mean $t_{1/2,ss}$ ranged from 12.1 h to 13.9 h. The amount of drug excreted unchanged in the urine ranged from 20.1% to 21.4% of the administered dose at steady state. The similarities in single dose and steady state parameters suggest linear PK. Consistent with the half-life, up to 17% drug accumulation was observed at steady state. Administration of empagliflozin resulted in increased UGE from baseline of up to 95.8 g over 24 h and reductions in FPG from baseline of up to 31.4 mg/dL.

In the population PK analysis, race was found to have only a slight, but statistically significant, impact on the PK of empagliflozin beyond differences in BMI. In the population PK dataset, the median BMI in Asians and Non-Asians was 25.6 and 31.6 kg/m², respectively. The typical $AUC_{\tau,ss}$ was 13.5% (95% CI: 9.61, 17.5) higher in Asians compared to non-Asian patients, assuming a BMI of 25 kg/m² for Asians. For a formal comparison of exposure between Black and non-Black patients, the sample size was small (68 versus 2693); however, an exploratory comparison did not reveal any differences. Overall, the effect of race was not considered to be clinically relevant [U12-2525].

4.2.3.5.2. Gender

The population pharmacokinetic analysis showed that the typical apparent oral clearance and the typical peripheral volume of distribution were slightly lower in females compared to males leading to a 12.8% (95%CI: 7.31, 19.5) higher $AUC_{\tau,ss}$ in females compared to males. These minor differences were not considered to be clinically relevant and, as such, no dose adjustment is recommended based on gender (U12-2525).

4.2.3.5.3. Age

The population pharmacokinetic analysis showed that age has a slight, but statistically significant, impact on the PKs of empagliflozin. The typical apparent oral clearance decreased with age leading to an increase in $AUC_{\tau,ss}$. The typical $AUC_{\tau,ss}$ changed by -8.06% (95% CI: -1.81, -14.0), +6.43% (95% CI: 1.55, 11.0), and +10.1% (95% CI: 4.62, 15.5) for patients of 35, 65, and 75 years age, respectively, compared to patients with an age of 50 years assuming normal renal function (eGFR 100 mL/min/1.73 m²). The observed changes in the PK of empagliflozin were not considered as clinically relevant and, as such, no dose adjustment is recommended based on age [U12-2525].

4.2.3.5.4. Population Pharmacokinetic analysis

A preliminary population PK-PD data set (U09-3890-01) was developed from the pooled data across four Phase I studies (1245.1, 1245.2, 1245.4 and 1245.5). Initial modelling was conducted using a two compartment model with first-order absorption. The BI 10773 preliminary population PK data set was comprised of 186 patients³ contributing a total of 5591 plasma BI 10773 concentrations. The typical population PK parameter estimates were consistent with previous non-compartmental analyses of the PK data from individual studies. The inter-individual variance estimates (IIV) were, in general, between 15 and 30 CV%, indicating minimal between subject differences in the extent (AUC_{ss}) of BI 10773 plasma exposure for a given oral dose. IIV for oral absorption and the central volume of distribution were 60 and 90 CV%, respectively, indicating greater between subject differences in the rate (T_{max}), compared to the extent, of BI 10773 plasma exposure. Between subject differences in C_{max}, which is a product of both the rate and extent of exposure, were expected to be only moderately greater than those for AUC_{ss}. Relative to the median weight (83 kg), body weight over a 56.1 to 119.6 kg range, which represented the 95th percentiles of the observed weights, affected only a 30% difference in the expected steady state exposure (AUC_{ss}) for BI 10773. Asian subjects, represented almost entirely by the Japanese healthy volunteers from Study 1245.5, did not exhibit differences in CL=F beyond that described by the allometrically scaled body weight effect on CL=F, noting that the Japanese subjects weighed, on average, 20 to 30 kg less than the subjects from the other studies. Distributive volumes were estimated to be 20 to 30% lower for these Asian subjects. Therefore, C_{max} was predicted to be greater for Asian compared to non-Asian subjects. All additional covariate effects on the PK parameters CL=F, Q=F, and V₃=F were considered to not affect PK variability.

U12-2524 characterized the impact of empagliflozin on renal glucose threshold using population PK/PD modelling approaches and is discussed in detail in section 5.

The population PK analysis (U12-2525) of empagliflozin in T2DM patients was described by a two-compartment model with first-order absorption. The empagliflozin PK data set comprised 2761 patients contributing a total of 12503 empagliflozin plasma concentrations, dosing and covariate data. The analysis population consisted of 1585 (57.4%) male patients and 1176 female patients. At the time of first dose, age ranged from 19 to 98 years, BMI ranged from 16.8 to 89.9 kg/m², Weight ranged from 39.9 to 169 kg, and eGFR ranged from 15.3 to 234 mL/min/1.73 m². As expected, baseline BMI and weight were highly correlated (Pearson's correlation = 0.845). The study population included 1539 (55.7%) White patients, 1138 (41.2%) Asian patients, 68 (2.46%) Black patients and 16 (0.580%) American Indian, Alaska Native, or patients of other race. There were 1623 (58.8%) non-Asian subjects in the study population. Empagliflozin doses ranged from 1 to 100 mg, with 1129 patients (40.9%) receiving 10 mg empagliflozin and 1269 patients (46.0%) receiving 25 mg empagliflozin. Patients receiving placebo treatment were not included in the population PK analysis.

Variability in empagliflozin CL=F and AUC_{ss} was primarily affected by BMI, eGFR, TPRO, age, female sex, and Asian race; empagliflozin exposure was increased in females, with increasing age, Asian race and with lesser BMI. Under the PK model, typical CL=F and AUC_{ss} values were generally within 75 to 125% of the reference group value across the range of most commonly observed covariate values. 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

³ Majority of the subjects were white males, with a mixture of smoking history and alcohol consumption. Subject age ranged from 20 to 69 years, but was notably lower in the Phase I Studies 1245.1 (median = 38 years) and 1245.5 (median = 26 years) relative to multiple-dose Studies 1245.2 and 1245.4 (median = 58 years for both). Body weight ranged from 53 to 123 kg and was similar in the non-Japanese studies, whereas Japanese subjects (Study 1245.5), on average, weighed 20 to 30 kg less than the other subjects. The population PK of BI 10773 in Phase I subjects and early Phase II patients was described by a two-compartment model with lagged first-order oral absorption.

mL/min/1.73m². Other covariates tested included smoking status and liver enzymes (LDH, AST, ALT, and AP) and these did not have a significant effect on the PK of empagliflozin.

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

4.2.4.1.1. Drug interactions with other oral anti-diabetic drugs

Metformin: The Phase I, open label, randomised, multiple-dose, crossover study 1245.6 evaluated the PK interactions following multiple dosing with empagliflozin 50mg OD, metformin 1000mg twice daily given in combination and alone. Co-administration with metformin did not affect empagliflozin exposure (AUC_{τ,ss} GMR: 96.88%; 90% CI: 92.29 to 101.70% and C_{max,ss} GMR: 100.45%; 90% CI: 88.76 to 113.70%) or the fraction of empagliflozin excreted in the urine (18.0% of dose when given alone and 18.4% when given in combination with metformin). Co-administration with empagliflozin did not affect metformin exposure (AUC_{τ,ss} GMR: 100.67%; 90% CI: 95.93 to 105.64% and C_{max,ss} GMR: 103.59%; 90% CI: 96.52 to 111.18%) or the fraction of metformin excreted in the urine (27.7% of dose when given alone and 26.6% when given in combination with empagliflozin). Intra-individual variability for AUC_{τ,ss} and C_{max,ss} was low for both empagliflozin and metformin. Consistent with the mode of action of empagliflozin, increased UGE was observed after administration of empagliflozin alone, and in combination with metformin. The mean (± SD) cumulative amounts of glucose recovered in urine after oral administration of empagliflozin with and without metformin were 62.0 g (± 12.8 g) and 67.8 g (± 12.6 g), respectively.

Glimepiride: The results of study 1245.7 demonstrated that there is no drug-drug interaction between BI 10773 and glimepiride following multiple daily doses of 50 mg BI 10773 (for 5 days) and a single dose of 1 mg glimepiride in 16 healthy volunteers. Glimepiride co-administration had no effect on the PK of empagliflozin with respect to the standard BE boundaries of 80% to 125% (AUC_{τ,ss} GMR: 95.23; 90% CI: 92.03 to 98.54 and C_{max,ss} GMR: 95.55; 90% CI: 88.24 to 103.46). Intra-individual gCV% of empagliflozin between treatments was low for both AUC_{τ,ss} and C_{max,ss}. The urinary excretion of empagliflozin was not affected by co-administration of glimepiride (mean fe_{0-24,ss}: 20.0% when dosed alone versus 20.5% when co-administered). Co-administration of empagliflozin with glimepiride had no effect on the PK of glimepiride (AUC_{0-∞} GMR: 93.26; 90% CI: 86.08 to 101.04 and C_{max} GMR: 104.18; 90% CI: 89.47 to 121.30). Intra-individual gCV% of glimepiride between treatments was low for both AUC_{0-∞} and C_{max}. The mean (± SD) cumulative amounts of glucose recovered in urine over 24 h after oral administration of 50 mg BI 10773 once daily with and without 1 mg glimepiride were 72.7 g (± 14.4 g) and 68.7 g (± 12.3 g), respectively. The mean (± SD) cumulative amount of glucose excreted in urine following oral administration of 1 mg glimepiride alone was 0.059 g (± 50.5 mg).

Comments: This study only evaluated drug interaction following single dose of glimepiride.

Pioglitazone: Study 1245.17 evaluated drug-drug interaction between empagliflozin (50mg od) and pioglitazone (45mg od) following co-administration of multiple oral doses of both drugs. Peak plasma levels of empagliflozin were reached at 1.7 h when administered alone, and at 2 h when co-administered with pioglitazone. There were no differences in empagliflozin exposure when it was administered alone or with pioglitazone. GMRs were 100.32 (90% CI: 96.08 to 104.75) for AUC_{τ,ss} and 93.44 (90% CI: 85.08 to 102.62) for C_{max,ss}. In addition, the increased urinary glucose excretion observed with BI 10773 administration was not affected by pioglitazone coadministration. The total amounts of glucose excreted in urine were similar when BI 10773 was administered with and without pioglitazone (77.5 g and 74.9 g). Pioglitazone was rapidly absorbed reaching peak levels approximately 1.75 h after oral administration. Thereafter, plasma levels declined in a biphasic fashion. After multiple daily doses, pioglitazone exposure reached steady state by Day 7. The t_{1/2,ss} of pioglitazone decreased when co-administered with empagliflozin (15.6 versus 7.9 h). Exposure of pioglitazone was higher when co-administered with 50 mg empagliflozin than when given alone; GMRs were 157.97 (90% CI: 148.02 to 168.58) for AUC_{τ,ss} and 187.89 (90% CI: 166.35 to 212.23) for

$C_{max,ss}$. Exposure of the pioglitazone metabolites M-III and M-IV also increased when pioglitazone was co-administered with empagliflozin, contributing to an increase in overall exposure of active moieties by approximately 36% following co-administration with empagliflozin, compared to administration of pioglitazone alone (47900 versus 35330 ng.h/mL).

In a subsequent Phase I open label, parallel group study 1245.50, at steady state, both the extent of exposure and the rate of absorption of pioglitazone were lower when pioglitazone was given with BI 10773 (10mg, 25mg and 50mg od) compared with pioglitazone alone. The GMR for pioglitazone $AUC_{\tau,ss}$ and $C_{max,ss}$ ranged from 88% to 91%. The lower limits of 90% CIs for both parameters ranged from 67% to 78%, below the standard bioequivalence boundaries. Pioglitazone exposure ($C_{max,ss}$ and $AUC_{\tau,ss}$) at steady state following administration of pioglitazone alone was similar to that observed in the previous study (trial 1245.17). The $t_{1/2,ss}$ (Day 7) was similar to that observed after the first dose (11.3 h and 10.8 h, respectively), indicating linear PK with respect to time. Consistent with the $t_{1/2,ss}$, approximately 20% accumulation was observed at steady state when pioglitazone was administered alone, while accumulation of pioglitazone was only 3 to 5% when administered with empagliflozin. As a result, although pioglitazone exposure after a single dose was similar when given with or without empagliflozin, exposure of pioglitazone at steady state was slightly lower when pioglitazone was co-administered with empagliflozin than when given alone. This reduction could be explained by the higher oral clearance and higher volume of distribution of pioglitazone seen in this trial after co-administration with BI 10773. With regard to the active pioglitazone metabolites M-III and M-IV, the extent of exposure ($AUC_{\tau,ss}$) of both metabolites was similar when pioglitazone was given with and without BI 10773. The GMRs of $AUC_{\tau,ss}$ ranged from 95% to 101% and the 90% CIs fell within the standard bioequivalence boundaries.

Comments: The sponsors have stated that pioglitazone is available in multiple dose strengths (15 mg, 30 mg and 45 mg for once daily administration) and incremental dose titration is recommended for patients not responding to monotherapy, suggesting that there may be some variability in exposure over this dose range. Studies of other agents given in combination with pioglitazone have also noted changes in the PK of pioglitazone, which were not considered to warrant dose adjustment. For example, exposure of a single 15 mg dose of pioglitazone increased more than 3 fold when co-administered with the fibrate gemfibrozil but no dose adjustment of pioglitazone is recommended when it is co-administered with gemfibrozil. Co-administration of linagliptin with pioglitazone had no effect on pioglitazone $AUC_{\tau,ss}$, but reduced $C_{max,ss}$ by 14% which did not warrant dose adjustment. Available epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone; while a causal relationship between empagliflozin and bladder cancer is unlikely due to inconsistent results across the 2 PK studies described above, it would be prudent to exercise caution during co-administration of empagliflozin with pioglitazone in treatment of T2DM.

DPP-4 inhibitors: Study 1245.27 evaluated PK-PD interaction following multiple oral doses of sitagliptin (100mg od) alone and in combination with BI10773 (50mg OD). Sitagliptin co-administration had no clinically relevant effect on empagliflozin exposure ($AUC_{\tau,ss}$ GMR: 110.39; 90% CI: 103.91 to 117.27 and $C_{max,ss}$ GMR: 107.61; 90% CI: 97.01 to 119.37). Intra-individual gCV% between the treatments was low for both $AUC_{\tau,ss}$ (9.8%) and $C_{max,ss}$ (16.9%) of empagliflozin. The urinary excretion of empagliflozin was not affected by co-administration with sitagliptin (17.1% of dose without versus 19.3% of dose with co-administration). Co-administration of empagliflozin with sitagliptin had no effect on sitagliptin exposure ($AUC_{\tau,ss}$ GMR: 103.06; 90% CI: 98.97 to 107.34 and $C_{max,ss}$ GMR: 108.48; 90% CI: 100.68 to 116.88). Increased UGE was observed after administration of empagliflozin alone and in combination with sitagliptin (73.4 g and 62.6g, respectively).

4.2.4.1.2. *Other drug interaction studies:*

In study 1245.18, co-administration with warfarin had no effect on the PK of empagliflozin and the Intra-individual variability was low for both $AUC_{\tau,ss}$ and $C_{max,ss}$; gCV% values were 7.0%

and 19.9%, respectively. Co-administration with empagliflozin had no effect on the PK of warfarin and the Intra-individual variability was low for $AUC_{0-\infty}$ and C_{max} ; $gCV\%$ values were 5.7% and 12.4%, respectively, for R-warfarin and 4.5% and 12.7%, respectively, for S-warfarin.

In study 1245.40, the mean plasma concentration-time profiles of digoxin were similar when administered alone or with empagliflozin following administration of single dose of digoxin (0.5mg) with multiple dosing of empagliflozin (25mg od). Co-administration with empagliflozin had no relevant effect on the $AUC_{0-\infty}$ (GMR: 106.11%; 90% CI: 96.71 to 116.41%) of digoxin and resulted in a slight increase in digoxin C_{max} (GMR: 113.94%; 90% CI: 99.33 to 130.70%). Digoxin t_{max} and $t_{1/2}$ were similar whether administered alone or with empagliflozin. Mean CLR of digoxin was similar with and without co-administration of empagliflozin (139 mL/min and 153 mL/min, respectively), as was mean fe_{0-96} (40.1% and 40.6%, respectively).

Comments: Empagliflozin is a substrate for P-gp but does not inhibit P-gp activity in vitro. Inhibition of P-gp by empagliflozin in vivo is considered unlikely. The study was carried out with multiple oral dosing of empagliflozin in order to maintain steady state conditions of empagliflozin at the time of digoxin administration and through the entire sampling period. It enabled a more reliable estimation of any potential effect of empagliflozin on digoxin absorption and disposition. The effects of digoxin on the PK-PDs of empagliflozin were not evaluated in this study.

An open label, two period, fixed sequence study (1245.41) showed that the steady state PK of EE and LNG were not affected by co-administration with empagliflozin (25mg od) in 18 healthy premenopausal women. When Microgynon was given with and without empagliflozin, the mean $AUC_{\tau,ss}$ of ethinylestradiol was 956 versus 932 pg·h/mL and the mean $C_{max,ss}$ was 99 pg/mL in both treatments; the mean $AUC_{\tau,ss}$ of levonorgestrel was 102 versus 99.6 ng·h/mL and the mean $C_{max,ss}$ was 8.71 vs 8.24 ng/mL. The plasma concentration time profiles and other PK parameters of both ethinylestradiol and levonorgestrel were similar in both treatments.

Comments: A fixed sequence study design was chosen to ensure that PK parameters were determined at the same time point in the menstrual cycle of all subjects. The effect of oral contraceptives on the PK-PDs of empagliflozin was not evaluated.

Study 1245.43 evaluated the relative bioavailability of a single dose of empagliflozin (25mg) when given alone compared with co-administration with a single dose of the model P-gp inhibitor verapamil (120mg). PKs of empagliflozin were similar when empagliflozin was administered alone or with verapamil ($AUC_{0-\infty}$ GMR: 102.95%; 90% CI: 98.87 to 107.20% and C_{max} GMR: 92.39%; 90% CI: 85.38 to 99.97%). These results demonstrate that there is no relevant effect of P-gp inhibition on the pharmacokinetics of BI 10773. Therefore, no dosage adjustment of BI 10773 is required when prescribed concomitantly with a P-gp inhibitor in clinical practice.

Comments: The effect of empagliflozin on PKs of verapamil was not evaluated.

In study 1245.45, the PKs of empagliflozin were similar when empagliflozin was administered alone or with ramipril. Based on standard BE boundaries of 80% to 125%, the PK of empagliflozin ($AUC_{\tau,ss}$ GMR: 96.55; 90% CI: 93.05 to 100.18; $C_{max,ss}$ GMR: 104.47; 90% CI: 97.65 to 111.77) were not affected by co-administration with ramipril. Mean plasma concentration time profiles of ramipril and ramiprilat (an active metabolite of ramipril) were comparable when ramipril was given alone or with empagliflozin. The PK of ramipril and ramiprilat were similar when ramipril was administered alone or with empagliflozin. The PKs of ramipril ($AUC_{\tau,ss}$ GMR: 108.14; 90% CI: 100.51 to 116.35; $C_{max,ss}$ GMR: 103.61; 90% CI: 89.73 to 119.64) and ramiprilat ($AUC_{\tau,ss}$ GMR: 98.67; 90% CI: 96.00 to 101.42; $C_{max,ss}$ GMR: 98.29; 90% CI: 92.67 to 104.25) were not affected by co-administration with empagliflozin. The results indicate that there was no clinically relevant PK interaction between empagliflozin and ramipril.

In study 1245.58, empagliflozin exposure was higher when co-administered with gemfibrozil compared to empagliflozin alone; $AUC_{0-\infty}$ of empagliflozin was roughly 59% higher (GMR: 158.50%; 90% CI: 151.77 to 165.33%) during the combined treatment than during treatment

with empagliflozin alone. Although the C_{max} of empagliflozin was numerically higher during the combined treatment than during treatment with empagliflozin, the GMR of 115.00% and the corresponding 90% CI of 106.15% to 124.59 % were within the standard BE range.

Comments: The observed increase in the overall exposure of empagliflozin was less than 2 fold and was not considered to be clinically relevant and the sponsors recommend no dosage adjustment of empagliflozin when administered concomitantly with gemfibrozil. However, due to the almost 60% increase in exposure it is recommended that gemfibrozil should be administered with caution during treatment with empagliflozin.

Results from study 1245.63 indicate that there is no clinically relevant drug-drug interaction between empagliflozin (25mg) and simvastatin (40mg) and no dose adjustments for either drug are necessary when co-administered. The PK of empagliflozin were similar after co-administration with simvastatin compared with empagliflozin alone. Plasma concentration time profiles of simvastatin were similar after co-administration with empagliflozin compared with simvastatin alone. Minor deviations from standard BE boundaries were observed for simvastatin AUC_{0-∞} (GMR: 101.26; 90% CI: 80.06 to 128.07) and C_{max} (GMR: 97.18; 90% CI: 76.30 to 123.77) after co-administration of simvastatin with empagliflozin compared with simvastatin alone. However, simvastatin is a prodrug and the PK of its active metabolite, simvastatin acid were similar following co-administration of simvastatin with empagliflozin compared with simvastatin alone.

Comments: Drug interactions were only evaluated following single dosing with both empagliflozin and simvastatin and PK-PD interactions at steady state levels following multiple dosing were not evaluated.

In study 1245.83, co-administration with OAT1B inhibitor, rifampicin led to an increase in empagliflozin AUC_{0-∞} by approximately 35% (GMR: 135.20; 90% CI: 129.58 to 141.06) and C_{max} by 75% (GMR: 175.14; 90% CI: 160.14 to 191.56) compared with empagliflozin alone. Co-administration with OAT3 inhibitor, probenecid led to an increase in empagliflozin AUC_{0-∞} by approximately 53% (GMR: 153.47; 90% CI: 146.41 to 160.88) and C_{max} by 26% (GMR: 125.60; 90% CI: 113.67 to 138.78) compared with empagliflozin alone. Intra-individual variability between the treatments was low for both AUC_{0-∞} and C_{max}. The 35 to 53% increase in empagliflozin exposure following concomitant administration of single doses of empagliflozin 25 mg and rifampicin and probenecid is not clinically relevant and no dosage adjustments are required.

Comments: The PK-PD interaction at steady state following multiple dosing was not evaluated.

4.2.4.2. *Clinical implications of in vitro findings*

In vitro investigations were also carried out to evaluate reversible inhibition of the major human CYP450 isoforms, that is, CYP450s 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4, by empagliflozin. All IC₅₀ values for these CYP450 enzymes were > 50 μM. Additionally, IC₅₀ values for reversible inhibition of CYP2C8 and CYP3A4 by the three glucuronide metabolites of empagliflozin were all > 20 μM. Empagliflozin did not inactivate CYP450 isoforms 2C8, 2C9, 2D6, and 3A4 at concentrations up to 100 μM. Additionally, the three glucuronide metabolites of empagliflozin did not inactivate CYP2C8 and CYP3A4 at concentrations up to 100 μM. Using human liver microsomes, it was determined that the IC₅₀ value for inhibition of human UGT1A1 by empagliflozin was > 50 μM. Thus, at the highest planned therapeutic dose of 25 mg (mean C_{max,ss}: 687 nmol/L and AUC_{τ,ss}: 4740 nmol.h/L; trial 1245.4), the potential for empagliflozin to reversibly inhibit or inactivate the major CYP450 isoforms, or inhibit UGT1A1, is low. As such, DDIs involving the major CYP450 isoforms or UGT1A1 with empagliflozin and concomitantly administered substrates of these enzymes are considered unlikely.

4.3. Evaluator's overall conclusions on pharmacokinetics

All the PK studies were well conducted, compliant with guidelines and used validated analytical methods. The pharmacokinetics of empagliflozin have been extensively characterised in healthy volunteers and patients with T2DM.

In healthy volunteers, empagliflozin showed linear PK characteristics following single oral doses over the dose range from 0.5 mg to 800 mg. Empagliflozin was rapidly absorbed reaching peak levels after a median t_{max} of 1 to 2 h. After reaching peak levels, plasma concentrations declined in a biphasic fashion with a rapid distribution phase and a slower elimination phase. The mean $t_{1/2}$ for doses 10 mg and above ranged from approximately 10 to 13 h. The proportion of drug excreted unchanged in urine over 72 h post-dose ranged from approximately 11 to 19% of dose. Renal clearance of empagliflozin ranged from 32 to 51 mL/min. Over the dose range studied, empagliflozin exposure ($AUC_{0-\infty}$ and C_{max}) increased in a roughly dose proportional manner (study 1245.1).

The PKs of empagliflozin were similar after a single dose and after multiple doses at steady-state. After multiple oral dosing, empagliflozin reached steady-state by Day 5. At steady-state, peak levels were achieved at a median t_{max} of 1.5 h post-dose and, thereafter, plasma concentrations declined in a biphasic manner. The $t_{1/2}$ of empagliflozin at steady state, after 4 weeks of treatment, was similar to that observed with single doses indicating linear PK with respect to time. The mean steady state $t_{1/2}$ with 10 mg and 25 mg empagliflozin once daily (qd) was approximately 13 h. Consistent with $t_{1/2}$, up to 22% drug accumulation, in terms of overall exposure (AUC), was observed at steady-state. The proportion of unchanged parent compound excreted in urine at steady state was independent of the dose and averaged approximately 18% of dose. Renal clearance of empagliflozin at steady state ranged from 36 to 37 mL/min. Empagliflozin exposure increased proportionally with an increase in dose over the dose range 2.5 to 100 mg after repeated dosing at steady state (studies 1245.2 and 1245.4).

There were no clinically relevant differences in empagliflozin pharmacokinetics between healthy volunteers and patients with T2DM.

Absorption: After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations (C_{max}) with a median time to reach C_{max} (t_{max}) of 1.5 h post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma area under the curve (AUC) was 4740 nmol.h/L and C_{max} was 687 nmol/L with 25 mg empagliflozin once daily. Systemic exposure of empagliflozin increased in a dose proportional manner. The single dose and steady state PK parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time. Administration of 25 mg empagliflozin after intake of a high-fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and C_{max} decreased by approximately 37%, compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

Distribution: The apparent steady state volume of distribution was estimated to be 73.8 L, based on a population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, the RBC partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Metabolism: No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug related material. In vitro studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Elimination: The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic

analysis. The inter-subject and residual variabilities for empagliflozin oral clearance were 39.1% and 35.8%, respectively. With once daily dosing, steady state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady state. Following administration of an oral [¹⁴C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug related radioactivity was eliminated in faeces (41.2%) or urine (54.4%). The majority of drug related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Dose proportionality: Empagliflozin exposure increased in a roughly dose proportional manner over the dose range 0.5 mg to 800 mg following single oral administration in healthy volunteers (trial 1245.1). 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 PK characteristics of empagliflozin were similar after multiple dosing at steady-state compared to single dose suggesting that empagliflozin demonstrates linear PK (trial 1245.2). Consistent with these findings, increases in empagliflozin exposure were proportional to dose at steady state.

Bioequivalence between CT and final marketing formulation: All 3 formulations used in the empagliflozin clinical development program had the same qualitative composition. TF-I and TF-II were uncoated tablets, and FF is a film coated tablet with a hypromellose based standard film coat. In vitro dissolution profiles depict immediate release characteristics and were similar for TF-II and FF. Bioequivalence between the proposed commercial formulation and the TF-II formulation used in earlier clinical trials was demonstrated unequivocally. The 90% confidence intervals for the geometric mean ratios of both AUC_{0-∞} and C_{max} were within the standard bioequivalence criteria of 80% to 125%.

PKs in special patient populations: The PKs of empagliflozin has not been evaluated in the paediatric population. Based on population PK analysis, there were no changes in empagliflozin PKs in elderly patients; gender, race, BMI also did not have any clinically relevant effect on empagliflozin PKs.

In patients with mild (eGFR: < 90 mL/min/1.73 m²), moderate (eGFR: < 60 mL/min/1.73 m²), severe (eGFR: <30 mL/min/1.73 m²) renal impairment and patients with kidney failure/ESRD patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to patients with normal renal function (eGFR: > 90 mL/min/1.73 m²). Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Plasma C_{max} of empagliflozin was roughly 20% higher in subjects with mild and severe renal impairment as compared to patients with normal renal function. In line with the Phase I study 1245.12, the population PK analysis showed that the apparent oral clearance of empagliflozin decreased significantly with a decrease in eGFR leading to an increase in drug exposure. The changes in AUC_{τ,ss} were +18.5%, +49.2%, and +88.1% for patients with eGFR of 60, 30, and 15 mL/min/1.73 m², respectively, compared to patients with a eGFR of 100 mL/min/1.73 m². The changes are not considered clinically relevant and, based on PK, no dosage adjustment is recommended in patients with renal insufficiency. However, because of the lack of efficacy in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²), empagliflozin is not recommended for these patients (study 1245.36, section 7).

In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased approximately by 23%, 47%, and 75% and C_{max} by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function. The population PK analysis showed that elevations of liver enzyme levels (AST, ALT, AP, and LDH) had no statistically significant impact on the apparent oral clearance of empagliflozin. The observed changes in empagliflozin exposure are not considered clinically relevant and, based on PK, no dosage adjustment is recommended in patients with hepatic impairment.

Drug interactions: Empagliflozin PK characteristics were similar with and without co-administration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, simvastatin, warfarin, verapamil, ramipril, hydrochlorothiazide, and torasemide. Empagliflozin exposure (AUC) increased by 1.59 fold following co-administration with gemfibrozil, 1.35 fold with rifampicin, and 1.53 fold with probenecid. The observed increases in the overall exposure of empagliflozin were not considered to be clinically relevant and no dosage adjustment of empagliflozin is recommended when administered concomitantly with gemfibrozil, rifampicin, or probenecid. Empagliflozin had no clinically relevant effect on the PK of metformin, glimepiride, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, hydrochlorothiazide, torasemide, and oral contraceptives when co-administered.

The effects of smoking, diet, herbal products, and alcohol use on the pharmacokinetics of empagliflozin have not been specifically studied.

Two studies (1245.17 and 1245.50) investigated PK drug interactions between empagliflozin and pioglitazone (and its active metabolites) and showed contrasting results. Due to inconsistent results across the 2 studies, it would be prudent to exercise caution during co-administration of empagliflozin with pioglitazone in treatment of T2DM. Available epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone. While a causal relationship between empagliflozin and bladder cancer is unlikely (see Adverse Events), as a precautionary measure, empagliflozin should not be recommended for use in patients concomitantly treated with pioglitazone (similar to PI for dapagliflozin).

Overall, the PK characteristics of empagliflozin are stable, relatively free from interference by subject characteristics or external factors and not prone to interaction with co administered drugs.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 3 below shows the studies relating to each pharmacodynamic.

Table 3: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	PK-PD study effect on urinary glucose excretion and glucose control	1254.2 1254.4
Secondary Pharmacology	Effect on QT interval	1245.16
Gender other genetic and Age-Related Differences in PD Response	Effect of race- in Japanese subjects	1245.15
	Effect of age	None
	Effect of gender	None
	Effect of genetic characteristic	None
PD Interactions	HCTZ or toresemide	1245.42
Population PD and PK-PD	Healthy subjects	None

PD Topic	Subtopic	Study ID
analyses	Target population	U12-2524

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

Empagliflozin is a reversible, highly potent and selective competitive inhibitor of SGLT2 with an IC₅₀ of 1.3 nM. It has a 5000 fold selectivity over human SGLT1 (IC₅₀ of 6278 nM), responsible for glucose absorption in the gut. Furthermore high selectivity could be shown toward other glucose transporters (GLUTs) responsible for glucose homeostasis in the different tissues. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible as the predominant transporter for re-absorption of glucose from the glomerular filtrate back into the circulation. In patients with T2DM and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with T2DM by reducing renal glucose re-absorption. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and glomerular filtration rate (GFR). Through inhibition of SGLT2 in patients with T2DM and hyperglycaemia, excess glucose is excreted in the urine. In patients with T2DM, urinary glucose excretion increased immediately following the first dose of empagliflozin and is continuous over the 24 hour dosing interval. Increased urinary glucose excretion was maintained at the end of 4-week treatment period, averaging approximately 78 g/day with 25 mg empagliflozin once daily. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with T2DM. Empagliflozin improves both fasting and post-prandial plasma glucose levels.

The insulin independent mechanism of action of empagliflozin contributes to a low risk of hypoglycaemia. The effect of empagliflozin in lowering blood glucose is independent of beta cell function and insulin pathway. Improvement of surrogate markers of beta cell function including Homeostasis Model Assessment- β (HOMA- β) and proinsulin to insulin ratio were noted. In addition urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction. The glucosuria observed with empagliflozin is accompanied by mild diuresis which may contribute to sustained and moderate reduction of blood pressure (BP).

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

In the Phase I study 1245.2, oral administration of empagliflozin increased UGE above the level of placebo, with both the amount and rate of glucose excretion increasing with dose. After a single dose under OGTT conditions, the amount of glucose excreted in the urine over 24 h was 46.3 g with 2.5 mg empagliflozin compared with 5.84 g with placebo. Glucose excretion seemed to plateau after the 10 mg dose, with total cumulative amounts excreted ranging from 75.5 mg to 93.0 g with 10 to 100 mg empagliflozin. Similar results were observed after multiple doses with or without OGTT. The effect of empagliflozin treatment on lowering FPG increased with treatment duration. The mean decrease in FPG from baseline (Day -1) to Day 9 ranged from 17.2% to 25.8% with empagliflozin, compared with 12.7% with placebo. A decrease in plasma glucose levels was also observed following OGTT immediately after the first dose. The mean decrease in mean daily glucose (MDG) from baseline was 24.1% to 37.0% with empagliflozin,

compared with 13.5% for placebo (comparison of Day 8 [without OGTT] with baseline [Day -2]). Serum insulin levels did not change to a relevant degree.

In study 1245.4, after administration of multiple oral doses of BI 10773 (10, 25 and 100mg OD) for 28 days, the cumulative amount of UGE in 24 h increased sharply with 10 mg BI 10773 and remained elevated with 25 mg and 100 mg BI 10773 with similar increase in UGE under OGTT conditions (Day 28). The cumulative amount of glucose excreted in urine was similar with and without OGTT (Day 28 versus Day 27). Both mean area under the effect time curve (AUEC₀₋₂₄) and Emax values of glucose were lower at Day 27 than at baseline in all dose groups including placebo. Plasma glucose levels declined immediately after initiation of BI 10773 treatment (Day 1) and decreased further with multiple dosing (Day 27). Reductions in glucose were greater in BI 10773 treated groups than in the placebo group with a similar trend observed on OGTT days. Similarly, relative reductions in mean FPG were greater with multiple oral doses of BI 10773 than with placebo.

In study 1245.15, 100 Japanese patients with T2DM were treated with single daily dose of empagliflozin (1, 5, 10 and 25mg OD) for 28 days. Adjusted mean changes from baseline to Day 27 in UGE increased with empagliflozin dose (40.8 g, 77.1 g, 80.9 g, 93.0 g and -2.1 g for the 1 mg, 5 mg, 10 mg, 25 mg empagliflozin and placebo groups, respectively). After the first and multiple drug administrations, even the lowest-dose group (the BI 10773 1 mg group) tested in this trial showed an apparent increase in the rate of UGE and this increased with doses up to 10 mg. The rates in the BI 10773 10 mg and 25 mg groups were similar. Adjusted mean changes from baseline to Day 28 in FPG also increased with dose (-28.1 mg/dL, -35.4 mg/dL, -41.6 mg/dL, -42.7 mg/dL and -15.4 mg/dL for the 1 mg, 5 mg, 10 mg, 25 mg empagliflozin and placebo groups, respectively). Adjusted mean changes from baseline to Day 27 in 8-point glucose profile⁴ decreased dose dependently in all empagliflozin groups (-35.3 mg/dL, -39.9 mg/dL, -43.6 mg/dL, -45.7 mg/dL and -17.4 mg/dL for the 1 mg, 5 mg, 10 mg, 25 mg empagliflozin and placebo groups, respectively). Differences between the BI 10773 groups and the placebo group for UGE, FPG and 8-point glucose profile were statistically significant in favour of empagliflozin (ANCOVA: p<0.0001). The adjusted mean changes from baseline (Day -1) in HbA1c on Day 28 were -0.66%, -0.72%, -0.85%, -0.82%, and -0.42% in the BI 10773 1mg, 5mg, 10mg, 25 mg and placebo groups, respectively. Differences in decreases between the BI 10773 5 mg, 10 mg, or 25 mg group and the placebo group were statistically significant (ANCOVA: p = 0.0014 to 0.0203), although the changes were similar between the BI 10773 10 mg and 25mg groups. Likewise, in the analyses with the model including the previous antidiabetic medication use as a fixed effect, differences in decreases between the BI 10773 groups and the placebo group were statistically significant on Day 28 (ANCOVA: p = 0.0005 to 0.0397).

Comments: Due to short duration of trial (only 4 weeks), HbA1c results should be interpreted with caution.

5.2.2.2. Secondary pharmacodynamic effects

In study 1245.16, single oral doses of 25 mg (therapeutic) and 200 mg (supra-therapeutic) empagliflozin were not associated with a QT(c) interval prolongation. The placebo corrected adjusted mean changes from baseline in QTcN between 1 h and 4 h after dosing were 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. Thus, the upper 90% confidence limits for the mean differences to placebo over the time interval 1 h to 4 h were clearly within the non-inferiority margin of 10 ms. The placebo corrected adjusted mean changes from baseline in QTcN at any point in time between 0.5 and 24 h after dosing ranged from -2.67 ms to 2.16 ms for 25 mg empagliflozin and from -1.76 ms to 1.59 ms for 200 mg empagliflozin. The maximum effects reached 2.16 ms (90% CI: -0.34, 4.67) at 24 h after dosing of 25 mg empagliflozin and 1.59 ms (90% CI: -0.35, 3.53) at 2.5 h after

⁴ An eight-point glucose profile was estimated by dividing the area under the 24-h glucose curve (AUEC₀₋₂₄) by 24.

dosing of 200 mg empagliflozin. Overall, the upper 90% CIs of the placebo corrected means of the QTcN change from baseline were within the non-inferiority margin of 10 ms according to ICH E14 guidelines.

In addition to plasma glucose and UGE, insulin, 1,5-AG, fructosamine, and glucagon were monitored in several trials as exploratory biomarkers.

Insulin: Insulin is produced in the beta cells of the pancreas from the proinsulin precursor molecule by the action of proteolytic enzymes. Beta cells in the islets of Langerhans release insulin in two phases in response to a meal. The first phase insulin release is rapidly triggered in response to increasing blood glucose concentrations. The second phase is a sustained, slow release of newly formed vesicles in response to the absolute blood glucose values. Once released, insulin decreases blood glucose concentrations by stimulation of glucose uptake into cells, inhibiting glucose production in the liver, activating glycogen synthesis and activating glycolysis. As empagliflozin reduces plasma glucose levels via an (insulin-independent) increase in urinary glucose excretion, treatment with empagliflozin was expected to reduce insulin and C-peptide levels.

Empagliflozin administration did not have any relevant effect on serum insulin levels following multiple oral dosing of empagliflozin, serum insulin levels on Day 8 in the 1245.2 study and after 4-week treatment in the 1245.4 study were similar to baseline values. In study 1245.15, differences in the area under the curve of insulin (AUEC₁₋₅) and predose insulin levels (Epre) from baseline to Day 28 between the BI 10773 10 mg or 25 mg group and the placebo group were statistically significant, whereas no trend was seen between a dose and peak insulin levels (E_{max}).

In two of the pivotal Phase III trials (1245.20 and 1245.23), biomarkers and derived indices were analysed and a treatment comparison was carried out using an ANCOVA based on the FAS (LOCF). In both trials, including both substudies of 1245.23, notable reductions from baseline after 24 weeks of treatment with empagliflozin (both doses) compared with placebo were observed for C-peptide and fasting plasma insulin. The disposition index increased in both empagliflozin groups compared with placebo. No differences from placebo were noted for the derived parameters proinsulin/insulin ratio, insulin/glucose ratio, and HOMA-IS.

1,5-Anhydroglucitol: 1,5-AG is a naturally occurring monosaccharide found in nearly all foods. After ingestion, 1,5-AG is not metabolized and is filtered by the kidney glomerulus. Once in the renal proximal tubules, 1,5-AG is nearly completely re-absorbed via a glucose transporter back into the blood. Thus glucose and 1,5-AG compete for reabsorption. In subjects with hyperglycemia, the high concentrations of glucose in the kidney block 1,5-AG from being reabsorbed and 1,5-AG is excreted in the urine at a higher rate than normal. Consequently 1,5-AG blood concentrations decrease with hyperglycemia and return to normal levels in approximately 2 weeks after plasma glucose concentration reach normal levels. 1,5-AG blood levels therefore reflect the average glucose levels over the last two weeks [R10-2438]. However, increased urinary glucose levels observed with SGLT-2 inhibitors may potentially inhibit reabsorption of 1,5-AG even under normoglycemic conditions. As such, reductions in plasma levels of 1,5-AG could be expected following treatment with empagliflozin.

In the 4-week study in Caucasian patients (1245.4), post-treatment data for 1,5-anhydroglucitol were missing in many patients in the PD set due to lipaemia or haemolysis. Of the patients with data, significant reductions from baseline compared with placebo were observed in all BI 10773 treatment groups on Day 28; no dose response relationship was observed. Following 4-week empagliflozin treatment in Japanese patients (study 1245.15), difference in decreases in the area under the curve 1,5-anhydroglucitol⁵ from baseline to steady state between the BI 10773

⁵ 1,5-anhydroglucitol values were missing in many patients with BI 10773 because these 1,5-anhydroglucitol measurements were below the limit of quantification (BLQ; <1.8 µg/mL). The frequency of patients with a missing value of 1,5-anhydroglucitol was greatest in the BI 10773 25 mg group.

groups and the placebo group were statistically significant; and the decreases were greater in the BI 10773 groups than in the placebo group.

Fructosamine: Fructosamine is formed when the carbonyl group of glucose reacts with an amino group of a protein, and is used to identify the plasma glucose concentration over time. Thus fructosamine reflects an average of blood glucose concentrations over an intermediate period of 2 to 3 weeks. Plasma concentrations of fructosamine were measured in two studies. In study 1245.15, decreases in fructosamine from baseline to Day 28 were greatest in the BI 10773 10 mg and 25 mg groups, but the difference between the BI 10773 groups and the placebo group were not statistically significant. In study 1245.4, 4 weeks treatment with empagliflozin did not produce any significant changes in fructosamine.

Glucagon: Glucagon is a hormone produced by the pancreas and is released when blood glucose concentrations fall below a threshold value. Glucagon induces the liver to convert stored glycogen into glucose as well as to produce glucose by gluconeogenesis if glycogen stores become depleted. Thus the action of glucagon is opposite to that of insulin. After a meal, glucagon secretion is suppressed in subjects with normal glucose control; however, this is often not well controlled in T2DM patients. Glucagon was measured in two studies; 4-week treatment in Caucasian patients (trial 1245.4) and 4-week treatment in Japanese patients (trial 1245.15). There were no consistent trends in changes observed in glucagon levels with empagliflozin treatment.

5.2.3. Time course of pharmacodynamic effects

In study 1245.4, plasma glucose levels declined immediately after initiation of BI 10773 treatment (Day 1) and decreased further with multiple dosing (Day 27) with similar results observed for FPG. The cumulative amount of UGE also increased after first day and was maintained till end of 4-week treatment period. In most of the empagliflozin studies, dosing was done in morning and there was no evaluation of effect of time of dosing (morning versus evening dosing) on the efficacy or safety of empagliflozin.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

In study 1245.2, the relationship between BI 10773 exposure and glucose excretion in urine was weak. After a single dose of BI 10773 (Day 1), both the amount of glucose excreted and the rate of glucose excretion increased slightly with increases in AUC_{0-24} and C_{max} and reached a plateau at 10 mg BI 10773. A similar trend was observed after multiple doses of BI 1003 (Day 9). Overall, increases in BI 10773 exposure reached a maximal effect on urinary glucose excretion at a dose of about 10 mg BI 10773.

In study 1245.4, after administration of multiple oral doses of BI 10773, the cumulative amount of UGE in 24 h increased sharply with 10 mg BI 10773 and remained elevated with 25 mg and 100 mg BI 10773. The amounts of UGE recovered after treatment with BI 10773 under OGTT conditions (Day 28) were similar to that observed when the drug was administered in the fasted state (Days 1 and 27). The cumulative amount of glucose excreted in urine was similar with and without OGTT (Day 28 versus Day 27). In all dose groups, BI 10773 resulted in increased UGE compared with placebo.

Reductions in glucose were greater in BI 10773 treated groups than in the placebo group. A similar trend was observed on OGTT days when comparing Day 28 with Day -1. Similarly, relative reductions in mean FPG were greater with multiple oral doses of BI 10773 than with placebo.

In study 1245.5, both $AUEC_{0-24}$ and $E_{max, 0-24}$ of glucose were similar among subjects treated with 1 to 100 mg BI 10773 and subjects treated with placebo; the increased UGE did not have a significant effect on plasma glucose levels. The total amount of UGE in 24 h (Ae_{0-24}) and 72 h (Ae_{0-72}) increased with BI 10773.

Treatment with empagliflozin at doses up to 25 mg qd for 4 weeks in Japanese patients with T2DM (study 1245.5) resulted in significant and clinically meaningful improvements in

glycemic control; however, improvements with 25mg were similar to those observed with the 10 mg empagliflozin dose.

5.2.5. Genetic, gender and age related differences in pharmacodynamic response

U12-2524 characterized the impact of empagliflozin on renal glucose threshold using population PK/PD modelling approaches and to estimate the effects of covariates, such as demographic and clinical factors, which may be important predictors of variability in empagliflozin PD parameters. The population data set was comprised of 223 subjects contributing 1,150 urine and 11,357 plasma glucose observation records, dosing and covariate data (age, weight, sex, race CrCL, eGFR). The typical estimates (95% CI) of PD model parameters for the reference covariate effects (58 years, Male, white race) were 374 (347, 391) mg/min for G_{max} , 144 (113, 163) mg/dL for K_m , 0.559 (0.545, 0.607) for I_{max} , 5.28 (3.53, 8.91) nmol/L for IC_{50} , and 0.999 (0.998, 0.999) for FRAC. Intersubject variability estimates (%CV) for G_{max} , FRAC, and I_{max} were 8.62%, 153%, and 12.2%, respectively. Proportional residual error was 47.3%. The final population PK/PD model describes well the observed UGE data and thereby characterises empagliflozin's impact on renal glucose threshold. The resultant renal threshold for glucose (RTG) in placebo subjects was 230 mg/dL. Steady-state empagliflozin doses (average plasma concentration) of 1 mg (8.6 nmol/L), 5 mg (42.9 nmol/L), 10 mg (85.8 nmol/L), and 25 mg (214.6 nmol/L) yielded RTG values of 100.5, 43.8, 33.1, and 26.0 mg/dL, respectively. The tested covariates sex, race, and age did not significantly explain the variability in the PD parameters. Population simulations demonstrated that empagliflozin doses of 10 and 25 mg qd are likely to be similarly effective in terms of UGE with both dose strengths achieving near maximal response. Population PD simulations also suggest that BID and QD dosing regimens are likely to confer equal UGE efficacy. Variability in empagliflozin I_{max} was not significantly explained by sex, race, or age. Unexplained random variability was for I_{max} was 12.2 CV% in the final model, compared to the base model estimate of 16.3 CV%.

In the population PK-PD analysis U12-2525, the empagliflozin PK-PD data set for exposure-FPG and HbA1c response modelling was comprised of 4289 patients (2761 on active empagliflozin therapy and 1528 on placebo) contributing a total of 25361. FPG observations and dosing and covariate data, and 4065 patients (2584 on active empagliflozin therapy and 1481 on placebo) contributing a total of 22012 HbA1c observations and dosing and covariate data. More subjects were available for FPG analysis since it included data from studies 1245.2, 1245.4 and 1245.15 in addition to the data sets included in HbA1c modelling. The maximal observed decrease in FPG appeared to occur within 1-2 weeks after initiation of empagliflozin treatment and was described as being dependent on exposure (AUC_{ss}). Covariate effects included on GMAX indicated that eGFR most notably impacted the empagliflozin exposure response relationship: relative to a reference eGFR of 100 mL/min/1.73 m², GMAX was estimated to decrease by -59.4 (-69.0, -45.9)%, -43.5 (-52.4, -32.3)%, -21.5 (-27.0, -15.3)%, and -12.8 (-16.3, -8.91)% for eGFR of 15, 30, 60, and 75 mL/min/1.73m², respectively. An approximate increase in GMAX of 24.1% (12.7, 36.2) was estimated with concomitant SU administration. Other concomitant medications (MET, PIO) did not significantly impact GMAX, nor did the duration of T2DM or Asian race, where a precise and non-significant parameter estimate was considered if the 95%CI contained the null value and was contained within the -25% minimal effect region. The imprecision of the covariate effect for Black race (-16.2% (-44.6, 15.0)) resulted in an inconclusive effect of Black race on empagliflozin exposure response. Females, although significantly lower than the reference GMAX, were estimated to have only a -10.4% (-16.5, -4.07) decrease in this parameter. The remaining covariate effects, BMI and age, were expected to only marginally impact empagliflozin exposure response through the GMAX parameter. Notably, though, these effects were independent of each other and eGFR. In addition, these effects were noted after accounting for their independent effects on exposure (PK) described above. Relative to a reference BMI of 25 kg/m², GMAX was expected to decrease by -21.6% (-33.0, -8.74), -13.0% (-20.5, -5.10), -7.29% (-11.7, -2.80) for BMI of 45, 35 and 30 kg/m², respectively; and increase by 9.70% (3.53, 16.4) for BMI of 20 kg/m². Similarly, relative to the reference age of 50 years, GMAX was expected to decrease by -16.1% (-22.9, -8.41) and -10.7% (-15.5, -5.53) for ages of 75 and 65, respectively, and increase by 4.66% (2.31, 6.99) and 16.7% (8.03, 25.7) for ages of 45 and 35

years, respectively. Interindividual variability for BFPG and GMAX, and FPG residual variability estimates (CV%) were 12.9%, 50.7%, and 15.7%, respectively.

Overall, the FPG and corresponding HbA1c responses were dependent on drug exposure and the baseline FPG. For example, the predicted maximal decreases (steady-state) in FPG and HbA1c at the reference baseline FPG (8 mM, 144 mg/dL) were 1.6 mM (20%), or 28.8 mg/dL, and 0.8 percentage points, respectively. This reference baseline FPG (8 mM, 144mg/dL) equated to a baseline HbA1c of 8.0%. In addition, targets of 80% and 90% of the maximal response after 24 weeks of treatment for FPG and HbA1c were obtained by empagliflozin doses of approximately 10 and 25 mg, respectively, based on the AUC₅₀ estimate. Therefore, although both doses were expected to provide near maximal responses, the 25 mg QD dose of empagliflozin may provide additional HbA1c lowering. For example, the median HbA1c was predicted to decrease by -0.62% (10 mg) and -0.71% (25 mg) after 24 weeks of empagliflozin treatment for a baseline HbA1c of 8.0% in the typical patient.

Adverse event/tolerability exposure response: There were 4065 patients available in the safety/ tolerability data set (2584 on active empagliflozin therapy and 1481 on placebo). Overall, safety/ tolerability event rates were 8.09% (n = 329) for urinary tract infection, 2.85% (n = 116) for genital infection, and 11.5% (n = 466) for hypoglycemia. Exposure response logistic regressions were adjusted for other, non exposure related covariates (including age, gender, race, renal function category, and concomitant anti-diabetic medications) to allow a valid determination of the odds ratio for empagliflozin. Compared to placebo treated patients, there was an increase in odds of genital infection for being on active empagliflozin treatment (odds ratio: 5.08 (95% CI: 2.77, 9.34)), but no significant change in odds of urinary tract infection (odds ratio: 0.941 (95% CI: 0.687, 1.29)); or hypoglycemia (odds ratio: 1.1 (95% CI: 0.811, 1.52)). Given that a patient was on active treatment, neither hypoglycemia nor urinary tract infection rates changed significantly with changes in empagliflozin exposure (hypoglycemia: odds ratio for 3500 nmol.h/L increase in AUC_{τ,ss}: 1.01 (95% CI: 0.881, 1.16); urinary tract infection: 1.06 (95% CI: 0.935, 1.20)). Genital infection rate decreased with increasing empagliflozin exposure (odds ratio for 3500 nmol.h/L increase in AUC_{τ,ss}: 0.744 (95% CI: 0.574, 0.965)). In conclusion, the analysis revealed no statistically significant increases in the incidence of urinary tract infection, genital infection, and hypoglycemia with empagliflozin exposure for patients treated with empagliflozin.

5.2.6. Pharmacodynamic interactions

In study 1245.18, co-administration with empagliflozin had no clinically relevant effect on the anticoagulant effects of warfarin. The GMR (95% CI) (empagliflozin + warfarin to warfarin) for peak prothrombin time (PT) and International Normalized Ratio (INR) were 0.90 (0.79, 1.02) and 0.87 (0.73, 1.04), respectively. The GMR (95% CI) for AUEC₀₋₁₆₈ of PT and INR were 0.91 (0.84, 0.98) and 0.88 (0.79, 0.98), respectively. The small differences observed between the PT_{max}, PT AUEC₀₋₁₆₈, INR_{max} and INR AUEC₀₋₁₆₈ values when warfarin was administered with empagliflozin were not considered clinically relevant.

The Phase I study 1245.42 in 20 T2DM patients evaluated the effect of empagliflozin, given alone and with hydrochlorothiazide (HCT) or torasemide (TOR) on changes in serum and urine electrolytes, water balance, activation of the renin-angiotensin-aldosterone system (RAAS), acid base balance, glucose metabolism, bone metabolism, body weight urine volume and micturition frequency. Treatment with single and multiple doses of empagliflozin resulted in increases in UGE and reductions in fasting serum glucose concentration. Furthermore, small changes in serum and urinary electrolytes were observed in this mechanistic trial under standardised conditions of food and fluid intake.

Comments: The clinical relevance of these small changes in PD parameters evaluated in this Phase I PK-PD study will be determined in the ongoing empagliflozin Phase III program. Overall, the combination of empagliflozin and diuretics was well tolerated and no serious adverse events were reported, but the frequency of patients with AEs was higher when empagliflozin was combined with torasemide (60.0%) or hydrochlorothiazide (40.0%) than when any drug was

given alone (0% to 14.3%). Drug related thirst was reported only during combination therapy: in 60.0% of patients treated with empagliflozin and torasemide and 20.0% of patients treated with empagliflozin and hydrochlorothiazide.

5.3. Evaluator's overall conclusions on pharmacodynamics

Empagliflozin is a reversible, highly potent and selective competitive inhibitor of SGLT2 with an IC₅₀ of 1.3 nM. It has a 5000 fold selectivity over human SGLT1 (IC₅₀ of 6278 nM), responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible as the predominant transporter for re-absorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes mellitus (T2DM) and hyperglycaemia a higher amount of glucose is filtered and reabsorbed. Empagliflozin improves glycaemic control in patients with T2DM by reducing renal glucose re-absorption. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and glomerular filtration rate (GFR). Through inhibition of SGLT2 in patients with T2DM and hyperglycaemia, excess glucose is excreted in the urine.

Oral administration of empagliflozin resulted in a dose dependent increase in UGE. In healthy volunteers (study 1245.2), UGE was higher with all doses (0.5 mg to 800 mg) compared with placebo. 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 to 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 to 72 h. The time to reach the maximum rate of UGE was 7 h in most subjects and was similar in all dose groups.

Empagliflozin administration resulted in increased UGE in patients with T2DM (study 1245.4). Empagliflozin inhibited reabsorption of 39%, 46%, 58%, and 64% of filtered glucose with 2.5, 10, 25, and 100 mg qd doses, respectively. Consistent with the extent of inhibition of glucose reabsorption, UGE seemed to plateau after the 10 mg dose, with total cumulative amounts excreted ranging from 77.9 g to 89.8 g with 10 to 100 mg empagliflozin after a single dose. Increased UGE was maintained over the 8-day treatment duration and 4-week treatment, and similar results were observed after multiple doses with or without OGTT. Following a 4-week treatment in patients, increases in UGE from baseline were approximately 64.4 g, 78.4 g and 72.6 g with 10 mg, 25 mg, and 100 mg empagliflozin qd, respectively. Increased UGE with empagliflozin treatment did not result in clinically relevant changes in urine volume.

Following a 4-week treatment in Japanese patients with T2DM (1245.15), adjusted mean changes from baseline in UGE increased with empagliflozin dose; 40.8 g, 77.1 g, 80.9 g, 93.0 g and -2.1 g for the 1 mg, 5 mg, 10 mg, 25 mg empagliflozin and placebo groups, respectively. Following 8-day treatment in Chinese patients, the amounts of UGE were similar with 10 mg and 25 mg empagliflozin qd; 95.8 g and 82.6 g, respectively. The increase in UGE was maintained with multiple dosing.

As expected, increased glucosuria did not have any effect on plasma glucose levels in healthy volunteers. In patients with T2DM, all empagliflozin dose groups showed reductions in plasma glucose compared to placebo. Declines in FPG were observed immediately after the first dose of empagliflozin and were maintained over the entire treatment duration. After 4-week treatment, FPG decreased by approximately 44 mg/dL, 34 mg/dL and 29 mg/dL with 10 mg, 25 mg, and 100 mg empagliflozin qd, respectively, compared to 4 mg/dL with placebo. In addition, MDG levels, determined using 8-point plasma glucose profiles, decreased by approximately 20 mg/dL, 26 mg/dL, and 24 mg/dL with 10 mg, 25 mg, and 100 mg empagliflozin qd, respectively, compared to 5 mg/dL with placebo.

Overall, in patients with T2DM, urinary glucose excretion increased immediately following the first dose of empagliflozin and is continuous over the 24 h dosing interval. Increased urinary

glucose excretion was maintained at the end of 4-week treatment period, averaging approximately 78 g/day with 25 mg empagliflozin once daily. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with T2DM. Empagliflozin improves both fasting and post-prandial plasma glucose levels. The insulin independent mechanism of action of empagliflozin contributes to a low risk of hypoglycaemia.

The 5-period crossover trial (1245.16) in 30 healthy male and female subjects demonstrated that single oral doses of 25 mg BI 10773 (expected therapeutic dose) and 200 mg BI 10773 (supratherapeutic dose) were not associated with a QT(c) interval prolongation.

In population PK-PD analysis U12-2525, FPG and HbA1c responses were described as being dependent on drug exposure. The maximal effect (20% lowering of FPG) achieved by empagliflozin treatment was increased with increasing baseline FPG. The maximal effect is attenuated with decreased eGFR despite an increase in empagliflozin exposure, but was still maintained to nearly half of the maximal effect with eGFR as low as 30mL/min/1.73m². The exposure response modelling estimated that targets of 80% and 90% of the maximal response after 24 weeks of treatment for FPG and HbA1c were obtained by oral empagliflozin QD doses of approximately 10 and 25 mg. Rates of the adverse event/tolerability endpoints tested (UTI, GBV, HYPO) did not increase significantly with increasing empagliflozin AUCss. GBV events occurred at a higher rate in patients taking active empagliflozin compared to those taking placebo. There was no discernible effect of empagliflozin exposure (AUCss) on eGFR change from baseline.

6. Dosage selection for the pivotal studies

6.1. Phase IIb dose ranging study 1245.9

1245.9 was a Phase IIb, randomised, parallel group study to evaluate the safety, efficacy, and PK study of BI10773 (5 mg, 10 mg and 25 mg) administered orally once daily over 12 weeks compared double blind to placebo, as monotherapy, with an additional open label metformin arm in type 2 diabetic patients with insufficient glycemc control. The study was conducted from 15 Oct 2008 to 1 Oct 2009 at 75 study sites in 13 countries.

The main inclusion criteria were: Male and female patients, age ≥ 18 and < 80 years, with a diagnosis of type 2 diabetes mellitus, either treatment naive (on no antidiabetic therapy for the 10 weeks prior to screening) or on a maximum of 1 oral antidiabetic therapy (except glitazones, glucagons -like peptide 1 analogues or insulin) on a stable dose for the 10 weeks prior to screening; HbA1c at screening for patients treated with 1 other oral antidiabetic drug: HbA1c ≥ 6.5 to $\leq 9.0\%$ and for treatment naive patients: HbA1c > 7.0 to $\leq 10.0\%$; HbA1c at Visit 2 (start of run-in) for all patients: HbA1c > 7.0 to $\leq 10.0\%$; body mass index (BMI) ≤ 40 kg/m².

Patients in the open label group received metformin 500 mg twice daily for 4 weeks, then 1000 mg twice daily or up to the maximum tolerated dose for 8 weeks. Patients pre-treated with oral antidiabetic medication (maximum 1) required a 4-week wash out period. Treatment naive patients did not require a wash out period. All patients had a 2-week placebo run-in period and 12 weeks of treatment with study medication. The randomisation was stratified by country and by whether antidiabetic medication was previously used or not. Standard PK parameters were investigated. Safety data were analysed mainly descriptively. The primary endpoint was the change in HbA1c from baseline after 12 weeks of treatment. Secondary efficacy endpoints included the fasting plasma glucose (FPG) change from baseline after 12 weeks of treatment, the change of HbA1c and FPG over time, the proportions of patients achieving an HbA1c $\leq 7.0\%$ or an HbA1c lowering of at least 0.5% after 12 weeks of treatment, and the changes in fasting plasma insulin, HOMA index and body weight after 12 weeks of treatment. The efficacy endpoints were analysed with an ANCOVA model including the fixed effects treatment group, number of previously used anti-diabetic medications, baseline HbA1c, and country as random effect. The sample size for the interim analysis of 64 patients per group was based on a

treatment effect of 0.5% reduction in HbA1c after 12 weeks (for 10 mg BI 10773) and a SD of 1.0%, thus leading to a power of 80% using a fixed 2-sided alpha level of 0.05, determined using a t-test.

A total of 408 patients were randomised to 1 of the 5 treatment arms in a 1:1:1:1:1 ratio. All but 2 patients in the open label metformin arm were treated. Of the 406 treated patients, 385 (94.8%) completed the trial as planned and 21 (5.2%) prematurely discontinued study medication with 6, 6, 7, 1 and 1 patients discontinuing treatment in the placebo, metformin, BI 10773 5mg, 10mg and 25mg groups, respectively. The most frequent reasons for discontinuations were 'other reasons' (7 patients, 1.7%), AEs (6 patients, 1.5%), and lack of efficacy (5 patients, 1.2%). Out of the 406 randomised patients, 96 patients (23.6%) had at least 1 important protocol violation with similar incidence across the 4 blinded treatment groups (17.2 to 24.2%) and a slightly higher percentage in the open label metformin group (32.5%). The most frequent important protocol violations affecting efficacy were HbA1c measurement at last visit not performed in time window, that is, more than 3 days before or after anticipated visit date (70 patients, 17.2%), medication taken before blood draw (for biomarkers: 22 patients, 5.4%; for PK: 17 patients, 4.2%), and a too short treatment period (21 patients, 5.2%). Overall, 52.0% of the patients were male, 63.8% were White and 34.5% were Asian. The mean (SD) age was 57.5 (9.8) years, HbA1c 7.9% (0.8%), and BMI 29.0 (4.6) kg/m². At screening, 40.6% of the patients were taking antidiabetic medication and 59.4% were treatment-naive. At the time of enrolment, 31.0% of patients had diabetes for more than 5 years. The mean HbA1c per treatment group ranged from 7.8% to 8.1% at baseline. Demographics and baseline characteristics were comparable between treatment groups. Overall compliance was good and comparable between treatment groups with a mean compliance greater than 96% at all time points. The proportion of patients within the 80% to 120% compliance window ranged between 91.4% and 97.6% in the blinded treatment arms; in the open label metformin arm 85.0% of patients were within the compliance window during study treatment.

For all 3 blinded BI 10773 treatment groups, the reduction in HbA1c was statistically significant and clinically meaningful, compared with placebo (5 mg: -0.52%, 10 mg: -0.57%, 25 mg: -0.72%). The open label arm of metformin had been included in the trial as a sensitivity measure and there was no direct comparison between efficacy of metformin and BI 10773. The reported mean final dose of metformin after 12 weeks of treatment was 1668.8 mg. Mean adjusted HbA1c at week 12 for the open label arm was reduced by -0.82%.

Sensitivity analyses on the primary endpoint and the analyses of the secondary endpoints (change from baseline in FPG, FPI, HOMA indices, and categorical HbA1c response) supported the results of the primary analysis. For change from baseline of FPG at week 12, all BI 10773 treatment groups had a reduction in FPG, compared with placebo (5 mg: -24.05 mg/dL, 10 mg: -29.71 mg/dL, 25 mg: -31.88 mg/dL) with similar reductions in the adjusted mean body weight (5 mg BI 10773: -1.06 kg, 10 mg: -1.58 kg, 25 mg: -1.28 kg, open label metformin: -0.58 kg), compared with placebo. The change from baseline for FPI at Week 12 was comparable to placebo in all 4 active treatment groups. The adjusted HOMA-IR was numerically reduced in all 4 active treatment groups without reaching a statistically significant difference to placebo. The adjusted HOMA-%B increased in 4 active treatment groups, reaching a statistically significant difference to placebo in all treatment groups except 10 mg BI 10773. Sensitivity analyses were performed for HbA1c change over time and HbA1c categorical responses. A repeated measure analysis, including the open label metformin arm, showed that the HbA1c reductions were significant from Week 8 onwards for all active treatment groups. Logistic regression of the proportion of patients with $\leq 7\%$ HbA1c at Week 12 (Table 4 below) and of the proportion of patients with at least 0.5% HbA1c reduction at Week 12 showed statistical significance for all BI 10773 treatment groups and the open label metformin group, compared with placebo.

Table 4: Categorical HbA1c response at Week 12

	Placebo	BI 10773 5 mg	BI 10773 10 mg	BI 10773 25 mg	Open-label metformin
Treated patients	82	81	81	82	80
Patients achieving HbA1c $\leq 7\%$ at week 12, N (%)	18 (22.0)	27 (33.3)	24 (29.6)	37 (45.1)	36 (45.0)
Patients achieving at least 0.5% HbA1c decrease at week 12, N (%)	21 (25.6)	38 (46.9)	48 (59.3)	49 (59.8)	57 (71.3)

The incidence of AEs was comparable between treatment groups (32.9% for patients in the placebo group, 38.8% for patients in the metformin group, and 29.1% for patients in the 3 combined BI 10773 treatment groups). There was no dose dependent increase in the incidence of AEs in the BI 10773 treatment groups.

Comments: Results of this dose ranging Phase II study showed that 5 mg, 10 mg, and 25mg doses of BI 10773 were superior to placebo in terms of HbA1c reduction and lowering of FPG values following 12 weeks of treatment. The effect size for change from baseline for both HbA1c and FPG increased with the BI 10773 dose, indicating a dose response relationship. For change in body weight at week 12, the 10 mg dose had the highest reduction followed by the 25 mg dose and then the 5 mg dose. Based on the primary and secondary analysis, both the 10 mg and 25 mg doses of BI 10773 provided similar efficacy over time and the 5mg dose appeared to be minimum effective dose. Results obtained in this study were similar to those obtained in a Phase II prospective, randomised, parallel group, double blind, placebo controlled, 12-week dose finding trial with dapagliflozin, another SGLT2-inhibitor, with a patient population of treatment naive type 2 diabetes patients (R10-1081). Dapagliflozin doses of 2.5 to 50 mg resulted in placebo corrected reductions of HbA1c (-0.55 to -0.90%), FPG (-16 to -31 mg/dL), and body weight (-1.3 to -2.2%, approximately 1.1 to 2.0 kg).

6.2. Phase II dose ranging study 1245.10

1245.10 was a Phase II, randomised, parallel group safety, efficacy, and PK study of BI 10773 (1 mg, 5 mg, 10 mg, 25 mg, and 50 mg) administered orally once daily over 12 weeks compared double blind to placebo with an additional open label sitagliptin arm in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy. The study was conducted from 15 Oct 2008 to 1 Oct 2009 at multiple study sites in 16 countries (including Latvia, USA, Germany and Austria).

The main inclusion criteria were male and female patients with a diagnosis of T2DM and previously treated with metformin alone or with metformin and one other oral antidiabetic drug (antidiabetic therapy has to be unchanged for at least 10 weeks prior to screening); Age ≥ 18 and < 80 years, stable metformin therapy ≥ 1500 mg/day for at least 10 weeks, Body Mass Index (BMI) ≤ 40 kg/m²; HbA1c (glycosylated hemoglobin A1c) at Visit 1A (Screening): for patients treated with metformin and one other oral antidiabetic drug: HbA1c $\geq 6.5\%$ to $\leq 9.0\%$; for patients treated with metformin only: HbA1c $> 7.0\%$ to $\leq 10.0\%$; HbA1c at Visit 2 (start of Run-in) for all patients: HbA1c > 7.0 to $\leq 10.0\%$.

Patients were randomised to empagliflozin (double-blind), placebo (double-blind), or sitagliptin 100 mg once daily (open label). Patients with oral antidiabetic medication (other than metformin) stopped their therapy and entered a 4-week wash-out period. All patients had a 2-week placebo run-in period and 12 weeks of treatment with study medication, with metformin as background therapy. The randomisation was stratified by country and by the number of previous antidiabetic medications. Standard PK parameters were investigated. Safety data were analysed mainly descriptively.

The primary endpoint, change from baseline of HbA1c after 12 weeks of treatment, was analysed in a linear model with the fixed effects as treatment group, number of previously used

anti-diabetic medications, baseline HbA1c and random effect country. Similar methods were used to analyse the secondary endpoints as well as descriptive statistics. The sample size for the interim analysis of 64 patients per group was based on a treatment effect of 0.5% reduction in HbA1c after 12 weeks (for 10 mg BI 10773) and a SD of 1.0%, thus leading to a power of 80% using a fixed 2-sided alpha level of 0.05, determined using the t-test.

Out of the 495 patients who were randomised, 473 (95.6 %) completed the trial and 22 (4.4 %) prematurely discontinued study medication; the main reasons for premature discontinuation were AEs (9 patients, 1.8 %) and lack of efficacy (6 patients, 1.2 %). Of the 6 patients who discontinued due to lack of efficacy, 3 were in the placebo group and one each in the BI 10773 1 mg, 5 mg and 50 mg group. A total of 10.3% (51/495) patients had important protocol violations. Most common violations were medication taken before blood draw for PK (5.9%, 29/495) and medication taken before blood draw for HbA1c and FPG (5.1%, 25/495). Out of the 495 patients in the FAS, 381 (77%) were included in the PPS.

Overall, majority of the patients were male (50.6%), non-Hispanic White (84.6%) with mean (SD) age was 58.3 (8.8) years, HbA1c 7.9% (0.7%), and BMI 31.4 (4.5) kg/m². At screening, 63.2% of the patients were taking metformin only and 36.8% were taking metformin plus 1 additional antidiabetic medication (88.5% sulfonylurea and 7.1% DPP-4 inhibitors). At baseline, the majority of patients (97.0%) were taking \geq 1500 mg/day metformin. Demographics and baseline characteristics were comparable between treatment groups. Overall compliance was good with mean compliance > 95% at all time points. Proportions of patients who were within the 80% - 120% compliance range throughout the study were 93.0 % in the placebo and sitagliptin group, 93-98% in the empagliflozin groups.

All 5 doses of BI 10773 showed statistically significant placebo-corrected decrease in HbA1c, with largest decreases in the BI 10773 10 mg (-0.71%) and 25 mg dose (-0.70%) with no further reduction with the 50mg dose. Treatment with BI 10773 also showed a dose dependent, placebo-corrected decrease in FPG at Week 12 ranging from 6.45 mg/dL to 32.66 mg/dL. These changes were statistically significant in all BI 10773 treatment groups, except the BI 10773 1 mg group. After 12 weeks of treatment with BI 10773, the mean body weight reduction ranged from 1.55 kg to 2.85 kg in the BI 10773 1 mg and 50 mg groups, respectively. The body weight was reduced by 1.16 kg in the placebo group. Weight decrease was statistically different from placebo for all groups, except for the BI 10773 1 mg group.

The FPI showed statistically significant reduction in the BI 10773 50mg and 10mg groups only (by 1.95 and 2.21 μ U/mL, respectively) with no significant reductions in other dose groups and an increase noted in the sitagliptin group. The adjusted HOMA-IR decreased by 1.33, 0.76, 1.27, 0.83 and 0.35 in the BI 10773 50 mg, 25 mg, 10 mg, 5 mg and 1 mg groups respectively, compared to placebo after 12 weeks of treatment with statistically significant reductions compared with placebo for all BI 10773 doses except the 1mg dose; HOMA-IR increased by 0.25 for the sitagliptin arm compared to placebo. A repeated measure analysis demonstrated a statistically significant difference from placebo starting from Week 4 for all groups except for the BI 10773 1 mg group. A logistic regression of the comparison of the proportion of patients with HbA1c \leq 7% at week 12 showed a statistically significant difference for the BI 10773 10 mg (38.0%), 25 mg (37.1%) and 50 mg group (35.7%) compared to placebo (15.5%). Proportion of patients who had HbA1c reduction of at least 0.5% of at Week 12 ranged from 31% in the BI 10773 1 mg group to 60.6% and 60.0% in the BI 10773 10 mg and 25 mg groups, respectively, and it was statistically significantly different from placebo for all BI 10773 treatment groups in the logistic regression analysis.

Comments: Based on the analysis of the primary endpoint and some of the important secondary endpoints in the 2 dose-ranging studies discussed above, both 10 mg and 25 mg doses of BI 10773 were most efficacious in regard to HbA1c and FPG lowering with the 50mg dose showing no further increase in efficacy; in fact, the 50mg dose showed numerically lesser reductions in HbA1c and FPG compared with 10 and 25mg doses while the 1mg dose failed to show significant efficacy compared with placebo. All doses of BI 10773 were well tolerated.

Hence, the selection of the 10mg and 25mg doses of empagliflozin for the pivotal Phase III studies appears to be appropriate.

7. Clinical efficacy

7.1. As an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus

The main proof of efficacy is provided by four pivotal double-blind placebo-controlled Phase III trials in which empagliflozin was investigated as monotherapy (1245.20) or as add-on therapy to oral antidiabetic background medication (1245.19 and 1245.23). 1245.23 comprised two separate trials (based on the type of oral antidiabetic background medication) under a single trial number: 1245.23 (met) and 1245.23 (met+SU). The four extensions of the pivotal trials were conducted under one trial number (1245.31) and provide data to support the persistence of efficacy of empagliflozin up to 52 weeks.

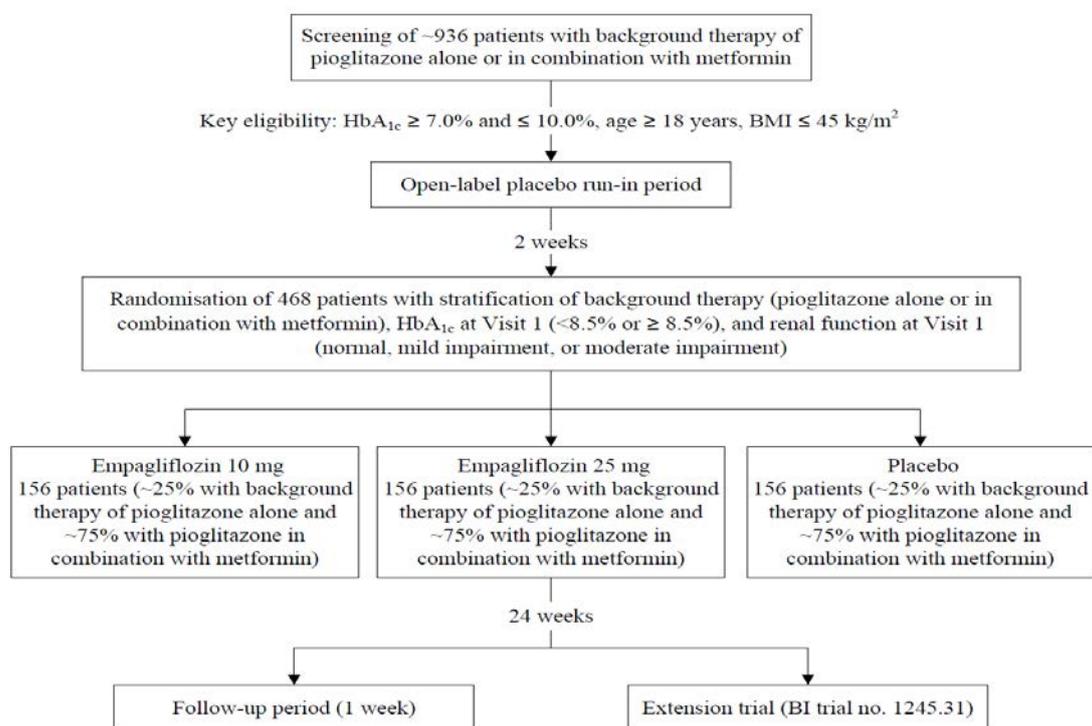
Further evidence of efficacy is provided by five additional double-blind studies conducted in patients with diabetes: an active-controlled trial comparing empagliflozin with glimepiride (1245.28), a trial including patients taking basal insulin as background therapy (1245.33), and trials including patients with hypertension (1245.48), increased cardiovascular risk (1245.25) and renal impairment (1245.36). With the exception of the 12-week trial 1245.48, all of these trials include long-term analyses of efficacy data over at least 52 weeks. Additional evidence of the persistence efficacy over 90 weeks is provided by a combined analysis of two dose finding trials (1245.9 and 1245.10) and their open label extension trial (1245.24).

7.1.1. Pivotal efficacy studies

7.1.1.1. Study 1245.19

7.1.1.1.1. Study design, objectives, locations and dates

1245.19 was a pivotal, Phase III, 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 T2DM with insufficient glycaemic control despite a background therapy of pioglitazone alone or in combination with metformin. The objective of this trial was to investigate the efficacy, safety, and tolerability of empagliflozin (10 and 25 mg once daily) compared with placebo given for 24 weeks as add-on therapy to pioglitazone alone or pioglitazone in combination with metformin in patients with T2DM with insufficient glycaemic control. The study was conducted from 12 Oct 2010 to 11 April 2012 at 69 centres in 7 countries (India, Philippines, Thailand, Greece, Ukraine, USA and Canada). Patients who completed the randomised treatment period of this trial were eligible to participate in a double-blind extension trial (BI trial 1245.31); patients continued with the study medication to which they were randomised in the current trial. The study design is summarised in the Figure below.

Figure 2: Study 1245.19: Overview of study design

7.1.1.1.2. Inclusion and exclusion criteria

The main inclusion criteria were: Diagnosis of type 2 diabetes mellitus prior to consent; Signed consent obtained by the date of screening (Visit 1) and in accordance with GCP and local legislation; Male and female patients on diet and exercise regimen and previously treated with pioglitazone⁶ alone or pioglitazone in combination with metformin⁷ (treatment regimen unchanged for 12 weeks before randomisation); HbA1c at screening (Visit 1): > 7.0% and < 10.0%; Age at screening ≥ 18 years, ≤ 65 years (India only); BMI at screening ≤ 45 kg/m². The main exclusion criteria were: uncontrolled hyperglycaemia during placebo run-in with a glucose level of > 240 mg/dL (> 13.3 mmol/L) after an overnight fast, confirmed by a second measurement (not on the same day); Any other antidiabetic medication taken within 12 weeks prior to randomisation, except those defined as the permitted background medication (see inclusion criteria); Acute coronary syndrome (non-STEMI, STEMI, and unstable angina pectoris), stroke, or transient ischaemic attack (TIA) within 3 months prior to consent; Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase > 3 times upper limit of normal (ULN) as determined during screening or during the placebo run-in period; Impaired renal function, defined as eGFR < 30 mL/min/1.73m² (severe renal impairment, MDRD formula) as determined during screening or during the placebo run-in period; Bariatric surgery within the past 2 years or other gastrointestinal surgeries that induce chronic mal-absorption; Medical history of cancer (except for basal cell carcinoma) or treatment for cancer within the last 5 years; Blood dyscrasias or any disorder causing haemolysis or unstable red blood cells (e.g. malaria, babesiosis, haemolytic anaemia); Contraindication to pioglitazone or metformin⁸ according to the local labels; Treatment with anti-obesity drugs 3 months prior to consent or any other treatment at the time of screening (that is, surgery, aggressive diet regimen etc.) leading to unstable body weight; Current treatment with systemic steroids at time of consent or change in dosage of thyroid hormones

⁶ Minimum dose for pioglitazone was to be ≥30 mg/day or the maximum tolerated dose or maximum dose according to the local label.

⁷ Minimum dose for metformin was to be ≥1500 mg/day or the maximum tolerated dose or maximum dose according to the local label.

⁸ Relevant only for patients entering the trial with both these background therapies.

within 6 weeks prior to consent or any other uncontrolled endocrine disorder except type 2 diabetes; Premenopausal women who were nursing or pregnant or were of child-bearing potential and were not practicing an acceptable method of birth control⁹ or did not plan to continue using this method throughout the trial and did not agree to submit to periodic pregnancy testing during the trial; Alcohol or drug abuse within the 3 months prior to consent; Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial; Any other clinical condition that would jeopardise patient safety while participating in this clinical trial.

7.1.1.1.3. Study treatments

Patients who met the trial eligibility criteria at the end of the 2-week placebo run-in period were randomly assigned to 1 of the 3 treatment groups (empagliflozin 10 mg, empagliflozin 25 mg, or placebo) in a 1:1:1 ratio. Two-week placebo run-in followed by 24-week treatment period and 1-week follow-up period. During the double-blind treatment period, each patient was to take 2 tablets daily in a double-blind, double-dummy design. Patients in the empagliflozin treatment groups were to take 1 active-drug tablet of their assigned dose (10 mg or 25 mg) and 1 placebo tablet matching the other dose. Patients in the placebo treatment group were to take 2 placebo tablets (1 tablet matching each empagliflozin dose). Treatment compliance was assessed at each visit, based on tablet count of dispensed and returned medication.

Background medication was to be taken during the entire trial (including placebo run-in period) with dosage unchanged. During the first 12 weeks of randomised treatment, rescue therapy was to be initiated only if a patient had a confirmed glucose level of > 240 mg/dL (13.3 mmol/L) after an overnight fast. During the subsequent 12 weeks, rescue therapy was to be initiated only if a patient had a confirmed¹⁰ glucose level of > 200 mg/dL (11.1 mmol/L) after an overnight fast. The decision to initiate rescue therapy was at the investigator's discretion. The choice of rescue therapy and its dosage were also at the discretion of the investigator; however, SGLT-2 inhibitors other than empagliflozin were not to be used.

7.1.1.1.4. Efficacy variables and outcomes

HbA1c¹¹ was measured as an efficacy endpoint in all empagliflozin Phase IIb and Phase III trials. In all trials, blood samples for the determination of HbA1c were to have been taken at almost all study visits. At the first visit in a particular trial, the blood sample could have been taken at any time during the visit, irrespective of fasting. At all other visits, the blood sample was to have been taken before breakfast and before administration of trial drug. The percentage of HbA1c of total haemoglobin in ambient ethylenediaminetetraacetic acid (EDTA) blood was analysed by automated ion exchange HPLC. The stability of HbA1c in ambient blood samples was established for 7 days and samples had to be measured within this timeframe. Samples were measured by selected central laboratories. For all studies where HbA1c was measured as an efficacy endpoint, the analysis was performed at National Glycohaemoglobin Standardisation Program (NGSP) level I certified laboratories.

The primary efficacy outcome in all pivotal studies was the change from baseline in HbA1c. The secondary efficacy endpoints for the pivotal studies were the changes from baseline in fasting plasma glucose (FPG), body weight, systolic blood pressure (SBP), and diastolic blood pressure

⁹ Acceptable methods of birth control include tubal ligation, transdermal patch, intra uterine devices/systems, oral, implantable or injectable contraceptives, sexual abstinence (if acceptable to local authorities), double barrier method, and vasectomised partner

¹⁰ 'Confirmed' was defined as a minimum of 2 measurements on 2 different days, with at least 1 measurement performed at the investigational site.

¹¹ Glycated haemoglobin (HbA1c) is a form of haemoglobin used primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed by nonenzymatic, irreversible glycosylation of haemoglobin. HbA1c therefore reflects the average level of glucose to which the red blood cell has been exposed during its life cycle. As the normal life span of the red blood cell is about 120 days, HbA1 reflects the average blood glucose concentration of up to 3 months.

(DBP). In all trials, samples for the determination of fasting plasma glucose (FPG) were to have been taken at all study visits except for the first screening visit. Body weight was to have been measured in all trials on the same centrally-provided scales for each patient. Blood pressure (SBP and DBP) was to have been measured with the patient in a seated position, preferably using a standard mercury sphygmomanometer. An exception was the dedicated blood pressure trial 1245.48; in addition to the standard seated blood pressure measurements, changes in 24 h blood pressure were assessed by ambulatory blood pressure monitoring.

For this pivotal study (1245.19), the primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment. The key secondary endpoints were the changes from baseline in fasting plasma glucose (FPG) and in body weight after 24 weeks of treatment. Other exploratory efficacy endpoints were: (1) For HbA1c- occurrence of treat-to-target efficacy response measured as HbA1c < 7.0% and < 6.5% after 24 weeks of treatment; occurrence of relative efficacy response measured as HbA1c reduction of at least 0.5% after 24 weeks of treatment; change from baseline in HbA1c by visit over time. (2) FPG- change from baseline in FPG by visit over time. (3) SBP and DBP: change from baseline to Week 24; Blood pressure treat-to-target efficacy response- occurrence of BP response (SBP < 130 mmHg and DBP < 80 mmHg) after 24 weeks of treatment; the percentage of patients with history of hypertension and not at blood pressure goal (SBP < 130 mmHg and DBP < 80 mmHg) at baseline, who achieved this goal at Week 24. (4) Waist circumference¹²: change from baseline to Week 24 (5) Body weight treat-to-target response: reduction in weight (kg) by more than 5% after 24 weeks of treatment. (6) Composite endpoint of the following conditions at Week 24: HbA1c lowering by at least 0.5%, lowering of systolic blood pressure by at least 3 mmHg and decrease in body weight by more than 2%. (7) Use of rescue therapy.

7.1.1.1.5. *Randomisation and blinding methods*

Patients who met the trial eligibility criteria at the end of the 2-week placebo run-in period were randomly assigned to 1 of the 3 treatment groups (empagliflozin 10 mg, empagliflozin 25 mg, or placebo) in a 1:1:1 ratio. Randomisation was performed at Visit 3, and was stratified by HbA1c at screening (< 8.5%; ≤ 8.5%), background medication (pioglitazone; pioglitazone plus metformin), and renal function at screening (normal renal function eGFR ≥ 90 mL/min/1.73 m²; mild impairment eGFR 60 to 89 mL/min/1.73 m²; moderate renal impairment eGFR 30 to 59 mL/min/1.73m²). To prevent unequal treatment allocation, blocks of 3 were used for randomisation, and the blocks were assigned to strata. Access to the randomisation codes was controlled and documented. The assignment of a patient to a treatment group was determined using an IXRS. The placebo run-in period of this trial was performed open label, that is, both the investigator and the patient knew that the patient received placebo during the run-in period. The randomised period of this trial was performed double-blind, i.e. after randomisation, the patient, the investigator, or anyone involved in analysing trial data or with an interest in this double-blind trial did not know the identity of a patient's treatment.

7.1.1.1.6. *Analysis populations*

Efficacy analyses were mainly based on the full analysis set (FAS), which included all randomised and treated patients who had a baseline HbA1c value. Other analysis populations included in the sensitivity efficacy analysis were: FAS-completers including all patients in the FAS who did not prematurely discontinue the trial and completed at least 161 days of treatment; Per-protocol set (PPS) including all patients in the FAS without important protocol violations leading to exclusion; PPS-completers including all patients in the PPS who did not prematurely discontinue the trial and completed a required minimum treatment duration as defined for the FAS-completers (161 days). Of the patients in the FAS, 90.6% were in the FAS-completers, 92.4% in the PPS, and 87.3% in the PPS-completers. The percentage of FAS-completers and PPS completers were lower in the placebo group (87.9% and 83.6%), consistent with the higher rate of premature discontinuation in this group.

¹² Waist circumference was to be measured with a tape made of non-stretchable material.

7.1.1.1.7. *Sample size*

Based on previous experience with empagliflozin, it was estimated that the mean change in HbA1c from baseline after 24 weeks would be -0.5% for either of the empagliflozin groups (10 mg or 25 mg) compared with placebo, with a standard deviation of 1.1%. To show a difference between empagliflozin and placebo treatment with a 2-sided significance level of 0.025 for either primary hypothesis, and assuming that the HbA1c values follow a normal distribution, a sample size of 148 was needed to provide a power of at least 95% for the pair-wise comparison and an overall power of at least 90%. Allowing a 5% dropout rate, the sample size needed was 156 for each randomised treatment arm and, with 3 treatment arms, a total of 468 patients for this trial.

7.1.1.1.8. *Statistical methods*

Each dose of empagliflozin (10 or 25 mg) was independently compared to placebo. The hypotheses were tested in a pre-specified hierarchical sequence (primary endpoint, first key secondary endpoint, second key secondary endpoint, and primary endpoint for patients with pioglitazone in combination with metformin background therapy). The analysis of the primary endpoint for patients with pioglitazone alone background therapy was removed from the hierarchical sequence and only performed as an exploratory analysis due to the reduced patient number after the implementation of a protocol amendment. The overall significance level for the trial is $\alpha = 5\%$ (2-sided); α was spent equally between the 2 test sequences for the 2 doses (i.e. 2.5% on each test). Each step in either test sequence was only regarded as 'confirmatory' if the null hypothesis tested before was rejected. If at any step the null hypothesis was not rejected, the subsequent step(s) of that dose level were regarded as 'exploratory'. Primary analysis: analysis of covariance (ANCOVA); the model included treatment, background medication, and renal function as fixed effects, and baseline HbA1c as a linear covariate (and the respective efficacy variable at baseline as another linear covariate for secondary endpoints). Sensitivity analyses were carried out using ANCOVA based on different analysis sets and imputation methods; in addition, a restricted maximum likelihood-based mixed model repeated measures (MMRM) approach was used to analyse changes over time for efficacy variables. Continuous exploratory endpoints were analysed using a similar model as for the primary analysis. Categorical exploratory endpoints were tabulated. Binary exploratory endpoints were analysed using logistic regression.

7.1.1.1.9. *Participant flow*

Of the 762 patients enrolled in this study, 499 were randomised; 166, 165 and 168 patients were randomised to the placebo empagliflozin 10 mg and 25 mg groups, respectively. All but 1 patient in the placebo group were treated with at least 1 dose of study medication. Of the 499 randomised patients, 54.3% were from Asia (China, India, the Philippines, and Thailand), 17.2% from Europe (Greece and Ukraine), and 28.5% from North America (Canada and USA). Of the treated patients, 10.9%, 6.7% and 7.1% in the placebo, empagliflozin 10mg and 25 mg groups, respectively discontinued study medication prematurely, with the most common reason being AEs, 91.8% of the treated patients completed the trial; 61.2% of the treated patients continued in the extension study (1245.31).

7.1.1.1.10. *Major protocol violations/deviations*

Overall, 7.8% of the randomised patients had important protocol violations leading to exclusion from the PPS with similar proportions in all 3 treatment groups. The most frequent important protocol violation leading to exclusion from the PPS was non-compliance with drug intake (4.4%). Overall, 4.4% of the randomised patients had important protocol violations not leading to exclusion from the PPS, the most frequent of which was weight measurement with wrong device at randomisation or end of treatment (2.8%).

7.1.1.1.11. *Baseline data*

The proportion of male patients was 48.4%. Most patients were Asian (57.8%) or White (39.6%) and the largest proportion of randomised patients was from India (41.1%). Half

(48.4%) of all patients were male. Mean age was 54.5 years and most patients (87.5%) were less than 65 years of age. Mean eGFR (according to MDRD formula) was 85.74 mL/min/1.73m² and most patients had normal renal function (38.2%) or mild renal impairment (51.0%); only 10.8% had moderate renal impairment. More than half of the patients (56.0%) were diagnosed with type 2 diabetes for up to 5 years. Mean (SD) age was 54.5 (9.8) years, BMI 29.2 (5.5) kg/m², baseline HbA1c 8.09% (0.88%), baseline FPG 151.9 (38.5) mg/dL, and baseline body weight 78.3 (19.7) kg. The demographics and baseline characteristics were in general balanced among the 3 treatment groups. 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 (n = 121, 24.3%). The majority of the patients (358 of 376) with metformin plus pioglitazone background medication had a daily metformin dose of \geq 1500 mg at baseline and almost all patients (99.4%) had a daily pioglitazone dose of \geq 30 mg at baseline. Overall, 56.8% of the patients took antihypertensives, 31.9% took lipid-lowering drugs, and 25.7% took acetylsalicylic acid at baseline; the proportion of patients taking these medications was balanced among the 3 treatment groups. More patients in the placebo group (14 patients) received additional antidiabetic medications during the treatment period than those in the empagliflozin groups (6 patients for 10 mg and 1 patient for 25 mg). The antidiabetic medication used most frequently was sulphonylurea. More than half the patients had history of hypertension (57-59% across treatment groups) and there were numerical imbalances in diabetic retinopathy, cerebrovascular disease, and diabetic nephropathy. Overall, 95.8% of the patients showed compliance within the accepted compliance window of 80 to 120% and the proportion of compliant patients was similar in the 3 treatment groups.

7.1.1.1.12. Results for the primary efficacy outcome

Compared with placebo, adjusted mean change from baseline at Week 24 in HbA1c was statistically significantly greater for empagliflozin 10 mg (-0.48%; 97.5% CI: -0.69% to -0.27%; p < 0.0001) and 25 mg (-0.61%; 97.5% CI: -0.82% to -0.40%; p < 0.0001). The null hypothesis for the first step in the testing sequence was rejected for both empagliflozin doses and both empagliflozin 10 and 25 mg treatments were superior to placebo treatment. Both doses of empagliflozin (10mg and 25mg) were also superior to placebo in the subpopulation of patients with pioglitazone in combination with metformin background medication. The change from baseline in HbA1c after 24 weeks of treatment for this sub-population of patients was the 4th step in the hierarchical testing. All null hypotheses in the previous steps of the hierarchy were rejected. All sensitivity analyses showed results consistent with the primary analysis, with regard to the placebo-corrected adjusted mean and the 95% CI.

7.1.1.1.13. Results for other efficacy outcomes

In both empagliflozin groups, the adjusted mean of HbA1c decreased from baseline up to Week 12; there was a slight increase in HbA1c from Week 12 to 18; HbA1c decreased again after Week 18, to a point below the Week 12 value. The placebo group showed a slight decrease in adjusted mean of HbA1c from baseline up to Week 24. The proportion of patients who reached target HbA1c levels of < 7.0% or of < 6.5% after 24 weeks of treatment (i.e. had an absolute efficacy response) and those who showed a decrease of at least 0.5% in their HbA1c levels after 24 weeks of treatment was greater in both empagliflozin groups compared with placebo.

Compared with placebo, the adjusted mean change from baseline at Week 24 in FPG (mg/dL) was statistically significantly greater for both empagliflozin 10 mg (-23.48; 97.5% CI: -31.81 to -15.15; p < 0.0001) and 25 mg (-28.46; 97.5% CI: -36.73 to -20.19; p < 0.0001). In both empagliflozin groups, the adjusted mean of FPG decreased from baseline up to Week 12; there was a slight increase in FPG from Week 12 to 18; FPG decreased again after Week 18, to a point below the Week 12 value. The adjusted mean of FPG for the placebo group was relatively stable over the 24 weeks.

Compared with placebo, adjusted mean reduction from baseline at Week 24 in body weight was statistically significantly greater for both empagliflozin 10 mg (-1.95 kg; 97.5% CI: -2.64 to -1.27 kg; p < 0.0001) and 25 mg (-1.81 kg; 97.5% CI: -2.49 to -1.13 kg; p < 0.0001). The proportion of

patients with a weight reduction response (> 5% reduction in body weight from baseline to week 24) was 5.5% in the placebo group, 18.8% in the empagliflozin 10 mg group, and 13.7% in the empagliflozin 25 mg group. At Week 24, both empagliflozin groups showed greater reduction in mean (SD) waist circumference from baseline (0.15 (5.22), -1.63 (4.35) and -0.91 (3.88) in placebo, empagliflozin 10mg and 25mg groups, respectively).

Compared with placebo, adjusted mean change from baseline at Week 24 in SBP (mmHg) was -3.86 (95% CI: -6.23 to -1.50) and -4.73 (95% CI: -7.08 to -2.37) for empagliflozin 10 mg and 25 mg, respectively. Similarly, compared with placebo, adjusted mean change from baseline at Week 24 in DBP (mmHg) was -1.78 (95% CI: -3.20 to -0.36) and -2.50 (95% CI: -3.92 to -1.08), respectively. About half of the patients in the empagliflozin groups (50.3% for 10 mg and 51.2% for 25 mg) achieved the blood pressure goal (SBP < 130 mmHg and DBP < 80 mmHg) after 24 weeks of treatment, whereas 35.2% in the placebo group achieved this goal. Among patients with a history of hypertension and not at blood pressure goal at baseline, 18.8 % in the placebo group, 33.3 % in the empagliflozin 10 mg group, and 31.8 % in the empagliflozin 25 mg group achieved the blood pressure goal.

The proportion of patients who achieved the composite goal of reduction in HbA1c by > 0.5%, in SBP by > 3 mmHg, and in body weight by > 2% at Week 24 was greater in the empagliflozin groups (13.3% for 10 mg and 14.3% for 25 mg) compared to the placebo group (3.6%).

More patients in the placebo group (15 patients) received rescue therapy than those in the empagliflozin groups (5 patients for 10 mg and 2 patients for 25 mg). The rescue therapy used most often was sulphonylurea. The odds ratio (95% CI) for empagliflozin 10 mg versus placebo was 0.323 (0.114 to 0.919), and for empagliflozin 25 mg versus placebo was 0.127 (0.029 to 0.570).

Comments: This well conducted pivotal study showed that treatment with both empagliflozin 10 mg and 25 mg od for 24 weeks produced statistically and clinically relevant reduction in HbA1c, FPG, body weight and BP in patients with T2DM and insufficient glycaemic control on background therapy of pioglitazone or pioglitazone and metformin. The higher dose of 25 mg showed numerically greater reduction in HbA1c and FPG than the 10mg dose (but body weight did not show a dose response). However, interpretation was limited by lack of statistical comparison between the 2 doses of empagliflozin.

7.1.1.2. Study 1245.20

7.1.1.2.1. Study design, objectives, locations and dates

1245.20 was a pivotal, 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 naive patients with type 2 diabetes mellitus and insufficient glycaemic control despite diet and exercise. The objective of this trial was to investigate the efficacy, safety and tolerability of empagliflozin (10 mg or 25 mg od) compared with placebo and sitagliptin (100 mg od) given for 24 weeks as monotherapy in drug naive patients with type 2 diabetes mellitus and insufficient glycaemic control. The study also had an open label (OL) arm to assess the efficacy and safety of empagliflozin 25 mg once daily in patients with type 2 diabetes and very poor glycaemic control (HbA1c > 10%). A 2-week open label placebo run-in period preceded randomisation. Patients allocated to the open label arm started treatment with empagliflozin 25 mg without a run-in period. Patients who completed the planned 24-week randomised treatment period in this trial were eligible to continue their randomised treatment by enrolling in the extension trial BI 1245.31. Patients who did not enter the extension trial were to be followed-up for 1 week. The study was conducted from 12 Aug 2010 to 19 March 2012 at 124 centres in 9 countries (Belgium, Canada, China, Germany, India, Ireland, Japan, Switzerland, and USA).

7.1.1.2.2. Inclusion and exclusion criteria

Drug naive patients with type 2 diabetes mellitus and insufficient glycaemic control (HbA1c ≥ 7.0% and ≤ 10.0%; Germany: ≥ 7.0 to ≤ 9.0%); age ≥ 18 years (Japan: ≥ 20 years; India: ≥ 18 years and ≤ 65 years); BMI ≤ 45 kg/m². Patients with an HbA1c of > 10% and fulfilling all

remaining inclusion criteria were eligible for inclusion in the empagliflozin 25 mg OL arm. Other exclusion criteria were similar to those described for study 1245.19 above.

7.1.1.2.3. Study treatments

Study treatments included Empagliflozin 10 and 25 mg tablets, Sitagliptin (100mg tablets purchased from Merck Sharp & Dohme Ltd under the commercial name Januvia) and placebo tablets matching to sitagliptin and empagliflozin. Patients who met the trial eligibility criteria at the end of the 2-week placebo run-in period were randomly assigned to 1 of the 4 treatment groups (empagliflozin 10 mg, empagliflozin 25 mg, sitagliptin 100 mg, or placebo) in a 1:1:1:1 ratio. Duration of double blind treatment period was 24-weeks and there was a 1-week follow-up period.

7.1.1.2.4. Efficacy variables and outcomes

The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment.

The key secondary endpoints were the change from baseline in body weight and blood pressure (systolic, SBP and diastolic, DBP) after 24 weeks of treatment.

Other endpoints were: occurrence of a treat-to-target response (HbA1c after 24 weeks of treatment < 7.0%), occurrence of relative efficacy response (HbA1c lowering by $\geq 0.5\%$ after 24 weeks of treatment), changes in HbA1c and fasting plasma glucose (FPG) by visit over time, FPG change from baseline after 24 weeks of treatment, use of rescue medication, the composite endpoint of the following conditions at Week 24 (all 3 had to be fulfilled): reduction from baseline in HbA1c of $\geq 0.5\%$, reduction from baseline in SBP of > 3 mmHg, and reduction from baseline in body weight of > 2%.

7.1.1.2.5. Randomisation and blinding methods

Patients who met the trial eligibility criteria at the end of the 2-week placebo run-in period were randomly assigned to 1 of the 4 treatment groups (empagliflozin 10 mg, empagliflozin 25 mg, sitagliptin 100 mg or placebo) in a 1:1:1:1 ratio. The assignment of a patient to a treatment group was determined using an IXRS. A triple-dummy design was followed, i.e. each patient received either 1 active treatment and 2 placebos matching the alternative active treatments or 3 placebos matching each of the possible active treatments.

7.1.1.2.6. Analysis populations

Efficacy analyses were mainly based on the full analysis set (FAS), which included all randomised and treated patients who had a baseline HbA1c value. Other analysis populations included in the sensitivity efficacy analysis were: FAS completers, Per-protocol set (PPS) and PPS completers. All randomised patients were treated; thus, the total number of patients in the TS, RS and FAS were identical. The number of patients was well balanced across treatment groups for the RS, FAS, and TS. Given the higher number of patients with important protocol violations and patients with premature discontinuation of trial medication in the placebo group, there was a slight imbalance across treatment groups in the PPS, FAS completers, and PPS completers; overall, fewer patients were included in the PPS, FAS completers and PPS completers than in the sets TS, RS, and FAS.

7.1.1.2.7. Sample size

Based on previous experience with empagliflozin, it was estimated that the change in HbA1c from baseline after 24 weeks would be -0.5% for an empagliflozin group (10 mg or 25 mg) compared with placebo, with a standard deviation of 1.1%. To show a difference between empagliflozin and placebo treatment with a 2-sided significance level of 0.025 for either primary hypothesis, and assuming that the HbA1c values follow a normal distribution, a sample size of 148 was needed to provide a power of at least 95% for the pair-wise comparison and an overall power of at least 90%. Allowing a 20% drop-out rate, the sample size for each randomised treatment arm would be 180 and for this trial of 4 arms would be 720 randomised patients in total. Furthermore, to provide enough power to show a difference in the first key

secondary endpoint (change in body weight from baseline at Week 24), the sample size for each randomised treatment had to be 210, resulting in a total of 840 randomised patients. Considering a 2% variation in body weight at Week 24, 210 patients/treatment group provided a power of $\geq 97\%$ for the pair-wise comparison and an overall power of $\geq 85\%$.

7.1.1.2.8. *Statistical methods*

The sitagliptin group comparison versus placebo was used for internal validation of the trial. The comparison of sitagliptin to the 2 empagliflozin doses was used to evaluate (no confirmatory test) the degree of similarity of efficacy and safety between the 2 compounds. Statistical analyses of efficacy endpoints were similar to those described for study 1245.19 above.

7.1.1.2.9. *Participant flow*

Of the 1616 patients enrolled, 986 patients were entered and all were treated: 899 patients with double blind trial medication (after the placebo run-in period) and 87 patients with open label medication. The 899 randomised patients received 10 mg empagliflozin (224 patients), 25 mg empagliflozin (224 patients), placebo (228 patients), or 100 mg sitagliptin (223 patients). Out of the 899 randomised and treated patients, 803 patients completed the 24-week treatment period and 96 patients (10.7%) prematurely discontinued trial medication. Of the treated patients in the open label group, 78 patients completed the 24-week treatment period whereas 9 patients (10.3%) prematurely discontinued trial medication. The most frequent reason in all treatment groups (2.2 to 5.3% across groups) was patient's refusal to continue trial medication (not due to AEs). The highest discontinuation rate by treatment occurred in the placebo group (18.0%); across the other randomised treatment groups, discontinuation rates were similar and numerically low: 8.0% for empagliflozin 10 mg, 8.9% for empagliflozin 25 mg, and 7.6% for sitagliptin. In the open label arm, the discontinuation rate was 10.3%, the most common reason being either 'adverse event' (3.4%) or 'refusal not due to adverse event' (3.4%).

7.1.1.2.10. *Major protocol violations/deviations*

Overall, 131 cases (122 in the RS and 9 in the OLS) were considered to be important protocol violations. Within the RS, important protocol violations leading to exclusion from the PPS were reported for 69 patients (7.7%). The proportion was low and similar for treatment with empagliflozin 25 mg (5.4%) and for treatment with sitagliptin (5.8%), with a higher value for treatment with empagliflozin 10 mg (8.0%), and the highest value for treatment with placebo (11.4%). The most frequent violation leading to exclusion was non-compliance with drug intake (6.0% of all randomised patients, 78% of all patients excluded from the PPS). Within the OLS, important protocol violations leading to exclusion from the PPS, were reported for 6 patients (6.9% of all OL patients). As also seen for the RS, non-compliance with drug intake was the most frequent reason leading to exclusion (for all these 6 patients). Important protocol violations not leading to exclusion from the PPS were reported for 69 patients (7.7%) in the RS and for 4 patients (4.6%) in the OLS, the most frequent reason being the body weight measurement using a wrong device at randomisation and/or end-of-treatment (1.8% in the RS and 1.1% in the OLS).

7.1.1.2.11. *Baseline data*

In the FAS, majority of the patients were male (61.3%), Asian (64.1%) with mean age of 55.0 years (48.6% were aged 50 to < 65 years; only 2.8% were older than 75 years). The mean BMI was 28.36 kg/m² across the randomised treatment groups. Most of the patients in all randomised groups were categorized as having normal renal function (41.4%) or mild renal impairment (54.4%). In the OLS, majority of the patients were males (73.6%), Asian (60.9%) with mean age of 50.2 years (50.6% were < 50 years old and 43.7% were 50 to < 65 years old). The mean BMI was 28.15 kg/m² and most patients in the OLS (56.3%) had normal renal function or mild renal impairment (39.1%).

In the FAS, the mean HbA1c value was 7.88%, mean weight was 78.42 kg, mean SBP was 131.4 mmHg, mean DBP 79.1 mmHg, and 50.7% patients had a history of hypertension, with

controlled BP in 38.0% patients overall. The majority of patients had been diagnosed with T2DM less than 5 years before entering the study. In the OLS, the mean HbA1c value was 11.50%, the mean weight was 80.72 kg, the mean SBP was 129.5 mmHg, the mean DBP 81.0 mmHg, and 36.8% patients had a history of hypertension, with controlled BP in 35.6% patients. The majority of OLS patients (51.7%) had been diagnosed with T2DM 1 year or less before entering the study. The baseline demographics and disease characteristics were similar across treatment groups.

Overall, 61.6% patients had at least 1 concomitant therapy at baseline in the FAS with anti-hypertensives (40%), lipid lowering agents (22%) and ASA (10.7%) being the most commonly used. In the OLS, 47% of patients used concomitant medications with 24.1%, 6.9% and 11.5% using antihypertensives, lipid lowering agents and ASA, respectively. The incidence of hypertension was 49-55% across treatment groups and the incidence of diabetic complications such as neuropathy, retinopathy and CAD was low and similar across treatment groups.

The use of antidiabetic medication on treatment was analysed as an efficacy endpoint in this trial and is discussed in below. Overall, 95.9% of all randomised patients and 93.1% of the patients from the OL arm showed an acceptable compliance of 80 to 120%, based on tablet count of dispensed and returned medication at each visit.

7.1.1.2.12. Results for the primary efficacy outcome

The primary analysis showed statistically significant greater reduction in HbA1c over placebo with empagliflozin 10 mg (adjusted mean diff from placebo: -0.74%, SE 0.07%; 97.5% CI: -0.90, -0.57 ($p < 0.0001$)), empagliflozin 25 mg (-0.85%, SE 0.07%; 97.5% CI: -1.01, -0.69 ($p < 0.0001$)) and sitagliptin 100mg (-0.73%, SE 0.07%; 95% CI: -0.88, -0.59). The open label arm was analysed descriptively and the mean change was -3.10% (SE 0.22%). The influence of important protocol violations and premature discontinuations on the primary endpoint was assessed by calculating the adjusted mean treatment difference in HbA1c versus placebo for the PPS, the FAS completers, the PPS completers (ANCOVA, using LOCF imputation). The robustness of the results of the primary analysis was confirmed by the results of the secondary analyses performed using different imputation approaches.

7.1.1.2.13. Results for other efficacy outcomes

For placebo, there was a slight increase from zero over time. Otherwise, reductions from baseline occurred in all other randomised treatment groups, with a similar profile. However, the reduction over time for empagliflozin 25 mg was numerically larger than for empagliflozin 10 mg and for sitagliptin. The treatment effects of both doses of empagliflozin increased up to Week 12 and were sustained thereafter. In the HbA1c over time analysis of the open label group, reduction in HbA1c was achieved mostly in the first 6 weeks of treatment with further decrease until Week 24. The majority of patients had their HbA1c levels lowered by 0.5% or more after 24 weeks of treatment (i.e. had relative efficacy response): for empagliflozin 10 mg: 120/224 (53.6%), for empagliflozin 25 mg: 131/224 (58.5%), and for sitagliptin: 139/223 (62.3%); the number of patients with such a reduction was lower for placebo: 44/228 (19.3%). In the OL arm, 27.6% of patients reached target HbA1c levels of $< 7\%$, 11.5% reached levels $< 6.5\%$, and 73.6% had a reduction from baseline $\geq 0.5\%$. The odds ratios (active treatment compared with placebo) for patients with a baseline HbA1c of 6.5% or greater to attain an HbA1c less than 6.5% at 24 weeks were 3.65 (95% CI: 1.82, 7.32) for the empagliflozin 10 mg group, 3.58 (95% CI: 1.79, 7.19) for the empagliflozin 25 mg group, and 4.44 (95% CI: 2.23, 8.85) for the sitagliptin group.

Statistically significant ($p < 0.001$) reductions in body weight compared with placebo were observed for both empagliflozin dose groups; the adjusted mean differences to placebo in body weight (FAS-LOCF) were -1.93 kg (SE 0.24 kg) in the empagliflozin 10 mg group, -2.15 kg (SE 0.24 kg) in the empagliflozin 25 mg group, and 0.52 kg (SE 0.25 kg) in the sitagliptin group; patients treated with empagliflozin in the OL treatment arm also showed reduction in body weight of -1.93kg. These results were confirmed in the sensitivity analyses. The frequency of patients with a reduction in body weight from baseline $> 5\%$ was higher in the empagliflozin

treatment groups than in the placebo and sitagliptin groups: 4.4% for placebo, 22.8% for empagliflozin 10 mg, 29.6% for empagliflozin 25 mg, and 6.3% for sitagliptin. In the OLS (NCF), 21.8% patients experienced a body weight reduction from baseline > 5% at Week 24.

Statistically significant reduction in SBP was noted with empagliflozin treatment; the differences to placebo in the adjusted mean changes from baseline (SE) in SBP (FAS-LOCF) at Week 24 were -2.6 mmHg (1.1) for empagliflozin 10 mg, -3.4 mmHg (1.1) for empagliflozin 25 mg, and 0.8 mmHg (1.2 mmHg) for sitagliptin. The differences for the adjusted mean changes from baseline versus placebo for SBP were statistically significant for both empagliflozin doses in the randomised groups. For sitagliptin, the difference from baseline versus placebo did not reach statistical significance.

The differences to placebo for the adjusted mean changes from baseline (SE) in DBP (FAS-LOCF) at Week 24 were -0.6 mmHg (0.7) for the 10 mg dose and -1.5 mmHg (0.7) for the 25 mg dose, and 1.1 mmHg (0.7) for sitagliptin and did not reach statistical significance. Patients treated with OL empagliflozin 25mg also showed reduction of 3.8 to 4mmHg in SBP and reduction of 1.5mmHg in DBP.

The frequency of patients with controlled BP at Week 24 who had uncontrolled BP at baseline was higher in the empagliflozin treatment groups than in the placebo and sitagliptin groups: 26.7% for empagliflozin 10 mg, 30.8% for empagliflozin 25 mg, 18.2% for sitagliptin, and 13.1% for placebo. The proportion of patients with uncontrolled BP was balanced between the randomised groups at baseline. In the OL arm, the frequency of patients with uncontrolled BP at baseline and controlled BP at Week 24 was 19.6%.

The differences versus placebo for the FPG adjusted mean changes from baseline (SE) at Week 24 were -31.2 mg/dL (SE 2.8 mg/dL) for empagliflozin 10 mg, -36.2 mg/dL (SE 2.8 mg/dL) for empagliflozin 25 mg, and -18.7 mg/dL (SE 2.8 mg/dL) for sitagliptin. The differences versus sitagliptin were -12.5 mg/dL (SE 2.8 mg/dL) for empagliflozin 10 mg and -17.5 mg/dL (SE 2.8 mg/dL) for empagliflozin 25 mg. In the OL arm, the mean change from baseline was -77.3 mg/dL (SE 5.8 mg/dL).

Changes from baseline in waist circumference (cm) at Week 24 were found for the empagliflozin 10 mg and for empagliflozin 25 mg and were negligible for placebo and sitagliptin. For the LOCF analyses, the mean change from baseline at Week 24 (SD) was -1.7 (3.8) cm for empagliflozin 10 mg, -1.7 (4.4) cm for empagliflozin 25 mg, 0.1 (4.2) cm for sitagliptin, and -0.1 (4.1)cm for placebo. For the OC analyses, the mean change from baseline at Week 24 (SD) was -1.8 (3.9)cm for empagliflozin 10 mg, -1.8 (4.5) cm for empagliflozin 25 mg, 0.1(4.5)cm for sitagliptin, and 0.0 (4.8)cm for placebo. In the open label arm, the values were -1.2 (4.8) cm for the LOCF analyses and -1.6 (5.3) cm for the OC analyses.

The proportion of patients who achieved the composite goal of reduction in HbA1c by > 0.5%, in SBP by > 3 mmHg, and in body weight by > 2% at Week 24 was greater in the empagliflozin groups (17% for 10 mg and 17.4% for 25 mg) compared to the placebo group (2.6%) and sitagliptin (5.4%) groups.

Rescue medication was seldom prescribed in the randomised treatment groups, to 3 patients (1.3%) in the empagliflozin 10 mg group, 2 patients (0.9%) in the empagliflozin 25 mg group, and 8 patients (3.6%) in the sitagliptin group. Rescue medication was prescribed to 33 patients (14.5%) in the placebo group and to 12 patients (13.8%) in the OL arm. The most commonly used rescue therapies were metformin and sulfonylurea.

Comments: The superiority of both empagliflozin doses over placebo was confirmed ($p < 0.0001$ for empagliflozin 10 mg and 25 mg) for the primary endpoint (HbA1c change from baseline at Week 24), and for the first 2 key secondary endpoints (change from baseline at Week 24 in body weight and SBP); all these changes were clinically relevant and statistically significant. The test for superiority with regard to DBP change from baseline at Week 24 did not reach statistical significance. For most endpoints, the exploratory comparison of both empagliflozin doses versus sitagliptin provided a larger treatment effect of empagliflozin.

Treatment with empagliflozin 25 mg showed a numerically greater reduction in HbA1c than treatment with sitagliptin; the reduction in HbA1c for treatment with empagliflozin 10 mg was almost identical to that for sitagliptin. Treatment with both empagliflozin 10 mg and 25 mg reduced body weight and BP compared with sitagliptin treatment, although there was no direct statistical comparison between empagliflozin and sitagliptin.

7.1.1.3. Study 1245.23

7.1.1.3.1. Study design, objectives, locations and dates

1245.23 was a pivotal, 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. The objective of this trial was to investigate the efficacy, safety, and tolerability of empagliflozin (10 mg and 25 mg once daily) compared with placebo given for 24 weeks as add-on therapy to metformin or metformin plus sulphonylurea in patients with type 2 diabetes mellitus with insufficient glycaemic control. A further objective was to investigate efficacy and safety of 25 mg empagliflozin in patients with very poor glycaemic control (HbA1c > 10%) in an open label arm. The study was conducted from 29 July 2010 to 3 Feb 2012 at 148 trial sites enrolled patients in 12 countries (Canada, China, France, Germany, India, Korea, Mexico, Slovakia, Slovenia, Taiwan, Turkey, United States).

The 2 parts of the study were defined by the background medication the patients received at baseline and were regarded as independent substudies; the background medication was either metformin alone (substudy A) or metformin plus sulphonylurea (substudy B). Background medication was to be taken during the entire trial duration (including placebo run-in period) with dose unchanged. Results of these two substudies will be discussed separately.

7.1.1.3.2. Inclusion and exclusion criteria

The main inclusion criteria were type 2 diabetes mellitus and insufficient glycaemic control (HbA1c ≥ 7.0 and $\leq 10.0\%$) despite therapy with metformin alone or metformin plus sulphonylurea; age ≥ 18 years; BMI ≤ 45 kg/m². Patients with an HbA1c > 10% and fulfilling all remaining inclusion criteria were eligible for inclusion in the 25 mg empagliflozin open label arm. The exclusion criteria were similar to those described for pivotal studies described above.

7.1.1.3.3. Study treatments

Patients who met the trial eligibility criteria at the end of the 2-week placebo run-in period were randomly assigned to 1 of the 3 treatment groups (empagliflozin 10 mg, empagliflozin 25 mg, placebo) in a 1:1:1 ratio. Two-week placebo run-in (except for patients allocated to the open label treatment arm); 24-week treatment period; 1-week follow-up period or enrolment in extension trial BI 1245.31.

7.1.1.3.4. Efficacy variables and outcomes

The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment. The key secondary endpoints were the change from baseline in body weight and mean daily plasma glucose (MDG) after 24 weeks of treatment. Further secondary endpoints were defined as the occurrence of a treat-to-target response (HbA1c under treatment of < 7.0% and < 6.5%), occurrence of relative efficacy response (HbA1c lowering by at least 0.5%), change in fasting plasma glucose (FPG), waist circumference, and systolic and diastolic BP from baseline, occurrence of BP response with blood pressure lower than 130/80 mmHg, percentage of patients with history of hypertension and not at BP goal of < 130/80 mmHg at baseline achieving BP response, weight reduction by > 5%, and a composite endpoint (HbA1c reduction of $\geq 0.5\%$, reduction of SBP by > 3 mmHg, and decrease in body weight > 2%); all of which were assessed after 24 weeks of treatment. In addition, change in HbA1c, FPG, and BP by visit over time were evaluated. Use of rescue medication was also assessed.

Endpoints based on biomarkers were defined as change from baseline after 24 weeks of treatment for C-peptide, fasting plasma insulin, ratios of proinsulin/insulin, insulin/C-peptide, and insulin/glucose, homeostasis model assessment for insulin resistance and secretion, and disposition index. Endpoints for a meal tolerance test were defined as change from baseline of post-prandial glucose after 24 weeks of treatment, incremental area under the curve (iAUC) for glucose, C-peptide, and insulin, and derived ratios.

7.1.1.3.5. *Randomisation, blinding and statistical methods*

Randomisation, blinding, statistical methods and sample size calculations were similar to those described for study 1245.20 above.

The results of the two substudies will be discussed separately below:

7.1.1.3.6. *Results of Substudy A: 1245.23 (met)*

7.1.1.3.6.1. Participant flow

This substudy included 970 enrolled patients from 136 centres in 12 countries in Asia, Europe, North America, and Latin America. A total of 638 patients were randomised in a 1:1:1 ratio to receive treatment with empagliflozin 10 mg (217 patients), empagliflozin 25 mg (214 patients) or placebo (207 patients) in addition to their metformin background therapy. Of the 637 randomised patients, 46 (7.2%) prematurely discontinued study medication (empagliflozin 10 mg: 3.7%, empagliflozin 25 mg: 8.0%, placebo: 10.1%) with the main reason for discontinuation being the occurrence of adverse events (empagliflozin 10 mg: 0.9%, empagliflozin 25 mg: 2.3%, placebo: 3.4%). Overall, 69 patients were entered into the open label treatment group. In total, 58 patients (84.1%) completed the 24-week treatment period.

7.1.1.3.6.2. Major Protocol violations/deviations, analysis populations

A total of 81 patients (12.7%) in the randomised set of this substudy were reported with important protocol violations and 58 (9.1%) of these patients were excluded from the PPS analysis, with a higher frequency in the placebo group (26 patients (12.6%)) than in the empagliflozin treatment groups (empagliflozin 10 mg: 15 patients (6.9%), empagliflozin 25 mg: 17 patients (7.9%)). The most frequent important protocol violation leading to exclusion from the PPS in all randomised treatment groups was non-compliance with drug intake (empagliflozin 10 mg: 3.2%, empagliflozin 25 mg: 4.2%, placebo: 8.2%). Important protocol violations not leading to exclusion from the PPS were reported for a total of 28 patients (4.4%) with similar frequencies in all randomised treatment groups.

Efficacy endpoints were primarily analysed based on the FAS, which was based on the ITT principle (all patients randomised and treated). Sensitivity analyses assessing the impact of premature discontinuation of trial medication and important protocol violations were performed on the FAS completers, PPS, and PPS completers. The proportions of patients in the analyses sets were generally balanced across the randomised treatment groups.

7.1.1.3.6.3. Baseline data

Majority of the patients were male (56.7%), White (53.1%) or Asian (45.4%) with mean (SD) age of 55.7 (9.9) years and mean weight of 80-82kg. At baseline, 44.3% of the patients had normal renal function, 50.2% had mild and 5.5% of patients had moderate renal impairment. Mean (SD) baseline HbA1c was similar across the randomised treatment groups (7.9%). Overall mean (SD) baseline FPG was 153.3 (33.0) mg/dL, waist circumference was 99.5 (13.7) cm, SBP was 129.4 (14.6), DBP was 78.7 (8.1) mmHg, and BMI was 29.18 (5.49) kg/m². Most patients had been diagnosed with diabetes for > 1 to 5 years (36.1%) or > 5 to 10 years (32.5%). In the open label group, majority of the patients were male (59.4%), White (71.0%), had normal renal function (62.3%) (36.2% had mild renal impairment and 1.4% had moderate renal impairment) and the mean age was 49.8 (11.5) years. Overall mean (SD) baseline HbA1c was 11.07 (1.29)%, weight was 85.07 (21.96) kg, BMI was 30.37 (5.51) kg/m², MDG was 226.32 (54.14) mg/dL, FPG was 203.6 (64.0) mg/dL, SBP was 126.2 (11.4), DBP was 79.3 (7.9) mmHg, and waist circumference was 99.8 (13.3) cm; 40.6% of patients had been diagnosed with diabetes for > 1

to 5 years. The demographic and baseline characteristics were comparable between the randomised treatment groups. The proportions of patients taking concomitant therapy at baseline were similar across the randomised treatment groups (67.1%, 71.0% and 72.3% in placebo, empagliflozin 10mg and 25mg groups, respectively) with the most common medications being antihypertensives (48.8%, 52.5% and 52.1%, respectively), lipid-lowering agents (35.3%, 40.1% and 35.7%, respectively) and ASA (26.1%, 28.6% and 20.2%, respectively). In the open label group, 56.5% of patients were taking concomitant therapies at baseline; antihypertensive drugs were taken by 31.9% of patients, lipid lowering drugs by 24.6% of patients and ASA by 10.1% of patients. All patients were required to be on metformin antidiabetic therapy, but a total of 9 patients in the randomised treatment groups and 1 patient in the open label group were taking metformin and sulphonylurea as background medication and were erroneously enrolled in the 'metformin only' substudy. The mean dose of metformin administered was 1700 mg with 95% of the patients taking > 1500mg metformin daily. The use of antidiabetic rescue medication on treatment was analysed as an efficacy endpoint in this trial; a higher proportion of patients in the placebo group (14.5%) than in the randomised empagliflozin groups (empagliflozin 10 mg: 5.5%, empagliflozin 25 mg: 2.8%) had antidiabetic medication introduced on treatment. In the open label group, 14.5% of patients had antidiabetic medication introduced on treatment. With regard to relevant medical history, more than half (55.7%) of all treated patients in the randomised groups had hypertension, 9.9% had diabetic neuropathy, 7.7% had coronary artery disease, 5.7% had chronic or recurrent urinary tract infection, and 4.7% had diabetic retinopathy with similar incidences in the 3 treatment groups. Overall compliance was between 80% and 120% for 95.9% of patients in the randomised treatment groups and 92.8% of patients in the open label group.

7.1.1.3.6.4. Results for primary efficacy outcomes

The mean change from baseline showed statistically significantly ($p < 0.001$) greater reduction in HbA1c with both empagliflozin doses compared with placebo (-0.13%, -0.70% and -0.71% with placebo, empagliflozin 10 mg and 25 mg, respectively). These results were confirmed in the sensitivity analysis. The treatment effects of both doses of empagliflozin increased up to Week 12 and were sustained thereafter, with a slight transient increase in HbA1c noted for both empagliflozin treatment groups at Week 18. Among patients with baseline HbA1c of 7.0% or greater, greater proportion of patients treated with empagliflozin attained HbA1c values of less than 7.0% after 24 weeks of treatment compared with placebo (37.7%, 38.7% and 12.5% in 10 mg, 25 mg and placebo groups, respectively); the odds ratios (empagliflozin compared with placebo) for patients with a baseline HbA1c of 7.0% or greater to attain an HbA1c less than 7.0% at 24 weeks were 4.716 ($p < 0.0001$) for the empagliflozin 10 mg group and 4.673 ($p < 0.0001$) for the empagliflozin 25 mg group. Similar results were observed among patients with baseline HbA1c of 6.5% or greater with 7.9%, 16.1% and 4.9%, respectively attaining HbA1c less than 6.5.0% at 24 weeks; however, the odds ratios (empagliflozin compared with placebo) for patients with a baseline HbA1c of > 6.5% to attain an HbA1c less than 6.5% at 24 weeks was statistically significant only for the 25 mg dose (4.114; $p = 0.0003$), but not for the 10 mg dose (1.947; $p = 0.1176$). Likewise, the proportions of patients that had a reduction in HbA1c of at least 0.5% after 24 weeks of treatment were higher in the empagliflozin 10 mg group (56.2%) and e25 mg group (56.3%) than in the placebo group (26.1%) and the odds ratios (empagliflozin compared with placebo) for patients to attain an HbA1c reduction of at least 0.5% were 4.012 ($p < 0.0001$) for the empagliflozin 10 mg group and 4.393 ($p < 0.0001$) for the 25 mg group.

For open label treatment with 25 mg empagliflozin the mean change (SD) from baseline at week 24 in HbA1c was -2.78 (1.73)% for LOCF imputation and -3.23 (1.49)% for OC (observed case) imputation. In the HbA1c over time analysis of the open label set, reduction in HbA1c was achieved mostly in the first 6 weeks of treatment with further decrease until Week 24. In the open label group, 8.7% of patients had an HbA1c less than 7.0% and 1.4% had an HbA1c less than 6.5% after 24 weeks of treatment, while 66.7% of patients attained an HbA1c reduction of at least 0.5% after 24 weeks of treatment.

7.1.1.3.6.5. Results for other efficacy outcomes

Key secondary efficacy endpoints

The adjusted mean change from baseline in body weight showed statistically significantly greater reduction in both empagliflozin groups (-2.08, -2.46 and -0.45 kg for the empagliflozin 10 mg, 20 mg and placebo groups, respectively). The analysis of body weight showed superiority ($p < 0.0001$) of both doses of empagliflozin to placebo in the randomised treatment groups and the adjusted mean difference versus placebo for change in body weight from baseline at Week 24 was -1.63 kg (97.5% CI: -2.17, -1.08) for the empagliflozin 10 mg group and -2.01 kg (97.5% CI: -2.56, -1.46) for the empagliflozin 25 mg group; these results were confirmed in the sensitivity analysis. The proportion of patients that had a reduction in body weight of more than 5% from baseline were higher in the empagliflozin 10 mg group (21.2%) and empagliflozin 25 mg group (23.0%) than in the placebo group (4.8%). In the open label group, the mean change in body weight from baseline at Week 24 was -1.33 kg from a baseline body weight of 85.07 kg and 15.9% of patients had a reduction in body weight of more than 5% from baseline.

After 24 weeks of treatment, there were clinically relevant and statistically significant reductions in MDG with both doses of empagliflozin (adjusted mean change from baseline in MDG was -9.64, -14.36 and -1.99 mg/dL for empagliflozin 10 mg, 25 mg and placebo groups, respectively). Due to strict time windows for this endpoint, a substantial proportion of patients had measurements excluded from the sensitivity analyses. As a consequence many patients did not have baseline values for MDG and were excluded from the analyses; explaining the lower number of analysed patients as compared to other endpoints. In addition, many patients had only a baseline value; these values were carried forward and included in the LOCF analysis which may account for a smaller treatment effect. In the open label group, the mean change in MDG from baseline at Week 24 was -35.47 mg/dL from a baseline MDG value of 226.32 mg/dL.

In line with the reduction in HbA1c, consistent reductions in FPG from baseline were noted in comparison to placebo treatment for both doses of empagliflozin (adjusted mean change from baseline in FPG was -20.04, -22.28 and +6.38 mg/dL in the empagliflozin 10 mg, 25mg and placebo groups, respectively).

Clinically meaningful reductions in BP were noted for both doses of empagliflozin. Among those patients not already at the BP goal at baseline, more patients in the empagliflozin groups (10 mg = 35.9%; 25 mg = 30.4%) reached the BP goal after 24 weeks of treatment, compared with the placebo group (13.2%). A similar pattern was apparent when this analysis was repeated for patients who had a history of hypertension. Of those patients with a history of hypertension, and who were not already at the BP goal at baseline, the proportion of patients who reached the BP goal after 24 weeks of treatment was 33.3%, 22.8% and 14.1% in the empagliflozin 10 mg, 25 mg and placebo groups, respectively.

Reductions in waist circumference in the empagliflozin treatment groups were consistent with reduction in body weight after 24 weeks of treatment; mean change (SD) in waist circumference in the FAS (LOCF) at Week 24 was -1.52 (4.17), -1.61 (3.63) and -0.52 (3.21) in the empagliflozin 10 mg, 25 mg and placebo groups, respectively.

The proportion of patients who achieved the composite endpoint (reduction in HbA1c by $\geq 0.5\%$, SBP by > 3 mmHg, and body weight by $> 2\%$ at Week 24) was higher in the empagliflozin groups than in the placebo group (23.0%, 24.4% and 3.4%, respectively. In the open label group, 18.8% of patients fulfilled the criteria for the composite endpoint.

Notable differences to placebo in change from baseline were seen for several biomarkers: C-peptide, fasting plasma insulin, as well as the derived parameters insulin/C-peptide ratio, and HOMA-IR decreased in the empagliflozin treatment groups when compared with placebo treatment; the disposition index increased after 24 weeks for both empagliflozin treatment groups when compared with placebo treatment. No differences to placebo in change from

baseline were noted for the derived parameters proinsulin/insulin ratio, insulin/glucose ratio, and HOMA-IS.

An MTT (meal tolerance test) was an optional part of this trial and was carried out for 224 patients in this substudy. The MTT set included 167 patients and was performed at baseline and Week 24. After 24 weeks of treatment, there were clinically relevant reductions in 2 h postprandial glucose (2 h PPG) with both doses of empagliflozin. After 24 weeks of treatment, there were clinically relevant reductions in glucose iAUC with both doses of empagliflozin.

Lower proportions of patients in the empagliflozin groups (empagliflozin 10 mg: 12 patients (5.5%), empagliflozin 25 mg: 7 patients (3.3%)) than in the placebo group (29 patients (14.0%)) required the use of rescue medication at least once during randomised treatment. The associated odds ratios of using rescue medication for patients treated with empagliflozin compared with placebo were 0.334 (95% CI: 0.160, 0.698; $p = 0.0035$) for empagliflozin 10 mg and 0.179 (95% CI: 0.072, 0.447; $p = 0.0002$) for empagliflozin 25 mg. Of the 19 patients who required rescue medication while on randomised treatment with empagliflozin, the additional antidiabetic therapy was either a sulphonylurea (6 patients on empagliflozin 10 mg, 3 patients on empagliflozin 25 mg), a glitazone (3 patients on empagliflozin 10 mg, 2 patients on empagliflozin 25 mg), a DPP-IV-inhibitor (1 patient on empagliflozin 25 mg), a GLP-1 agonist (1 patient on empagliflozin 10 mg), or insulin (1 patient on empagliflozin 10 mg). An increase in dose of background medication was required for 2 patients on empagliflozin 10 mg, 1 patient on empagliflozin 25 mg, and 1 patient on placebo. In the open label group, 10 patients (14.5%) required the use of rescue medication.

7.1.1.3.7. Results of Substudy B: 1245.23 (met+sulf)

7.1.1.3.7.1. Participant flow

This substudy included 1010 enrolled patients from 129 centres in 12 countries in Asia, Europe, North America, and Latin America. A total of 669 patients were randomised in a 1:1:1 ratio to receive treatment with either empagliflozin 10 mg (226 patients), empagliflozin 25 mg (218 patients) or placebo (225 patients) in addition to their metformin plus sulphonylurea background therapy. A total of 666 patients were treated with randomised study medication. Of those, 58 patients (8.7%) prematurely discontinued study medication (empagliflozin 10 mg: 7.6%, empagliflozin 25 mg: 7.9%, placebo: 10.7%) with the main reason for discontinuation being the occurrence of adverse events (empagliflozin 10 mg: 2.7%, empagliflozin 25 mg: 3.2%, placebo: 3.6%). Overall, 101 patients were treated with empagliflozin 25 mg on an open label basis. In total, 85 patients (84.2%) completed the 24-week treatment period.

7.1.1.3.7.2. Major Protocol violations/deviations, analysis populations

A total of 123 patients (18.4%) in the randomised set were reported with important protocol violations and 79 patients (11.8%) were excluded from the PPS analysis, with similar frequencies of patients in the treatment groups (empagliflozin 10 mg: 23 patients (10.2%), empagliflozin 25 mg: 27 patients (12.4%), placebo: 29 patients (12.9%)). The most frequent important protocol violation leading to exclusion from the PPS in all randomised treatment groups was noncompliance with drug intake (empagliflozin 10 mg: 4.9%, empagliflozin 25 mg: 8.7%, placebo: 7.6%). Important protocol violations not leading to exclusion from the PPS were reported for a total of 45 patients (6.7%).

Efficacy endpoints were primarily analysed based on the FAS, which was based on the ITT principle (all patients randomised and treated). Sensitivity analyses assessing the impact of premature discontinuation of trial medication and important protocol violations were performed on the FAS completers, PPS, and PPS completers. The proportions of patients in the analyses sets were generally balanced across the randomised treatment groups.

7.1.1.3.7.3. Baseline data

Majority of the patients were male (50.9%), Asian (57.2%; 39.3% were White) and the mean (SD) age was 57.1 (9.2) years, mean HbA1c was 8.1%, mean body weight was 77 kg and BMI was 28.18 (5.27) kg/m². At baseline, 42.0% of patients had normal renal function, 49.2% had

mild renal impairment, and 8.7% had moderate renal impairment. Overall mean (SD) baseline MDG was 170-173mg/dL, FPG was 153.0 (34.2) mg/dL, waist circumference was 96.4 (13.4) cm, SBP was 128.9 (14.1), DBP was 78.6 (8.8) mmHg. Most patients had been diagnosed with diabetes for > 5 to 10 years (37.1%) or for more than 10 years (40.4%). The demographic and baseline characteristics were comparable between the randomised treatment groups. In the open label group, majority of patients were male (53.5%), White (49.5%; 47.5% were Asian) and the mean (SD) age was 53.4 (10.5) years., HbA1c was 11.18 (1.25)%, weight was 76.43 (18.21) kg, BMI was 28.70 (5.49) kg/m², MDG was 233.07 (63.34) mg/dL, FPG was 200.4(60.8) mg/dL, SBP was 126.4 (12.4), DBP was 78.3 (8.8) mmHg, and waist circumference was 97.6 (13.9) cm. The majority of patients had normal renal function (53.5%) or mild renal impairment (41.6%); 5.0% had moderate renal impairment at baseline; 37.6 % of patients had been diagnosed with diabetes for more than 10 years, 32.7% for > 5 to 10 years. The frequency of patients taking concomitant therapy at baseline was slightly higher in the empagliflozin treatment groups when compared with the placebo group (82.7% empagliflozin 10 mg, 81.9% empagliflozin 25 mg, 75.1% placebo); the most common medications were antihypertensive drugs (empagliflozin 10 mg: 51.1%, empagliflozin 25 mg: 59.1%, placebo: 51.1%), followed by lipid lowering drugs (empagliflozin 10 mg: 43.1%, empagliflozin 25 mg: 42.6%, placebo: 43.6%) and ASA (empagliflozin 10 mg: 31.1%, empagliflozin 25 mg: 28.2%, placebo: 31.1%). In the open label group, 78.2% of patients were taking concomitant therapies at baseline: antihypertensive drugs by 55.4%, lipid lowering drugs by 36.6% and ASA by 20.8% of patients.

The substudy inclusion criteria required the patients to be on antidiabetic treatment with metformin plus sulphonylurea. However, a total of 4 patients in the randomised treatment groups and 1 patient in the open label group who were taking metformin only as background medication were erroneously enrolled in the 'metformin and sulphonylurea' substudy. Furthermore, 1 patient in the randomised groups was taking insulin and 1 patient in the open label group was taking a DPP-IV inhibitor as background therapy in addition to metformin and sulphonylurea. Majority of the patients were on metformin daily doses > 1500 mg. With regard to relevant medical history, more than half (59.6%) of all treated patients in the randomised groups had hypertension, 15.3% had diabetic neuropathy, 11.9% had coronary artery disease, and 10.2% had diabetic retinopathy; there were some numerical imbalances in the incidence of these conditions in the randomised treatment groups. In the open label group, hypertension was reported in the medical history of more than half (58.4%) of patients, while 10.9% had diabetic neuropathy and 10.9% had diabetic nephropathy.

Overall compliance was between 80% and 120% for 95.2% of patients in the randomised treatment groups. In the open label group, 93.1% of patients had overall compliance within this range.

7.1.1.3.7.4. Results for primary efficacy outcomes

After 24 weeks of treatment, there were clinically relevant and statistically significant ($p < 0.001$) reductions in HbA1c with both doses of empagliflozin; the adjusted mean change from baseline in HbA1c was -0.82%, -0.77% and -0.17% in the empagliflozin 10 mg, 25 mg and placebo groups, respectively. All sensitivity analyses using different imputation approaches showed results consistent with the primary analysis.

The treatment effects of both doses of empagliflozin increased up to Week 12 and were sustained thereafter, with a slight transient increase in HbA1c noted for both empagliflozin treatment groups at Week 18. In the HbA1c over time analysis of the open label group, reduction in HbA1c was achieved mostly in the first 6 weeks of treatment with further decrease until Week 24.

Among patients with baseline HbA1c of 7.0% or greater, more patients in the empagliflozin groups attained HbA1c values of less than 7.0% after 24 weeks of treatment compared with placebo (26.3%, 32.2% and 9.3% , respectively; odds ratios was 3.851, $p < 0.0001$ for the empagliflozin 10 mg group and 5.222, $p < 0.0001$ for the 25 mg group. Similar results were observed among patients with baseline HbA1c of 6.5% or greater with 10.8%, 11.7% and 3.1%

of patients in the empagliflozin 10 mg, 25 mg and placebo groups, respectively attaining HbA1c values of less than 6.5% after 24 weeks of treatment (odds ratios: 10 mg versus placebo = 3.797, $p = 0.0032$ and 25mg versus placebo = 4.348, $p = 0.011$). Likewise, the proportion of patients that had a reduction in HbA1c of at least 0.5% after 24 weeks of treatment was higher in the empagliflozin groups compared with placebo (58.7%, 62.5% and 31.6%, respectively; odds ratios: 10 mg versus placebo = 3.453, $p < 0.0001$; 25 mg versus placebo = 4.031, $p < 0.0001$). In the open label group, 8.9% of patients had an HbA1c less than 7.0% and 3.0% had an HbA1c less than 6.5% after 24 weeks of treatment, while 66.3% of patients attained an HbA1c reduction of at least 0.5% after 24 weeks of treatment.

7.1.1.3.7.5. Results for other efficacy outcomes

Key secondary endpoints

After 24 weeks of treatment, there were clinically relevant and statistically significant reductions in body weight with both doses of empagliflozin (adjusted mean change from baseline in body weight was -2.16, -2.39 and -0.39 kg in the empagliflozin 10 mg, 25 mg and placebo groups, respectively. The analysis was repeated for the FAS (OC), FAS (OC-IR), FAS completers (LOCF), the PPS (LOCF), and the PPS completers (LOCF). All sensitivity analyses performed in the different analysis sets showed results consistent with the main analysis of change in body weight respectively. The proportion of patients that had a reduction in body weight of more than 5% from baseline were higher in the empagliflozin groups compared with placebo (27.6%, 23.6% and 5.8%, respectively. In the open label group, the mean change in body weight from baseline at Week 24 was -1.29 kg from a baseline body weight value of 76.43 kg and 18.8% of the patients showed a reduction in body weight of > 5% from baseline.

After 24 weeks of treatment, there were statistically significant and clinically relevant reductions in MDG with both doses of empagliflozin compared with placebo. The adjusted mean change from baseline in MDG was -10.01 mg/dL for the empagliflozin 10 mg group and -13.06 mg/dL for the empagliflozin 25 mg group, compared with no change in the placebo group. It is important to note that due to strict time windows for measurement of this endpoint, many patients were excluded from the analysis, and the numbers of analysed patients for MDG analysis were lower than for the other key secondary endpoint. In the open label group, the mean change in MDG from baseline at Week 24 was -29.34 mg/dL from a baseline MDG value of 233.07 mg/dL.

Other efficacy endpoints

After 24 weeks of treatment, there were clinically relevant reductions in FPG with both doses of empagliflozin (adjusted mean change from baseline was -23.30, -23.27 mg/dL for the empagliflozin 10 and 25 mg groups, respectively compared with an increase of 5.52 mg/dL in the placebo group. In the open label group, the mean change (SD) in FPG from baseline at Week 24 for the open label set (LOCF) was -55.29 (57.97) mg/dL and for the open label set (OC) was -54.34 (54.03) mg/dL from a baseline FPG value of 200.40 mg/dL.

After 24 weeks of treatment, there were clinically meaningful reductions in SBP with both doses of empagliflozin (adjusted mean change from baseline was -4.1, -3.5 and -1.4 mmHg in the empagliflozin 10 mg, 25 mg and placebo groups, respectively). However, there were no clinically meaningful reductions in DBP with empagliflozin compared with placebo (-2.1, -2.2 and -1.8 mmHg, respectively). Among those patients not already at the BP goal at baseline, 32.9%, 31.3% 25.4% of patients in the empagliflozin 10 mg, 25 mg and placebo groups, respectively reached the BP goal after 24 weeks of treatment. A similar pattern was apparent when this analysis was repeated for patients who had a history of hypertension with 30.8%, 26.0% and 21.5% of patients, respectively reaching the BP goal after 24 weeks of treatment. In the open label group, the mean (SD) change in SBP from baseline at Week 24 was -3.6 (1.0) mmHg from a mean (SD) baseline SBP value of 126.4(1.2) mmHg. And that in DBP was -3.0 mmHg from a baseline DBP value of 78.3 mmHg. At baseline, 57.4% of patients in the open label group were not at BP control. Of those patients, 24.1% reached the BP goal after 24 weeks of

treatment. Of those patients in the open label group with a history of hypertension, and who were not already at the BP goal at baseline, 25.0% reached the BP goal after 24 weeks of treatment. The change in waist circumference from baseline at Week 24 was analysed descriptively and showed reductions which were in line with the observed changes in body weight (mean change from baseline to week 24 was -1.50, -1.52 and -0.24 in the empagliflozin 10 mg, 25 mg and placebo groups, respectively). Patients treated with empagliflozin 25 mg in the open label arm also showed reduction of -1.17cms at 24 weeks.

The proportion of patients who achieved the composite endpoint (reduction in HbA1c by $\geq 0.5\%$, SBP by > 3 mmHg, and body weight by $> 2\%$) at Week 24 was higher in the empagliflozin groups than in the placebo group (24.4%, 25.0% and 7.1%, respectively) and 17.8% of patients achieved the composite endpoint in the 25 mg empagliflozin OL group.

Notable differences to placebo in change from baseline were seen for several biomarkers C-peptide, fasting plasma insulin, as well as the derived parameters insulin/C-peptide ratio, and HOMA-IR decreased in the empagliflozin treatment groups when compared with placebo treatment; the disposition index increased after 24 weeks for both empagliflozin treatment groups when compared with placebo treatment. No differences to placebo in change from baseline were noted for the derived parameters proinsulin/insulin ratio, insulin/glucose ratio and HOMA-IS.

An MTT was an optional part of this trial and was carried out for 169 patients in this substudy. The MTT set included 125 patients and it was performed at baseline and Week 24. After 24 weeks of treatment, there were clinically relevant reductions in 2 h postprandial glucose (2 h PPG) with both doses of empagliflozin; the adjusted mean change from baseline in 2 h PPG was -35.72, -36.59 and -2.28 mg/dL in the empagliflozin 10 mg, 25 mg and placebo groups, respectively. After 24 weeks of treatment, there were notable reductions in glucose iAUC with both doses of empagliflozin.

Fewer patients in the empagliflozin groups (10 mg = 5 patients (2.2%); 25 mg = 2 patients (0.9%)) than in the placebo group (26 patients (11.6%)) required the use of rescue medication at least once during randomised treatment period. The associated odds ratios of using rescue medication for patients treated with empagliflozin compared with placebo were 0.175 (95% CI: 0.065, 0.474; $p = 0.0006$) for empagliflozin 10 mg and 0.065 (95% CI: 0.0015, 0.283; $p = 0.0003$) for 25 mg. Of the 7 patients who required rescue medication while on randomised treatment with empagliflozin, the additional antidiabetic therapy was either a glitazone (4 patients on empagliflozin 10 mg, 1 patient on empagliflozin 25 mg) or an alpha-glucosidase inhibitor (1 patient on empagliflozin 10 mg, 1 patient on empagliflozin 25 mg). In the open label group, 11 patients (10.9%) required the use of rescue medication.

Comments: The results of this well-conducted pivotal study provided evidence for efficacy of empagliflozin (10mg and 25mg) in T2DM patients with inadequate glycaemic control on background therapy with metformin alone or on metformin in combination with SU.

7.1.2. Other efficacy studies

7.1.2.1. Study 1245.31

This was a Phase III double-blind, extension, placebo-controlled parallel group safety and efficacy trial of BI 10773 (10 and 25 mg once daily) and sitagliptin (100 mg once daily) given for minimum 76 weeks (including 24 weeks of preceding trial) as monotherapy or with different background therapies in patients with type 2 diabetes mellitus previously completing trial 1245.19, 1245.20 or 1245.23. The study was conducted at 243 trial sites in 20 countries (China, India, Japan, Korea, Philippines, Taiwan, Thailand, Belgium, France, Germany, Greece, Ireland, Slovakia, Slovenia, Switzerland, Turkey, Ukraine, Mexico, Canada, United States) from 29 Feb 2011 and is still ongoing with interim data up to 23 May 2012 provided in this submission.

The main objective of this extension study was to investigate the long-term safety/ tolerability and the long-term efficacy of empagliflozin (10 or 25 mg once daily) compared with sitagliptin (100 mg once daily) or placebo as monotherapy (preceding trial 1245.20); placebo on a

background of pioglitazone (preceding trial 1245.19); placebo on a background of metformin with or without sulfonylurea (preceding trial 1245.23). This extension study combines 4 studies under one study number, which varied with regard to background therapy (drug-naive patients and patients on 3 different background therapies, i.e. pioglitazone, metformin only, or metformin plus sulfonylurea). Each study was designed as a randomised, double-blind, active or placebo-controlled, parallel group comparison. Patients continued on the treatment to which they had been randomised in the preceding trial; no re-randomisation was performed in the extension trial. Screening, randomisation and start of treatment occurred in the preceding trials (1245.19, 1245.20, 1245.23).

This study included 1806 patients with type 2 diabetes mellitus who had successfully completed the preceding blinded studies 1245.19, 1245.20, or 1245.23. In addition to the 24 weeks of treatment in the preceding trial, patients were to be treated for at least 52 weeks in the extension trial. Patients were to remain in the trial until the last patient had been treated for 52 weeks in the extension trial.

No primary efficacy endpoint was defined (primary efficacy endpoint was analysed at Week 24 of the preceding trials). Secondary endpoints were the change from baseline in HbA1c, body weight, waist circumference, fasting plasma glucose (FPG), and systolic and diastolic blood pressure (SBP and DBP) after a total treatment duration of 52 weeks (24 weeks in the preceding trial plus 28 weeks in the extension). All statistical analyses were performed separately for each of the 4 studies (i.e. drug-naive patients and the 3 antidiabetic background therapies); no pooled analysis across studies was carried out.

7.1.2.1.1. *Drug-naive patients (preceding trial 1245.20)*

Both empagliflozin groups showed a significant decrease relative to placebo in mean HbA1c, FPG, body weight, waist circumference, SBP, and DBP at Week 52, based on exploratory treatment comparisons using an ANCOVA model applied to the FAS (LOCF). Both empagliflozin groups also showed a significant decrease in mean values for all secondary endpoint parameters relative to sitagliptin, except for HbA1c and DBP, which decreased significantly vs. sitagliptin in the 25 mg group but only numerically in the 10 mg group. Both empagliflozin groups showed numerically higher incidences than placebo and sitagliptin with regard to patients achieving HbA1c < 7.0% (31.9%, 38.6%, 11.5% and 25.5% in the empagliflozin 10 mg, 25 mg, placebo and sitagliptin groups, respectively), HbA1c reduction by at least 0.5% (42%, 49.1%, 14.5% and 38.6%, respectively), body weight reduction by more than 5% (19.6%, 19.2%, 4.4% and 4.5%, respectively), BP below 130/80 mmHg (33.0%, 30.4%, 16.2% and 18.4%, respectively) and achieving the composite endpoint¹³ (14.7%, 17.9%, 2.6% and 4.9%, respectively); use of rescue medication was less frequent in the empagliflozin groups (5.8%, 3.6% 27.6% and 11.2%, respectively). Parameters for which both empagliflozin groups showed a relevant difference to placebo and sitagliptin in the adjusted mean change from baseline were C-peptide, fasting plasma insulin, HOMA-IR, and the disposition index. For C-peptide, both empagliflozin groups showed a more pronounced decrease than the placebo group and the sitagliptin group. For fasting plasma insulin and HOMA-IR, values decreased for both empagliflozin doses, while they increased for placebo and sitagliptin. For the disposition index, values increased for the empagliflozin doses, while they decreased for placebo and sitagliptin. Mean values for all biomarkers generally remained stable from Week 24 to Week 52 in both empagliflozin groups.

7.1.2.1.2. *Pioglitazone background medication (preceding trial 1245.19)*

Both empagliflozin groups showed a significant decrease from baseline in mean HbA1c, body weight, waist circumference, FPG, SBP, and DBP at Week 52 relative to placebo, based on exploratory treatment comparisons. Both empagliflozin groups showed numerically higher incidences than placebo with regard to patients achieving HbA1c < 7.0% (14.6%, 23.8% and

¹³ Descriptive statistics were calculated for the number of patients who fulfilled the following criteria after 52 weeks: reduction in HbA1c by at least 0.5%, SBP by > 3 mmHg, and body weight by > 2%

7.1% in empagliflozin 10 mg, 25 mg and placebo groups, respectively), HbA1c reduction by a least 0.5% (33.9%, 36.9% and 19.4%, respectively), weight reduction by more than 5% (10.9%, 8.3% and 0.6% in empagliflozin 10 mg, 25 mg and placebo groups, respectively), BP below 130/80 mmHg (27.9%, 30.4% and 15.8%, respectively) and achieving the composite endpoint¹⁴ (4.8%, 10.1% and 1.2%, respectively); use of rescue medication was less frequent in the empagliflozin groups (8.5%, 7.1% and 22.4%, respectively). No biomarker and pharmacodynamic analyses were performed for patients rolling over from study 1245.19 (only for those rolling over from 1245.20 and 1245.23).

7.1.2.1.3. *Metformin background medication (preceding trial 1245.23)*

Both empagliflozin groups showed a significant decrease relative to placebo in mean HbA1c, body weight, waist circumference, FPG, SBP, and DBP at Week 52, based on exploratory treatment comparisons using an ANCOVA model applied to the FAS (LOCF). The analysis of secondary endpoint parameters over time showed a reduction of the adjusted mean values for up to 24 weeks after baseline that was generally sustained until Week 52. Both empagliflozin groups showed numerically higher incidences than placebo with regard to patients achieving HbA1c < 7.0% (28.1%, 30.9% and 10.3% in empagliflozin 10mg, 25mg and placebo groups, respectively), HbA1c reduction by a least 0.5% (41.5%, 42.7% and 14.5%, respectively), weight reduction by more than 5% (20.3%, 20.7% and 6.8%, respectively), BP below 130/80 mmHg (33.2%, 26.8% and 16.9%, respectively) and achieving the composite endpoint (15.7%, 14.6% and 1.4%, respectively); use of rescue medication was less frequent in the empagliflozin groups (9.2%, 6.6% and 28.5%, respectively). Parameters for which both empagliflozin groups showed a relevant difference to placebo in the adjusted mean change from baseline (those with an associated p-value < 0.05) were C-peptide, fasting plasma insulin, HOMA-IR, and the disposition index. For C-peptide, fasting plasma insulin, and HOMA-IR, both empagliflozin groups showed a decrease, while an increase was seen for placebo. For the disposition index, values increased for the empagliflozin doses, while the placebo group showed a decrease. Mean values for all biomarkers generally remained stable from Week 24 to Week 52 in both empagliflozin groups.

7.1.2.1.4. *Metformin and sulfonylurea background medication (preceding trial 1245.23)*

Both empagliflozin groups showed a significant decrease relative to placebo in mean HbA1c, body weight, waist circumference, FPG, SBP, and DBP at Week 52, based on exploratory treatment comparisons using an ANCOVA model applied to the FAS (LOCF). The analysis of secondary endpoint parameters over time showed a reduction of the adjusted mean values for up to 24 weeks after baseline that was generally sustained until Week 52, with a slight increase in mean SBP and mean DBP seen in both empagliflozin groups from Week 24 to Week 52. Both empagliflozin groups showed numerically higher incidences than placebo with regard to patients achieving HbA1c < 7.0% (18.7%, 20.8% and 4.6% in empagliflozin 10mg, 25mg and placebo groups, respectively), HbA1c reduction by a least 0.5% (41.8%, 42.1% and 15.1%, respectively), weight reduction by more than 5% (16%, 16.7% and 3.6%, respectively), BP below 130/80 mmHg (26.7%, 28.7% and 17.8%, respectively) and achieving the composite endpoint (14.7%, 15.7% and 0.9%, respectively); use of rescue medication was less frequent in the empagliflozin groups (5.3%, 7.9% and 20.4%, respectively). Parameters for which both empagliflozin groups showed a relevant difference to placebo in the adjusted mean change from baseline were C-peptide, fasting plasma insulin, the insulin/C-peptide ratio, and HOMA-IR. For all 4 parameters, both empagliflozin groups showed a decrease, while an increase or no change was seen for placebo. Mean values for all biomarkers generally remained stable from Week 24 to Week 52 in both empagliflozin groups.

Comment: Overall, treatment with empagliflozin 10 mg or 25 mg resulted in a clinically meaningful improvement of glucose control, weight, and blood pressure in patients with type 2 diabetes mellitus who were either drug-naive or on a background treatment with pioglitazone,

¹⁴ Descriptive statistics were calculated for the number of patients who fulfilled the following criteria after 52 weeks: reduction in HbA1c by at least 0.5%, SBP by > 3 mmHg, and body weight by > 2%

metformin alone, or metformin and sulfonylurea, which was sustained over 52 weeks of treatment.

7.1.2.2. Study 1245.33

This was a Phase IIb, randomised, double-blind, placebo-controlled, parallel group, safety and efficacy study of BI 10773 (10 mg and 25 mg) administered orally, once daily over 78 weeks in type 2 diabetic patients receiving treatment with basal insulin (glargine, detemir, or NPH insulin only) with or without concomitant metformin and/or sulfonylurea therapy and insufficient glycaemic control. The study was conducted at 97 centres in 7 countries (Denmark, France, Ireland, Republic of Korea, Portugal, United Kingdom, and United States) from 11 Nov 2009 to 9 May 2012.

The study included 498 patients aged > 18 years with T2DM with HbA1c > 7% and ≤ 10.0% and on basal insulin (glargine or detemir insulin of ≥ 20 IU/day or NPH insulin ≥ 14 IU/day) with or without concomitant metformin and / or sulfonylurea therapy. After an open label placebo run-in period, patients were randomised to the 3 treatment groups in a 1:1:1 ratio. Comparisons between treatment groups of the change of HbA1c from baseline after 18 weeks of treatment (primary efficacy endpoint) were performed using an analysis of covariance model (ANCOVA) that included treatment group and geographic region as fixed effects along with baseline HbA1c as covariate. The second part (after Week 18) of the study was a 'treat to target' study, and, therefore, any comparisons post Week 18 were to provide underestimates of the treatment effect of empagliflozin. The key secondary endpoints analysed at 78 weeks were intended to show decreased use of insulin (difference) accompanied by similar levels of HbA1c (non-inferiority) or even greater decrease in HbA1c (difference) compared with placebo. The non-inferiority margin of 0.3% was considered based on the FDA Guidance for developing drugs in diabetes mellitus. In terms of effect sizes and standard deviations (SD), and using a significance level of $\alpha = 0.025$ the planned sample size of 150 patients per group would provide 88% power to detect an effect of 0.40 between 2 treatment groups assuming a common SD of 1.0%. With a slightly higher SD of 1.1%, power is reduced to 81% (the observed SD in this study ranged from 0.78% to 1.07% for baseline and 18 week HbA1c levels). The observed average treatment differences were greater than 0.4% so that the actual power was more than the projected power.

Overall, 494 patients were randomised to double-blind treatment with either empagliflozin 10 mg (169 patients), empagliflozin 25 mg (155 patients), or placebo (170 patients). At Week 78, 360 patients (72.9%) had completed the treatment period: 131 (77.5%), 111 patients (71.6%) and 118 patients (69.4%) in the empagliflozin 10mg, 25 mg and placebo groups, respectively. A total of 134 patients (27.1%) prematurely discontinued trial medication during the 78-week treatment period (22.5%, 28.4% and 30.6%, respectively) with majority of discontinuations due to AEs. Only 65 (13.2%) of the patients were discontinued at Week 18 with higher incidence in the empagliflozin 25mg group mainly due to AEs. The primary endpoint was based on the FAS completer analysis. Sensitivity analyses assessing the impact of premature discontinuation of trial medication and important protocol violations were performed on the FAS-completers (FAS-78 completers as a sensitivity analysis for Week 18), PPS, and PPS-completers. Overall, 117 (23.7%) and 137 (27.7%) of patients had important protocol violations at week 18 and 78, respectively (non-compliance was most common) but incidence was similar across treatment groups. The proportions of patients in the analyses sets were generally balanced across the treatment groups.

Majority of the patients were male, White (66.5%), had T2DM history of > 5 years (90%), had a history of hypertension (> 75%) and had normal renal function or mild renal impairment at baseline. The mean age of 59 years, mean BMI was 32kg/m² and mean HbA1c was 8.2%. Mean FPG levels were slightly lower at baseline in the empagliflozin 10 mg group compared with the empagliflozin 25 mg and the placebo groups (138.4, 146.4 and 142.1 mg/dL in the empagliflozin 10mg, 25mg and placebo groups, respectively). Other demographic and baseline disease characteristics were generally balanced among the 3 treatment groups. Metformin plus insulin, either with (37-40%) or without SU (36-45%) was the most common background antidiabetic

regimen in all 3 treatment groups. Overall, > 90% of patients in the 3 treatment groups had compliance of 80-120%.

The primary endpoint of change from baseline in HbA1c at 18 weeks showed statistically significantly ($p < 0.001$) greater reduction in both empagliflozin groups compared with placebo; the adjusted mean differences versus placebo were -0.56% (97.5%CI: -0.78, -0.33) and -0.70% (97.5% CI: -0.93, -0.47) in the empagliflozin 10 and 25mg groups, respectively. All sensitivity analyses of the primary endpoint confirmed these results. An analysis of HbA1c change over time showed that the treatment effects of both doses of empagliflozin increased up to Week 12 and were sustained thereafter.

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). Superiority vs. placebo was achieved and the robustness of these results was confirmed by sensitivity analyses. After 78 weeks of treatment, there were also clinically meaningful and statistically significant ($p \leq 0.0001$) reductions in HbA1c with both doses of empagliflozin versus placebo. The adjusted mean differences versus placebo were -0.46% in the empagliflozin 10 mg group (97.5% CI: -0.73, -0.19) and -0.62% in the empagliflozin 25 mg group (97.5% CI: -0.90, -0.34). These results were confirmed by sensitivity analyses. A greater proportion of patients treated with empagliflozin 10mg and 25mg showed HbA1c levels < 7% and reduction in HbA1c of at least 0.5% from baseline at Week 18 which was sustained till Week 78.

In the first part of the study, up to Week 18, the insulin dose was supposed to remain stable. During this period FPG levels increased in the placebo group and decreased in the empagliflozin group: the placebo corrected difference at Week 18 was -28.40 (95% CI: -37.54, -19.27) in the empagliflozin 10 mg group and -34.21 (95% CI: -43.67, -24.76) in the empagliflozin 25 mg group. During the second part of the trial it was recommended that patient insulin dose be titrated to achieve FPG levels < 110 mg/dL.

As a result of the titration, FPG levels decreased in the placebo group through Week 78 (adjusted mean change from baseline of -5.48 mg/dL) compared to the result at Week 18 (adjusted mean change from baseline of 11.15 mg/dL). In the empagliflozin groups, the FPG lowering effect was maintained through Week 78. Clinically meaningful reductions in MDG were also reported at Week 18 and Week 78 for both doses of empagliflozin in the subset of patients for whom data were available.

The adjusted mean change from baseline in body weight at Week 78 was -2.47, -1.96 and +1.16kg in the empagliflozin 10mg, 25 mg and placebo groups, respectively with greater proportion of patients treated with empagliflozin 10 mg and 25 mg achieved > 5% reduction in weight compared with placebo at weeks 18 and 78. These reductions in weight were also reflected in reductions in BMI and waist circumference (median change from baseline of -1.75, -1.75 and +1.00cms, respectively at Week 78).

There were clinically meaningful reductions in both SBP and DBP when comparing patients treated with empagliflozin 10 mg or 25 mg versus placebo after 18 weeks of treatment and these changes were sustained through Week 78.

Rescue therapy was used at least once during the first 18 weeks of treatment by 12 (7.1%), 5 (3.2%) and 19 (11.2%) patients in the empagliflozin 10mg, 25 mg and placebo groups, respectively. Over the 78 weeks of treatment, the proportion of patients having rescue therapy was 6.5%, 5.8% and 8.2%, respectively although interpretation was limited due to change in insulin dose which was allowed after first 18 weeks of treatment.

Comments: In this 78-week study, treatment with empagliflozin 10 mg and 25 mg resulted in statistically significant and clinically meaningful reductions versus placebo in HbA1c at Week 18 in patients receiving a stable background insulin dose. As insulin background dose could be adjusted after Week 18 to meet an FPG of < 110 mg/dL, insulin sparing was achieved along with the reductions in HbA1c, BP, weight, and FPG at Week 78.

7.1.2.3. Study 1245.38

This was a Phase IIb, double-blind, randomised, parallel group efficacy and safety study of BI 10773 (5 mg, 10 mg, 25 mg, and 50 mg) compared to placebo when administered orally once daily over 12 weeks, as monotherapy, in patients with type 2 diabetes and insufficient glycaemic control despite diet and exercise, followed by a 40 week randomised extension study to assess long term safety of BI 10773 (10 mg and 25 mg). The objective was to evaluate the efficacy and safety of empagliflozin (5 mg, 10 mg, 25 mg, and 50 mg once daily) compared with placebo given for 12 weeks as monotherapy in patients with type 2 diabetes mellitus with insufficient glycaemic control and also to evaluate the long-term safety of empagliflozin (10 mg and 25 mg once daily) given in a 40-week extension study. The study was conducted at 32 study centres in Japan from 10 Sept 2010 to 23 June 2012. Following the 4-week washout period, there was a 2-week open label placebo run-in period and then the 12-week double-blind, placebo-controlled treatment period. The 40-week second treatment period was a double-blind extension study with empagliflozin 10 mg and 25 mg, which was predefined at the start of the first treatment period; patients who completed the 12-week treatment period were switched to the following treatments during the 40-week extension: those on 5mg, 50mg empagliflozin or placebo were switched to either 10mg or 25mg; patients on 10mg and 25mg empagliflozin during the initial 12-week treatment period continued on the same dose during extension study. Hence, the treatment groups in the extension period were 5 mg/10 mg, 5 mg/25 mg, 10 mg/10 mg, 25 mg/25 mg, 50 mg/10 mg, 50 mg/25 mg, placebo/10 mg, and placebo/25 mg groups.

The primary endpoint was the change from baseline in HbA1c after 12 weeks of treatment and secondary endpoints were: Occurrence of a treat to target response (HbA1c under treatment of < 7.0%) after 12 weeks of treatment and change from baseline in FPG after 12 weeks of treatment. Other efficacy endpoints were similar to those evaluated in the other pivotal and supportive empagliflozin studies. For the primary endpoint, changes from baseline in HbA1c after 12 weeks of treatment were analysed by using an analysis of covariance (ANCOVA) approach in the full analysis set (FAS). The FAS was defined as consisting of all randomised patients who were treated with at least 1 dose of study drug and had a baseline HbA1c assessment. This model included “treatment,” “renal function,” and “number of previous antidiabetic medications” as a fixed effect and baseline HbA1c as a covariate. Missing data were imputed by using the last observation carried forward approach. For secondary endpoints and other endpoints, ANCOVA analyses were performed for continuous variables and logistic regression analyses for binary variables. On the basis of the previous experiences with empagliflozin (studies 1245.9 and 1245.10), it was estimated that the difference of mean change from baseline in HbA1c after 12 weeks was 0.5% between empagliflozin and placebo, and pooled SD was 1.0. When the significant level was 5% (two-sided), the sample size of 86 patients per arm would provide a power of 90% for each comparison.

Of the 724 enrolled patients, 615 patients were entered in the 2-week placebo run-in period and then 547 patients were entered in the 12-week first treatment period. Of the 547 patients, 19 (3.5%) patients were withdrawn from the trial mostly because of AEs (11 patients). A total of 528 patients completed the 12-week first treatment period and were entered in the 40-week second treatment period. Of the 528 patients, 28 (5.3%) patients were withdrawn from the trial mostly because of AEs (13 patients) and 500 patients completed the 40-week second treatment period. Overall, the number of important protocol violations was low in this trial (16/547 (2.9%) patients). Efficacy endpoints were primarily analysed based on the FAS, which was based on the intention to treat (ITT) principle. Sensitivity analyses assessing the impact of premature discontinuation of trial medication and important protocol violations were performed on the PPS and PPSC52.

Majority of the patients were male (75%), all were Japanese with mean age of 57.5 years, mean BMI was 25.47 kg/m², mean HbA1c (%) ranged from 7.92 to 8.02 and mean FPG ranged from 154.0 to 158.0mg/dL. Overall, 33.6% had normal renal function, 65.1% and 1.3% had mild and moderate renal impairment, respectively. The baseline demographics and disease characteristics were well-balanced across treatment groups. Of the 547 patients, 185 (33.8%)

patients used one antidiabetic medication and 362 (66.2%) patients had not received previous antidiabetic medication before entering this study. The proportions of patients with previous oral antidiabetic medication were similar among the 5 treatment groups. Treatment compliance was approximately 99% during the 12-week and 40-week extension period.

The primary analysis showed that all empagliflozin doses led to statistically significant reduction in HbA1c compared with placebo. Empagliflozin 5 and 10 mg doses showed similar efficacy; the efficacy of 25 and 50 mg doses were also similar to each other but greater than that of the 5/10mg doses. Reduction in HbA1c was observed during first 12 weeks and was maintained over 52 weeks of treatment with empagliflozin 10mg and 25mg. Among patients with baseline HbA1c $\geq 7.0\%$, the proportion of patients who achieved the target HbA1c response was higher in all empagliflozin groups than in the placebo group (26.2%, 19.0%, 32.1%, 32.7% and 2.8% for the empagliflozin 5mg, 10mg, 25mg, 50mg and placebo groups, respectively). At Week 52, 36.7% of the patients in the empagliflozin 10 mg group and 45.0% of the patients in the empagliflozin 25 mg group achieved HbA1c $<7.0\%$; 5.5% of the patients in the empagliflozin 10 mg group and 11.0% of the patients in the empagliflozin 25 mg group achieved HbA1c $<6.5\%$; 54.1% of the patients in the empagliflozin 10 mg group and 65.1% of the patients in the empagliflozin 25 mg group had a HbA1c reduction of $\geq 0.5\%$.

The change in FPG from baseline at Week 12 also showed greater reduction in FPG in all empagliflozin groups compared with placebo; empagliflozin 10 mg showed a slightly greater reduction than empagliflozin 5 mg, and empagliflozin 25 mg and 50 mg showed a similar effect which was greater than that observed with the 5/10mg doses. The reduction in FPG in the patients treated with empagliflozin 10 mg and 25 mg was observed by Week 4 and this reduction in FPG was maintained up to Week 52. Among other endpoints, the change in HbA1c, FPG, blood pressure, body weight, and waist circumference over time showed better reduction in all empagliflozin treatment groups than in the placebo group for 12 weeks and the effects were sustained up to Week 52 in the empagliflozin 10 mg and 25 mg groups. Empagliflozin 10 mg showed the largest reduction in SBP and DBP among the all treatment groups, and empagliflozin 10mg and 25mg also showed consistent dose-dependent reduction in body weight. At Week 12, the proportion of patients who achieved the composite endpoint (reached target HbA1c level of $<7.0\%$ or HbA1c reduction of $\geq 1.0\%$, no symptomatic confirmed hypoglycaemia, and reduction in body weight $>2\%$) was higher in the empagliflozin groups than in the placebo group (40.5%, 28.9%, 41.9%, 47.7% and 1.1% for the empagliflozin 5mg, 10mg, 25mg, 50mg and placebo groups, respectively). At Week 52, the proportion of patients who achieved the composite endpoint was similar between the empagliflozin 10 mg (41.3%) and 25 mg (45.9%) groups.

7.1.2.4. Study 1245.28

This was a Phase III randomised, double-blind, active-controlled parallel group efficacy and safety study of BI 10773 compared to glimepiride in patients with type 2 diabetes mellitus and insufficient glycaemic control despite metformin treatment. The objective of this trial was to investigate the efficacy, safety, and tolerability of empagliflozin (25 mg once daily) compared with glimepiride (Amaryl; 1 to 4 mg once daily) as add-on therapy to immediate release metformin given for 104 weeks, with a 104-week extension period in patients with type 2 diabetes mellitus with insufficient glycaemic control. The study was designed to show non-inferiority of empagliflozin to glimepiride with the option to show superiority if non-inferiority was met. The study was conducted at 173 trial sites in 23 countries (Argentina, Austria, Canada, Colombia, Czech Republic, Finland, Hong Kong, India, Italy, Malaysia, Mexico, Netherlands, Norway, the Philippines, Portugal, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, the UK, and the USA) from 28 Aug 2010 and is still ongoing with database lock for interim analysis at 23 Aug 2012. After a 2-week placebo run-in period, patients were randomised 1:1 to empagliflozin 25mg or glimepiride (1 to 4mg od) for 104 weeks. Patients who completed the planned 104-week treatment period in this trial were eligible to continue their randomised treatment in a 104-week, double-blind, double-dummy, extension treatment period. Randomisation was stratified by HbA1c at screening, renal function at screening, and

geographical region. Patients could sign separate informed consents to participate in a body composition substudy, a meal tolerance test (MTT) substudy, and a substudy with 8-point glucose profile sampling to assess mean daily glucose (MDG).

The study included patients with type 2 diabetes mellitus and insufficient glycaemic control at screening (HbA1c ≥ 7.0 to $\leq 10.0\%$) despite therapy with immediate release metformin at the maximum tolerated dose (≥ 1500 mg/day) unchanged for at least the last 12 weeks prior to randomisation; age ≥ 18 years; body mass index at screening ≤ 45 kg/m². This interim report included all data up to database lock for the interim analysis, in which all patients still in the trial had completed Visit 10 (52 weeks in the study).

The primary endpoint for the main report for this study is the change from baseline in HbA1c after 52 and 104 weeks of treatment. For the interim analysis included in this report, the prespecified primary endpoint was the change from baseline in HbA1c after 52 weeks of treatment. The key secondary endpoints for the interim analysis were the change from baseline in body weight at 52 weeks, the occurrence of confirmed hypoglycaemic adverse events (AEs) over 52 weeks, the change in SBP and DBP from baseline at 52 weeks. Primary endpoint for the interim analysis: testing of non-inferiority hypothesis versus glimepiride with an analysis of covariance (ANCOVA) with randomised treatment, geographical region, and renal function at baseline as fixed effects and baseline HbA1c as linear covariate. The non-inferiority margin for the primary endpoint was defined as $\delta = 0.3\%$. The 2 treatments were compared at the nominal significance level of $\alpha_2 = 0.0125$ 1-sided for the interim analysis at 52 weeks. Key secondary endpoints for the interim analysis: ANCOVA similar to that for the primary endpoint was performed for change in body weight, SBP, and DBP, and Cochran-Mantel-Haenszel testing for the occurrence of confirmed hypoglycaemic adverse events. If non-inferiority for HbA1c was established, tests for the superiority of empagliflozin vs. glimepiride with regard to the key secondary endpoints were conducted in hierarchical order: 1) change in body weight [kg]; 2) occurrence of confirmed hypoglycaemic AEs; 3) change in SBP [mmHg]; 4) change in DBP [mmHg].

Of the 1545 patients randomised and treated in this study, 765 patients were randomised to empagliflozin and 780 to glimepiride. At Week 52, 88.9% of patients were still on trial medication and 93.3% of patients were still in the trial. In total, 9.9% of patients in the empagliflozin group and 12.3% of patients in the glimepiride group prematurely discontinued trial medication. The most frequent reasons for premature discontinuation were AEs (3.2%) and 'other reason' (2.8%). The proportions of patients with important protocol violations leading to exclusion from the PPS were comparable in the 2 treatment groups (empagliflozin: 10.3%; glimepiride: 10.8%). The most common reasons for exclusion from the PPS were non-compliance with drug intake, last treatment more than 7 days prior to next visit, and background antidiabetic therapy not taken as specified in the protocol. Efficacy endpoints were primarily analysed based on the FAS, which was based on the ITT principle (all patients randomised and treated and with a baseline HbA1c value). Sensitivity analyses assessing the impact of premature discontinuation of trial medication and important protocol violations were performed on the FAS52-completers, PPS52, and PPS52-completers. The proportions of patients in the analyses sets were generally balanced across the randomised treatment groups.

Majority of the patients were male (55%), White (66%) and aged <65 years ($>75\%$) with mean age of 56 years, mean BMI was 25.47 kg/m², mean HbA1c [%] ranged from 7.92 to 8.02 (with 76% having HbA1c $<8.5\%$) and mean FPG ranged from 150 to 158.0mg/dL. Overall, 41% had normal renal function, 56.8% had mild and 2.8% had moderate renal impairment. Overall, 43.8% had diabetes for 1 to 5 years, 27.5% for 5 to 10 years, and 17.5% had T2DM for more than 10 years. The baseline demographics and disease characteristics were well-balanced across treatment groups. All patients in both treatment groups were to be treated with immediate release metformin at baseline; all patients except 1 (on extended release metformin) were treated with immediate release metformin at baseline. The mean daily dose of metformin was comparable in both treatment groups (empagliflozin: 1880.7 mg, SD 455.4; glimepiride: 1885.8 mg, SD 458.6). In total, 95.4% of patients the empagliflozin group and 95.8% of patients

in the glimepiride group were treated with a daily dose of ≥ 1500 mg metformin. The dose of glimepiride was uptitrated during the first 12 weeks of the treatment period. For 40.1% of patients on glimepiride, the highest dose of glimepiride taken during the 52 weeks of treatment was 4 mg daily. The mean dose of glimepiride during the treatment period was 2.71 mg (SD 1.24) daily. The proportion of patients introducing an antidiabetic medication during treatment period was lower in the empagliflozin group than in the glimepiride group (empagliflozin: 8.8%; glimepiride: 15.3%). Treatment compliance was 97% in both treatment groups.

The adjusted mean change in HbA1c from baseline at Week 52 was -0.73% and -0.66% for the empagliflozin and glimepiride groups, respectively and non-inferiority between empagliflozin and glimepiride was statistically confirmed (diff = -0.07%; 97.5% CI: -0.16, 0.02; $p_{\text{non-inferiority}} < 0.0001$). While the initial reduction up to Week 12 was greater for glimepiride than for empagliflozin, the reduction observed with empagliflozin at Week 12 was sustained until Week 52 for patients in the empagliflozin group but not with glimepiride; the reduction was almost identical in the 2 groups at week 40 but there was a greater reduction with empagliflozin than with glimepiride at week 52. Empagliflozin appeared to be more effective than glimepiride in younger patients and glimepiride more effective than empagliflozin in older patients. In the categorical analysis of HbA1c, the percentage of patients reaching HbA1c levels of $< 7.0\%$ was 41.8% and 41.7% for the empagliflozin and glimepiride groups, respectively. HbA1c $< 6.5\%$ was achieved by 14.5% and 19.1% of patients, respectively and HbA1c levels were lowered by $\geq 0.5\%$ for 59.5% and 53.6% of patients, respectively.

The analyses of all key secondary endpoints showed empagliflozin to be superior to glimepiride. Patients treated with empagliflozin showed statistically significantly greater reduction in body weight at 52 weeks (empagliflozin vs glimepiride: -3.21 vs +1.60 kg; diff= -4.81 kg, $p < 0.0001$). Empagliflozin-treated patients also showed statistically significant greater reduction in SBP (-3.6 vs +2.2 mmHg; diff=-5.8 mmHg, 97.5% CI -7.3, -4.4; $p < 0.0001$) and DBP (-1.9 vs +0.9 mmHg; diff=-2.8 mmHg, 97.5% CI -3.7, -2.0; $p < 0.0001$). In all patients and in patients with hypertension, empagliflozin-treated patients were more likely to have BP control at 52 weeks compared to those treated with glimepiride. Reduction in FPG was also statistically significantly greater with empagliflozin compared with glimepiride.

The frequency of patients achieving the composite endpoint (of HbA1c $< 7\%$ or a reduction of at least 1% in combination with no confirmed hypoglycaemic AEs and weight loss $> 2\%$) was much higher in the empagliflozin group (41.4%) compared with glimepiride (5.1%). When including an HbA1c response of $< 6.5\%$ in the composite endpoint, 28.4% of patients on empagliflozin achieved the composite endpoint compared with 4.4% of patients on glimepiride.

MDG substudy: In total, 142 patients on empagliflozin and 139 patients on glimepiride were included. The adjusted mean change in MDG from baseline at Week 52 showed a trend towards greater improvement for patients on empagliflozin than for patients on glimepiride.

MTT substudy: In total, 112 patients on empagliflozin and 117 patients on glimepiride were included. There were reductions in 2 h postprandial glucose, glucose area under the curve (AUC), and glucose incremental AUC from baseline at Week 52 in both treatment groups that were consistent with the primary analysis of HbA1c. Changes in fasting biomarkers were consistent with the different modes of action of empagliflozin and glimepiride.

Body composition substudy: In total, 49 patients on empagliflozin and 38 patients on glimepiride were included. For patients in the empagliflozin group, there was a mean loss of trunk and limb fat approximately equivalent to the fat free weight loss; there were decreases in both VAT and SAT, and no change in VAT/SAT ratio. For patients in the glimepiride group, there was a mean increase in both trunk and limb fat as well as an increase in fat free mass, increases in both VAT and SAT, and no change in the VAT/SAT ratio. At Week 52, there were no relevant changes from baseline in bone mineral density (for T-scores or absolute values) in either treatment group.

Comments: In this interim analysis following 52 weeks of treatment with 25 mg empagliflozin or 1 to 4 mg glimepiride in patients with type 2 diabetes mellitus and insufficient glycaemic

control despite treatment with immediate release metformin, empagliflozin was non-inferior to glimepiride in the primary analysis of efficacy based on the change in HbA1c from baseline at Week 52. Empagliflozin showed a numerically greater reduction in HbA1c compared with glimepiride, with significantly fewer confirmed hypoglycaemic AEs. In addition, empagliflozin provided the additional benefits of statistically significant and clinically relevant reductions in body weight, SBP and DBP compared with glimepiride.

7.1.2.5. Study 1245.36: Renal impairment patients

This was a Phase III, randomised, double-blind, placebo-controlled, parallel group study. The main objective was to investigate the efficacy, safety and tolerability of empagliflozin treatment (10 mg and 25 mg, once daily) compared to placebo treatment as add-on to pre-existing antidiabetic therapy in patients with type 2 diabetes mellitus with insufficient glycaemic control and different degrees of renal impairment¹⁵ over 52 weeks. The study was conducted at 127 trial sites in 15 countries (Canada, France, Hong Kong, India, Malaysia, Netherlands, Philippines, Poland, Portugal, Russia, Slovakia, South Africa, Spain, United States, United Kingdom) from 3 Sept 2010 to 23 July 2012.

The main inclusion criteria type 2 diabetes mellitus and insufficient glycaemic control (HbA1c ≥ 7.0 and $\leq 10.0\%$) despite antidiabetic therapy and renal impairment with eGFR between 15 and <90 mL/min/1.73m²; age ≥ 18 ; body mass index (BMI) ≤ 45 kg/m².

Following a 2-week open label placebo run-in period, eligible patients were randomised to study treatments for 52 weeks. Randomisation was stratified by HbA1c, renal function, and background medication at screening. Patients were to be followed up for 3-weeks after last intake of study drug or after the premature discontinuation visit. The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment for a combined set of patients with mild or moderate renal impairment, for patients with mild, and for patients with moderate renal impairment. Other efficacy endpoints were similar to those used in other studies described above.

Based on previous experience with empagliflozin, it was estimated that the reduction in HbA1c from baseline after 24 weeks of treatment would be 0.5% for empagliflozin treatment (10 mg or 25 mg) of patients with mild renal impairment, 0.3% for empagliflozin treatment (25 mg) for patients with moderate renal impairment and 0% for placebo treatment. The standard deviation of the difference was expected to be 1.1%; the alpha (type I error) was assumed to be 5%. Assuming that the HbA1c values follow a normal distribution and that a two-sided test would be employed, a sample size of 85 patients with mild renal impairment in each treatment group was needed to provide a power of 83%. A further 167 patients with moderate renal impairment were to be assigned to each empagliflozin 25 mg and placebo, providing a power of 70%. Additionally, 30 patients with severe renal impairment were to be assigned to the empagliflozin 25 mg and placebo treatment groups in order to provide safety data. Therefore, a total of 649 patients were required. Allowing a 5% drop-out rate, the sample size for the randomised, double-blind treatment period of the study would be 682 patients.

A total of 741 patients were randomised based on their renal function at screening; 738 patients were treated with study medication. Overall, 292 patients with mild renal impairment were randomised in a 1:1:1 ratio (97, 98 and 97 to empagliflozin 10 mg, 25mg and placebo, respectively), 375 patients with moderate renal impairment were randomised in a 1:1 ratio to either placebo (187 patients) or empagliflozin 25 mg (188 patients) and 74 patients with severe renal impairment were randomised in a 1:1 ratio to either placebo (37 patients) or empagliflozin 25 mg (37 patients) treatment. In addition, a combined set of patients with mild or moderate renal impairment was defined for analysis, which comprised 282 and 284 patients treated with placebo and empagliflozin 25 mg, respectively. Of the treated patients, 91.0%,

¹⁵ Renal impairment based on the estimated glomerular filtration rate (eGFR) at screening (mild: eGFR ≥ 60 to < 90 ml/min/1.73m², moderate: eGFR ≥ 30 to < 60 ml/min/1.73m², severe: eGFR ≥ 15 to < 30 ml/min/1.73m²).

88.5%, 68.9% and 89.6% of patients with mild, moderate, severe and combined (mild+moderate) renal impairment, respectively completed the 52-week treatment period. The most frequent reason for premature treatment discontinuation was AEs (4.5, 4.3% and 18.9% of patients with mild, moderate and severe renal impairment). Overall, 115 patients (15.5%) were reported with important protocol violations in this study. Important protocol violations leading to exclusion from the per-protocol set (PPS) were reported for 88 patients (11.9%) overall. The most frequent important protocol violation leading to exclusion from the PPS in all treatment groups was non-compliance with study drug intake, reported for 54 patients (7.3%). Important protocol violations not leading to exclusion from the PPS were reported for a total of 38 patients (5.1%). Efficacy endpoints were primarily analysed based on the FAS, which was based on the modified ITT principle (all patients randomised and treated). Sensitivity analyses assessing the impact of premature discontinuation of trial medication and important protocol violations were performed on the FAS-completers, PPS, and PPS-completers.

Majority of the patients were male (58.3%), White (60.3%) and had been diagnosed with diabetes for more than 10 years (61.5%). The demographic and most baseline characteristics were well balanced across the treatment groups for the overall patient population although the proportion of White patients was higher in the group of patients with mild renal impairment (68.3%) than in patients with moderate (56.1%) or severe (54.1%) renal impairment. More than half of all patients (58.9%) were taking metformin (as monotherapy or in combination with other antidiabetic drugs); most of these patients were in the group with mild renal impairment. The proportion of overall patients in the empagliflozin 10 mg treatment group who were taking metformin at baseline (82.7%) was higher than in the empagliflozin 25 mg (57.0%) and placebo (53.6%) groups. Just over half of all patients (52.7%) were taking insulin as background medication. Treatment compliance was 96.6%, 97.1% and 87.8% in patients with mild, moderate and severe renal impairment, respectively with similar rates in empagliflozin and placebo treatment groups.

Superiority of empagliflozin 25 mg over placebo was demonstrated for the change of HbA1c after 24 weeks of treatment for patients with mild renal impairment, moderate renal impairment, and for the combined set of patients with mild or moderate renal impairment. The change in HbA1c after 24 weeks of treatment with empagliflozin 10 mg was tested only for patients with mild renal impairment; the analysis demonstrated superiority of empagliflozin 10 mg over placebo. Similar improvements in HbA1c were observed with empagliflozin compared with placebo at 52 weeks. In patients with mild or moderate renal impairment, analysis of HbA1c changes at Week 52 and over time showed that reductions achieved at Week 24 in the empagliflozin treatment groups were maintained until the end of the study. In patients with mild/moderate renal impairment, the proportion of patients achieving HbA1c <7% was higher in the empagliflozin 25 mg group compared with placebo at 24 weeks (16.2% vs 7.5%) and at 52 weeks (15% vs 7.9%). Similarly more patients treated with empagliflozin 25mg showed HbA1c reduction of >0.5% at 24 weeks (41.5% vs 20.2%) and at 52 weeks (34.5% vs 16%). In patients with mild renal impairment both empagliflozin 10mg and 25mg showed higher proportion of patients achieving HbA1c <7%, <6.5% and reduction of > 0.5% after 24 and 52 weeks.

In patients with mild or moderate renal impairment, empagliflozin produced greater reduction in FPG compared with placebo at 24 and 52 weeks.

For patients with mild, moderate, or severe renal impairment, higher reductions in body weight, SBP, and DBP were observed at Week 24 in the empagliflozin treatment groups than in the placebo group; changes were maintained until Week 52. In all renal impairment categories, more patients in the empagliflozin treatment groups than in the placebo group showed a reduction in body weight of more than 5% from baseline at Week 24 and Week 52; among patients not already at the BP goal (SBP <130 mmHg and DBP <80 mmHg) at baseline, more patients in the empagliflozin treatment groups than in the placebo group reached this target

after 24 weeks of treatment. The proportion of patients that fulfilled the composite endpoint¹⁶ goal at 24 weeks was higher in the empagliflozin 25 mg group than in the placebo group (9.9% vs 3.5%) with similar results at 52 weeks (13.4% vs 3.2%).

For patients with severe renal impairment, the descriptive analyses of changes in HbA1c and FPG showed no reduction for the empagliflozin treatment group when compared with placebo.

In each renal impairment group, lower proportions of patients in the empagliflozin treatment groups than in the placebo group required the use of rescue medication during the first 24 weeks of the study.

Comments: There is a high prevalence of chronic kidney disease in patients with type 2 diabetes and only limited treatment options for patients with impaired renal function are available due to safety and tolerability concerns. Furthermore, based on the mode of action, the efficacy of empagliflozin is assumed to be dependent on renal function and so this study was designed to evaluate the efficacy of empagliflozin in T2DM patients with varying degrees of renal impairment.

Results from this well-conducted study showed that treatment with empagliflozin 10 mg and 25 mg in patients with mild renal impairment and empagliflozin 25 mg in patients with moderate renal impairment led to statistically significant and clinically meaningful reductions in HbA1c in comparison with placebo after 24 weeks of treatment which were maintained until the end of the study at Week 52. Furthermore, adequate glycaemic control, which is defined as HbA1c <7.0% (according to the American Diabetes Association and the European Association for the Study of Diabetes) was achieved for more patients treated with empagliflozin than patients treated with placebo in the mild and moderate renal impairment groups. However, efficacy was not demonstrated for patients with severe renal impairment.

The results of the primary endpoint were supported by clinically meaningful and consistent reductions in FPG, body weight and blood pressure for empagliflozin treatment. This finding was supported by categorical responses of weight and blood pressure change, as more patients treated with empagliflozin achieved the expected targets than patients treated with placebo. Furthermore, in each of the renal impairment categories, lower proportion of patients in the empagliflozin treatment groups than in the placebo group required the use of rescue medication during the first 24 weeks of the study.

7.1.2.6. Study 1245.48: Hypertensive patients

This was a Phase III randomised, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of BI 10773 (10 mg, 25 mg) administered orally, once daily over 12 weeks in hypertensive patients with type 2 diabetes mellitus. The study was conducted at 121 trial sites in 12 countries (Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Lebanon, The Netherlands, Norway, Sweden, USA) from 20 June 2011 to 13 July 2012. The main inclusion criteria were: Patients with T2DM, insufficient glycaemic control (HbA1c ≥ 7.0 and $\leq 10.0\%$), age ≥ 18 years, BMI ≤ 45 kg/m², and hypertension (SBP of 130 to 159 mmHg and DBP of 80 to 99 mmHg); other exclusion criteria were similar to those described for the pivotal studies in section 7.1.1 above.

Randomisation was stratified by HbA1c at screening, renal function at baseline, background antihypertensive therapy, and geographical region. Two-week placebo run-in followed by a 12-week treatment period with empagliflozin (10 mg or 25 mg) or matching placebo tablets and a 2-week follow-up period. Background antidiabetic and antihypertensive medication was to be taken during the entire trial duration (including placebo run-in period) at an unchanged dose.

The primary endpoint was the change from baseline in HbA1c after 12 weeks of treatment. The co-primary endpoint was the change from baseline in mean 24-h SBP after 12 weeks of treatment. The key secondary endpoint was the change from baseline in mean 24-h DBP after

¹⁶ Fulfilled the following criteria after 24 weeks: reduction in HbA1c by $\geq 0.5\%$, SBP by >3 mmHg, and body weight by $>2\%$ at Week 24 and at Week 52.

12 weeks of treatment. Primary endpoint: Testing of superiority hypothesis versus placebo with an analysis of covariance (ANCOVA), with randomised treatment, geographical region, number of antihypertensive medications, and renal function as fixed effects, and baseline HbA1c as linear covariate. Co-primary endpoint and key secondary endpoint: ANCOVA similar to primary endpoint; for the co-primary endpoint the baseline mean 24-h SBP and for the key secondary endpoint the baseline mean 24-h DBP were additionally included in the analysis. The primary analysis was performed on the FAS; values after the patient started rescue medication were excluded from analysis and imputed with a LOCF procedure. The co-primary and key secondary analyses were performed on the FAS (LOCF-H), for which the values measured after a change in antihypertensive therapy or rescue therapy were set to missing before being imputed by the LOCF technique. Based on previous experience with empagliflozin, it was estimated that the difference in change from baseline in 24-h SBP would be 4 mmHg, with a SD of 14 mmHg. In order to show a difference between empagliflozin and placebo treatment a sample of 259 patients per treatment arm was needed to provide at least a power of 90% with the primary, co-primary and key secondary endpoint comparisons. Allowing a 5% drop-out rate, the sample size for each randomised treatment arm would be 272 and for this trial of 3 arms would be 816 randomised patients in total. With this sample size, the power to detect a 0.5% difference in HbA1c with a standard deviation of 1.1% would be >95% and the power to detect a difference in DBP of 2 mmHg with the standard deviation of 7 mmHg would be 90%.

Of the 1830 patients enrolled, 825 were entered and 824 were treated. Overall, 95.5% of patients assigned to treatment (94.5%, 96.0% and 96.0% of patients in the placebo, empagliflozin 10mg and 25 mg groups, respectively) completed the 12-week treatment period with 37 patients (4.5%) prematurely discontinuing trial medication (5.5%, 4.0%, and 4.0%, respectively) with the main reason for discontinuation being the occurrence of AEs (1.8%, 1.8% and 2.2%). A total of 194 patients (23.5%) in the RS were reported with important protocol violations and 146 patients (17.7%) were excluded from the PPS analysis, with similar frequencies in the treatment groups (16.5%, 19.2% and 17.3%, respectively). The most frequent important protocol violation leading to exclusion from the PPS was a violation of the exclusion criterion excluding patients with eGFR <60 mL/min/1.73m² (placebo: 5.9%, empagliflozin 10 mg: 7.6%, empagliflozin 25 mg: 8.7%)¹⁷.

Overall, majority of the patients were male (60.1%), White (93.7%), had mild renal impairment (62.7%; 32% had normal renal function) and had most frequently been diagnosed with diabetes for >10 years (39.5%) or >5 to 10 years (32.2%); the mean (SD) age was 60.2 (9.0) years, mean baseline BMI was 32.60 (5.08) kg/m², mean weight was 95.17 (18.22) kg, mean HbA1c was 7.90 (0.74)%, the mean fasting plasma glucose (FPG) was 159.9 (37.1) mg/dL, mean 24-h mean SBP and DBP (ambulatory blood pressure monitoring; ABPM) was 131.4 (12.3) and 75.0 (7.8) mmHg, respectively; the mean trough sitting SBP and DBP was 142.1 (12.3) and 83.9 (7.0) mmHg, respectively and 145 (17.6%) patients had a positive orthostatic BP test at baseline. The demographic and baseline characteristics were comparable between the randomised treatment groups.

Antidiabetic background medication was well balanced across the treatment groups; 32.7% of the patients received monotherapy and 44.8% received a dual therapy. Overall, 92.5% of the patients were receiving antihypertensive medication at baseline with most common being drugs acting on the renin-angiotensin system (77.3% of patients), beta blocking agents (23.7%), calcium channel blockers (15.2%), and diuretics (12.4%). The patients mostly took either a single (42.9% of patients) or 2 different (46.7%) antihypertensive medications. Antihypertensive background medication was well balanced across the treatment groups.

¹⁷ This high percentage was mostly due to a miscalculation of the eGFR screening values for all female patients by the central lab.

The adjusted mean change from baseline in HbA1c was statistically significantly greater for both empagliflozin groups compared with placebo with results confirmed in the sensitivity analysis¹⁸ (-0.59%, -0.63% and +0.03% in the 10mg, 25mg and placebo groups, respectively). After 12 weeks of treatment, there were statistically significant and clinically meaningful reductions with both doses of empagliflozin in mean 24-h SBP (adjusted mean change from baseline was -2.99, -3.59 and +0.42 mmHg, respectively) and mean 24-h DBP (the adjusted mean change from baseline in mean 24-h DBP was -1.10, -1.32 and + 0.30 mmHg, respectively).

The following other efficacy endpoints supported the findings for the primary, co-primary, and key secondary endpoints regarding the positive effect of the empagliflozin treatment (both doses) compared with placebo after 12 weeks of treatment:

- proportion of patients with HbA1c <7% (30%, 31% and 7%, respectively);
- change from baseline in FPG (adjusted mean change from baseline in FPG was -16.60, -23.04 and + 7.19 mg/dL, respectively) and the majority of the FPG-lowering response in the empagliflozin 10 mg and 25 mg groups was already achieved by Week 6 with a smaller further reduction in FPG until Week 12 in the empagliflozin 25 mg group;
- change from baseline in body weight after 12 weeks of treatment (adjusted mean change from baseline was -1.68, -2.16 and -0.19 kg, respectively) and proportion of patients that had a reduction in body weight of more than 5% from baseline to Week 12 (4.3%, 12% and 1.1%, respectively);
- change from baseline in daytime¹⁹ mean SBP and DBP (ABPM);
- change from baseline in night time²⁰ mean SBP and DBP (ABPM);
- change from baseline in trough mean sitting SBP and DBP;
- proportion of patients reaching trough mean sitting BP < 130/80 mmHg after 12 weeks of treatment (18%, 16% and 8%, respectively);
- composite endpoint²¹ at Week 12 (15%, 21% and 2.2%, respectively).

The proportion of patients who required the use of rescue medication at least once during treatment period was low and similar in all treatment groups (1.4%, 2.9% and 2.6%, respectively). Analyses of the change from baseline in trough mean sitting SBP and DBP at Week 14 indicated that the treatment-effect is reversed once empagliflozin administration is stopped.

Comments: Treatment with both empagliflozin doses (10mg and 25mg od) for 12 weeks produced statistically significant and clinically relevant reductions in HbA1c and 24-h SBP / DBP (ABPM) compared to placebo in T2DM patients with hypertension.

7.1.2.7. Uncontrolled, long-term study 1245.24

This was an open label, Phase IIb, 78-week extension trial of the blinded 12-week dose-finding studies 1245.9 and 1245.10. The objective of the current study was to investigate the safety (primary objective) and efficacy of empagliflozin 10 and 25 mg once daily monotherapy compared with metformin monotherapy (total daily dose between 1000 and 2000 mg), and empagliflozin 10 and 25 mg once daily as add-on therapy to metformin compared with sitagliptin 100 mg once daily as add-on therapy to metformin given for 78 weeks in patients with type 2 diabetes mellitus. Patients from the preceding empagliflozin 10 and 25 mg treatment groups (with or without metformin background) continued to take the same doses.

¹⁸ The influence of important protocol violations and premature discontinuations on the primary endpoint was assessed by calculating the adjusted mean change in HbA1c for the FAS-completers, PPS, and the PPS-completers patient sets (ANCOVA, using LOCF imputation).

¹⁹ daytime was defined as the clock time between 06:00 and 21:59.

²⁰ night-time was defined as the clock time between 22:00 and 5:59.

²¹ Composite endpoint had all 3 fulfilled: reduction in HbA1c by at least 0.5%, SBP (office measurement) by >3 mmHg, and body weight by >2% compared to baseline).

Patients on placebo and other empagliflozin doses (with or without metformin background) in the preceding trials were re-randomised to one of the empagliflozin treatments (10 or 25 mg). Patients on metformin monotherapy or sitagliptin added-on to metformin in the preceding trials continued their open label treatments.

No primary efficacy endpoint was defined for this open label extension trial, but the following secondary efficacy endpoints were evaluated: changes in HbA1c and fasting plasma glucose (FPG) from baseline over time to Week 78 of the current trial, the occurrence of a treat-to-target response (HbA1c <7.0% and <6.5%) and a relative efficacy response (lowering of HbA1c by $\geq 0.5\%$) over time. Additionally, changes from baseline over time to Week 78 of the current trial in body weight, waist circumference, blood pressure (BP), as well as the use of rescue therapy were also assessed as efficacy endpoints. All analyses were descriptive and based on the treated set, which included all patients treated with at least 1 dose of study drug. For efficacy evaluation, the baseline was defined as the last observed measurement before the first intake of active treatment (in the preceding trial or in the current extension trial).

Of the patients who completed either of the preceding trials (1245.9 or 1245.10), 660 were enrolled and entered in this extension trial. All but 1 were treated with at least 1 dose of study medication. Of the 659 treated patients, 52 (7.9%) discontinued treatment prematurely with the most common reasons being adverse events (3.5%) and refusal to continue with study medication (1.8%).

The demographics and baseline characteristics were balanced among the treatment groups within the monotherapy groups (empagliflozin 10 and 25 mg, metformin) and within the add-on to metformin IR groups (empagliflozin 10 and 25 mg, sitagliptin). For each group, fewer than 10% of the patients were excluded from the per protocol analysis and the percentages were comparable among the treatment groups. The most frequent reason for exclusion was non-compliance with drug intake (2.6% of all patients excluded), followed by treatment period too short (<539 days; 2.4%). The percentage of patients in each data analysis set was comparable for all treatment groups.

Overall, majority of the patients were male (50.7%), White (89.5%), had been diagnosed with T2DM for more than one year (83.5%); the mean age was 59 years, BMI was 30.0 (4.5) kg/m², baseline HbA1c 7.95% (0.83%), FPG 177.6 (41.6) mg/dL, body weight 87.27 (16.28) kg, systolic BP 133.32 (14.05) mmHg, and diastolic BP 80.33 (8.77) mmHg. The baseline demographics and disease characteristics were similar across treatment groups.

Compared with the values before the administration of active treatment, all groups treated with empagliflozin (10 or 25 mg, monotherapy or added-on to metformin) showed reductions in HbA1c; the 'old' empagliflozin 25 mg monotherapy group and the metformin monotherapy group showed similar reduction in HbA1c; the 'old'²² empagliflozin 25 mg added-on to metformin group appeared to have greater reduction in HbA1c than the sitagliptin added-on to metformin group. Similar results were observed for FPG, body weight and waist circumference at all visits over the 78 weeks of the extension trial. The reductions were generally stable over time. However, a reduction from baseline in both systolic and diastolic blood pressure was only seen with the empagliflozin added-on to metformin groups (10 and 25 mg) over the 78 weeks of the extension trial, with some fluctuations. The numbers of the patients in the 'new empagliflozin' groups (who switched from placebo in the 12-week preceding trials to empagliflozin in the 78-week extension trial) were relatively low (below 30 for each group); these groups also showed decreased HbA1c, FPG, and body weight at Week 78 of the extension trial, based on FAS LOCF. However, decreased waist circumference and SBP and DBP could only be observed in the added-on to metformin groups.

Responder rates for HbA1c <7.0% were relatively constant over the 78 weeks of the extension trial for all treatments. At Week 78 of the extension trial, the proportions of patients in the

²² Those patients who were on empagliflozin 25mg during initial 12 weeks treatment period and continued on 25mg empagliflozin during the extension.

monotherapy groups who showed response were 31.9% for empagliflozin 10 mg, 32.1% for empagliflozin 25 mg, and 31.0% for metformin; the proportions of responders in the add-on therapy groups were 27.0% for empagliflozin 10 mg, 44.6% for empagliflozin 25 mg, and 36.8% for sitagliptin. The trend was similar for the proportion of patients with HbA1c <6.5% or HbA1c lowered by at least 0.5% compared with the value before the administration of active treatment. The proportion of patients with rescue therapy over time was similar for the 3 monotherapy groups; at Week 78 of the extension trial, about a quarter of the patients (26.9% for empagliflozin 10 mg, 25.0% for empagliflozin 25 mg, 23.5% for metformin) had initiated rescue therapy. Patients treated with empagliflozin 25 mg added-on to metformin were less likely to receive rescue therapy at all visits (18.4% with rescue therapy at Week 78), compared to those with the 10 mg dose (24.8%) or sitagliptin added-on to metformin (23.5%).

Comment: The efficacy of empagliflozin in terms of reduction of HbA1c, FPG, body weight, and waist circumference was generally maintained over 90 weeks, adding the preceding studies (12 weeks) and the extension (78 weeks) together. Taken together, long-term treatment with empagliflozin demonstrated sustained glycaemic control and weight loss while being well tolerated.

7.2. Analyses performed across trials (pooled analyses and meta-analyses)

7.2.1. Meta analyses of the pivotal efficacy studies

The main proof of efficacy is provided by the 24-week analysis of efficacy groupings EFF-1 and EFF-2, which comprise the pivotal placebo-controlled trials. EFF-2 included all 4 pivotal efficacy studies discussed in section 7.1.1 while the EFF-1 pooling excluded trial 1245.23 (met+SU). However, in the meta analyses only results in the EFF-2 pooling is discussed.

A total of 4634 patients were enrolled (i.e. screened) into the pivotal placebo-controlled trials. Of these, 2964 patients were entered (i.e. were either randomised or assigned to open label treatment with empagliflozin 25 mg). A total of 2705 patients were randomised to receive placebo (826 patients), empagliflozin 10 mg (832 patients), empagliflozin 25 mg (824 patients), or sitagliptin 100 mg (223 patients). A further 259 screened patients were assigned to open label treatment with empagliflozin 25 mg.

EFF-2 comprises a combined analysis of all patients who entered the initial pivotal trials irrespective of whether or not they entered the extension trial. Of the 2477 patients in the pivotal trials who were randomised and treated with empagliflozin or placebo, 91.0% completed the 24-week treatment duration as planned and 68.7% of patients continued into the extension trial (data compiled from individual clinical trial reports). Most patients (64.2%) in EFF-2 were still taking study medication at the time of the interim database lock for extension trial 1245.31. The overall percentage of discontinuations from study medication up to this timepoint was lower for patients in the empagliflozin groups (empagliflozin 10 mg: 31.3%; 25 mg: 33.9%) than for patients in the placebo group (42.4%). In most cases, the reason for discontinuation was that the patient did not continue into the extension trial. The proportion of patients who did not continue into the extension trial was higher in 1245.19 than in the other pivotal trials. A total of only 5 patients (0.2%) in the pivotal trials discontinued due to lack of efficacy (4 patients (0.5%) in the placebo group and 1 patient (0.1%) in the empagliflozin 25 mg group).

The majority of patients (91.0%) in EFF-1 (i.e. the pivotal trials excluding trial 1245.23 (met+SU)) completed the 24-week treatment duration as planned. The percentage of premature discontinuations from study medication was lower for patients in the empagliflozin groups (empagliflozin 10 mg: 6.1%; 25 mg: 8.1%) than for patients in the placebo group (13.3%). This difference was mainly due to the higher percentage of patients in the placebo group than in the empagliflozin groups who refused to continue study medication, discontinued due to AEs, or were lost to follow-up.

Within the individual pivotal trials and the pooled efficacy groupings, the key demographic characteristics were generally balanced across the randomised treatment groups. In the EFF-2 pooling, majority of the patients were male (54.6%), Asian (56.2%; 41% were White, 1.9% Black), had a history of hypertension (55.5%) and had normal renal function (41.4%) or mild renal impairment (51.2%; only 7.4% had moderate renal impairment). The mean age was 55.6 years, mean BMI was 28.7 kg/m². The percentage of patients who had been diagnosed with diabetes for more than 5 years reflected the eligibility criteria for the individual trials. The proportion of patients who had been diagnosed with diabetes for more than 5 years was lowest in trial 1245.20 (21.7%), which recruited treatment-naïve patients, and highest in trial 1245.23 (met+SU) (77.5%), which recruited patients taking both metformin and a sulphonylurea as background therapy. The pivotal trials also differed with regard to gender and race. The percentage of male patients was highest in trial 1245.20 (60.7%) and lowest in trial 1245.19 (48.4%). The percentage of Asian patients was highest in trial 1245.20 (64.1%) and lowest in 1245.23 (met) (45.4%). Correspondingly, the percentage of patients who were White was higher in trial 1245.23 (met) (53.1%) than in studies 1245.19 (39.6%), 1245.20 (33.4%), and 1245.23 (met+SU) (39.3%).

Within the individual trials and the pooled efficacy groupings, the main baseline characteristics were generally similar across the randomised treatment groups. The patients in EFF-2 had a mean HbA1c value of 7.99%, a mean FPG value of 153.0 mg/dL, and a mean weight of 78.64 kg. The mean SBP was 129.1 mmHg and the mean DBP was 78.3 mmHg; overall, 38.5% of patients had controlled BP (i.e. SBP<130 mmHg and DBP<80 mmHg) at baseline. The reported frequencies of these conditions were comparable for the empagliflozin groups and placebo. More than half (55.5%) of patients in the FAS who were randomised to placebo or empagliflozin had hypertension. Diabetic neuropathy was reported for 11.6% of patients; 9.0% of patients had coronary artery disease, 6.4% of patients had diabetic nephropathy, and 5.3% of patients had diabetic retinopathy. With regard to diagnoses considered relevant to the SGLT-2 inhibitor class of drugs, 5.7% of patients had chronic or recurrent urinary tract infections, and 1.0% had chronic or recurrent genital infections. Concomitant medications were taken by 85.1% of patients in EFF-2, again with similar frequencies reported across the treatment groups with antihypertensive drugs being the most frequent concomitant therapies in the randomised treatment groups, followed by lipid-lowering drugs and aspirin. The antidiabetic therapies at baseline reflected the patient characteristics of the individual pivotal trials. Overall, 27.3% of patients in the FAS who were randomised to placebo or empagliflozin in EFF-2 were not taking antidiabetic drugs at baseline; 30.4% of patients were taking one antidiabetic drug and 42.3% of patients were taking two antidiabetic drugs. Most patients were taking metformin, either as monotherapy (25.5%) or in combination with a sulphonylurea (27.0%) or a glitazone (15.2%). In addition, 121 patients (4.9%) were taking a glitazone as monotherapy and 1 patient (<0.1%) was taking glitazone in combination with insulin. Of the patients assigned to open label treatment with empagliflozin 25 mg, 26.8% were taking metformin only and 38.9% were taking metformin in combination with a sulphonylurea. Overall, 33.9% of patients in the open label group were not taking antidiabetic drugs at baseline.

7.2.1.1. Change in HbA1c

The pooled data (EFF-2) of the pivotal trials showed that both doses of empagliflozin led to significant ($p<0.0001$) and clinically meaningful reductions in HbA1c levels compared with placebo; the adjusted mean change from baseline in HbA1c after 24 weeks of treatment was -0.08% for placebo, -0.70% for empagliflozin 10 mg (diff vs placebo=0.62% ; 95% CI: -0.69, -0.55), and -0.76% for empagliflozin 25 mg (-0.68% ;95% CI: -0.75, -0.61). The p-value for the treatment-by-study interaction term was 0.0945, indicating a potential influence of antidiabetic background medication on the treatment difference between empagliflozin and placebo. The trial with the numerically highest treatment effect of empagliflozin compared with placebo was 1245.20 (no background medication) and the trial with the lowest treatment effect was 1245.19 (background medication of pioglitazone with or without metformin). The results of all

sensitivity analyses²³ at 24 weeks were consistent with the results obtained for the primary analyses, both for the individual studies and for the efficacy groupings. For the pooled EFF-2 analysis, the adjusted mean treatment differences to placebo in the HbA1c change from baseline after 6 weeks were -0.49% (95% CI: -0.55, -0.44) in the empagliflozin 10 mg group and -0.55% (95% CI: -0.60, -0.49) in the empagliflozin 25 mg group. Almost full efficacy was achieved after 12 weeks for empagliflozin 10 mg (-0.63%; 95% CI: -0.70, -0.56) and empagliflozin 25 mg (-0.72%; 95% CI: -0.79, -0.65) with little further change up to 24 weeks.

7.2.1.2. HbA1c responder rate

The pooled data from all pivotal trials (i.e. EFF-2) showed that the overall proportion of patients achieving HbA1c <7.0% after 24 weeks was statistically significantly higher in the empagliflozin (10 mg and 25mg) groups compared with placebo (31.5%, 37.2% 10.5%, respectively). The odds of achieving HbA1c <7.0% after 24 weeks were higher for both empagliflozin dose groups than for placebo, with an odds ratio to placebo of 4.227 (95% CI: 3.170, 5.636) for the empagliflozin 10 mg group and 5.503 (95% CI: 4.136, 7.322) for the empagliflozin 25 mg group. Of the patients treated with open label empagliflozin 25 mg, HbA1c <7.0% was achieved after 24 weeks by 24 patients (27.6%) in trial 1245.20, by 6 patients (8.7%) in trial 1245.23 (met), and by 9 patients (8.9%) in 1245.23 (met+SU). The pooled analysis (EFF-2) showed that overall 15.2% of patients treated with open label empagliflozin 25 mg achieved HbA1c <7.0% after 24 weeks of treatment.

7.2.1.3. Change in FPG

The pooled data (EFF-2) of the pivotal trials showed that both doses of empagliflozin led to significant ($p < 0.0001$) and clinically meaningful reductions in fasting plasma glucose (FPG) levels compared with placebo; the adjusted mean change from baseline in FPG after 24 weeks of treatment was 7.4 mg/dL for placebo, -20.4 mg/dL for empagliflozin 10 mg, and -23.2 mg/dL for empagliflozin 25 mg. The treatment difference to placebo was -27.8 mg/dL (95% CI: -30.6, -25.0) for the empagliflozin 10 mg group and -30.6 mg/dL (95% CI: -33.5, -27.8) for the empagliflozin 25 mg group. The p-value for the treatment-by-study interaction term was 0.2783, indicating that the treatment effect was consistent across studies irrespective of the type of antidiabetic background medication. For the pooled EFF-2 analysis, almost the full treatment effect was reached by 6 weeks; the adjusted mean treatment differences to placebo in the FPG change from baseline after 6 weeks were -24.1 mg/dL (95% CI: -26.9, -21.3) in the empagliflozin 10 mg group and -27.3 mg/dL (95% CI: -30.1, -24.4) in the empagliflozin 25 mg group with little further change thereafter until 24 weeks. Furthermore, treatment with empagliflozin 25 mg on an open label basis in patients with baseline HbA1c >10% led to substantial and clinically meaningful reductions in FPG after 24 weeks (-66.2 mg/dL from a baseline value of 211.3 mg/dL).

7.2.1.4. Change in 2h post-prandial glucose levels

In 1245.23 (met) and 1245.23 (met+SU), a meal tolerance test (MTT) was performed in a subset of patients²⁴. After 24 weeks of treatment, there were clinically meaningful reductions in 2-h postprandial glucose (2-h PPG) with both doses of empagliflozin in both substudies. In 1245.23 (met) (167 analysed patients) the difference to placebo for the adjusted mean change in 2-h PPG from baseline at 24 weeks was -51.91 mg/dL (95% CI: -69.23, -34.59) for the empagliflozin 10 mg group and -50.47 mg/dL (95% CI: -67.38, -33.56) for the empagliflozin 25 mg group. In 1245.23 (met+SU) (124 analysed patients), the difference to placebo for the adjusted mean

²³ Primary efficacy analysis were based on the FAS, using the LOCF method to replace missing values, and with an ANCOVA model. In addition, the influence of important protocol violations was assessed by calculating the adjusted mean change in HbA1c for the PPS. Further sensitivity analyses were based on the FAS (OC) and FAS (OC-IR) using an MMRM model.

²⁴ The test was optional and was not available at all study sites. The analysis was based on the MTT set, which included all patients in the FAS with a valid MTT value at baseline and at least 1 valid on-treatment MTT value.

change in 2-h PPG from baseline at 24 weeks was -33.44 mg/dL (95% CI: -55.23, -11.66) for the empagliflozin 10 mg group and -34.31 mg/dL (95% CI: -56.28, -12.34) for the empagliflozin 25 mg group.

7.2.1.5. Change in body weight

The pooled data of the pivotal trials showed that the adjusted mean change from baseline in body weight after 24 weeks of treatment was -0.24 kg for placebo, -2.04 kg for empagliflozin 10 mg, and -2.26 kg for empagliflozin 25 mg. The treatment difference to placebo was -1.80 kg (95% CI: -2.05, -1.56) for the empagliflozin 10 mg group and -2.02 kg (95% CI: -2.26, -1.77) for the empagliflozin 25 mg group. The p-value for the treatment-by-study interaction term was 0.8343, indicating that the treatment effect was consistent across studies irrespective of the type of antidiabetic background medication. The pooled analysis of these trials showed that the overall mean change in body weight from baseline after 24 weeks in patients treated with open label empagliflozin was -2.05 kg from a baseline value of 80.21 kg. The overall proportion of patients achieving weight reduction >5% after 24 weeks in the EFF-2 dataset was 22.9% in each of the empagliflozin dose groups and 5.1% in the placebo group. The odds of achieving >5% weight reduction after 24 weeks were higher for both empagliflozin dose groups than for placebo, with an odds ratio to placebo of 5.565 (95% CI: 3.918, 7.905) for the empagliflozin 10 mg group and 5.580 (95% CI: 3.926, 7.930) for the empagliflozin 25 mg group. Overall, 19.1% of the patients who achieved a reduction in body weight of more than 5% after 24 weeks of open label treatment with empagliflozin 25 mg (19 patients (21.8%) in trial 1245.20, 11 patients (15.9%) in trial 1245.23 (met), and 19 patients (18.8%) in 1245.23 (met+SU)).

7.2.1.6. Change in blood pressure

The pooled data of the pivotal trials showed that the adjusted mean change from baseline in SBP after 24 weeks of treatment was -0.5 mmHg for placebo, -3.9 mmHg for empagliflozin 10 mg, and -4.3 mmHg for empagliflozin 25 mg. The treatment difference to placebo was -3.4 mmHg (95% CI: -4.4, -2.3) for the empagliflozin 10 mg group and -3.8 mmHg (95% CI: -4.9, -2.8) for the empagliflozin 25 mg group. The p-value for the treatment-by-study interaction term was 0.6130, indicating that the treatment effect was consistent across studies irrespective of the type of antidiabetic background medication. For the pooled EFF-2 analysis, the adjusted mean treatment differences to placebo in the SBP change from baseline after 6 weeks were -2.1 mmHg (95% CI: -3.1, -1.1) in the empagliflozin 10 mg group and -3.2 mmHg (95% CI: -4.3, -2.2) in the empagliflozin 25 mg group. Almost the full effect was achieved after 12 weeks for empagliflozin 10 mg (-2.7 mmHg; 95% CI: -3.8, -1.6) and empagliflozin 25 mg (-3.8 mmHg; 95% CI: -4.9, -2.7) with little further change up to 24 weeks. Overall mean change in SBP from baseline after 24 weeks in patients treated with open label empagliflozin was -4.1 mmHg from a baseline value of 127.4 mmHg.

The pooled data of the pivotal trials showed that the adjusted mean change from baseline in DBP after 24 weeks of treatment was -0.5 mmHg for placebo, -1.8 mmHg for empagliflozin 10 mg, and -2.0 mmHg for empagliflozin 25 mg. The treatment difference to placebo was -1.3 mmHg (95% CI: -1.9, -0.6) for the empagliflozin 10 mg group and -1.5 mmHg (95% CI: -2.2, -0.8) for the empagliflozin 25 mg group. The p-value for the treatment-by-study interaction term was 0.3618, indicating that the treatment effect was consistent across studies irrespective of the type of antidiabetic background medication. For the pooled EFF-2 analysis, the adjusted mean treatment differences to placebo in the DBP change from baseline after 6 weeks were -1.0 mmHg (95% CI: -1.7, -0.4) in the empagliflozin 10 mg group and -1.8 mmHg (95% CI: -2.5, -1.1) in the empagliflozin 25 mg group. After 12 weeks, the differences to placebo were -1.2 mmHg (95% CI: -1.9, -0.5) in the empagliflozin 10 mg group and -1.7 mmHg (95% CI: -2.3, -1.0) in the empagliflozin 25 mg group with little further change up to 24 weeks. The overall mean change in DBP from baseline after 24 weeks in patients treated with open label empagliflozin was -2.9 mmHg from a baseline value of 79.5 mmHg. The pooled data from the pivotal trials (i.e. EFF-2) showed that of the patients with high BP $\geq 130/80$ mmHg at baseline (overall 61.5% of patients), the proportion of patients achieving BP $<130/80$ mmHg after 24 weeks was 33.3% in the empagliflozin 10 mg group and 32.2% in the empagliflozin 25 mg group, compared with

18.6% in the placebo group. The odds of achieving BP <130/80 mmHg after 24 weeks were higher for both empagliflozin dose groups than for placebo, with an odds ratio to placebo of 2.224 (95% CI: 1.659, 2.981) in the empagliflozin 10 mg group and 2.126 (95% CI: 1.582, 2.856) in the empagliflozin 25 mg group. Overall, 26.7% of patients achieved BP <130/80 mmHg after 24 weeks of treatment with open label empagliflozin 25mg od.

7.2.1.7. Use of rescue medication

The pooled analysis based on EFF-2 showed that 4.1% of patients in the empagliflozin 10 mg group and 2.4% in the empagliflozin 25 mg group required rescue medication, compared with 15.8% of patients in the placebo group. For the pooled analysis the odds ratios (to placebo) of requiring rescue medication were 0.210 (95% CI: 0.140, 0.315) for empagliflozin 10 mg and 0.120 (95% CI: 0.073, 0.198) for empagliflozin 25 mg. Overall, 12.5% of patients treated with open label empagliflozin 25mg od for 24 weeks required rescue therapy.

7.2.2. Efficacy in subpopulations

Subgroup analyses were performed on the pooled data from the randomised patients in the pivotal placebo-controlled trials (EFF-2). Subgroup analyses were performed for the change in primary and key secondary efficacy parameters from baseline to Week 24 based on the FAS (LOCF). The following subgroup variables were investigated: baseline age, baseline HbA1c, baseline body mass index (BMI), baseline body weight, geographical region, race, sex, ethnicity, time since diagnosis of diabetes at baseline, baseline renal function, baseline blood pressure, and history of hypertension.

The analysis for most subgroups was performed at 24 weeks for the primary (HbA1c) and all secondary (FPG, body weight, SBP, DBP) endpoints. The subgroup analyses by time since diagnosis of diabetes and baseline HOMA indices were performed for HbA1c and FPG only. The subgroup analysis by blood pressure was performed only for the blood pressure endpoints.

7.2.2.1. Age

In all of the age categories below 75 years, both doses of empagliflozin provided significant and clinically meaningful and significant changes in HbA1c compared with placebo after 24 weeks of treatment. The adjusted mean treatment differences to placebo were higher in the category of patients aged under 50 years (-0.75% and -0.87% with empagliflozin 10mg and 25 mg, respectively) than in the categories of patients aged 50 to <65 years (-0.58% and -0.63%) and 65 to <75 years (-0.60% and -0.54%). In the category of patients aged 75 years or older, there were reductions in HbA1c from baseline after 24 weeks with both doses of empagliflozin (-0.55% and -0.67%, respectively). However, because of a reduction in HbA1c with placebo (-0.35%), the corresponding treatment differences to placebo (empagliflozin 10 mg: -0.21%; empagliflozin 25 mg: -0.33%) were smaller and markedly less than in the younger age groups. However, interpretation was limited by small sample size of patients in the age category 75 years or older (66 patients) compared with the other age categories. Nevertheless, the p-value for the treatment-by-age interaction term (p=0.0168) indicated that age may have had an influence on the treatment effect of empagliflozin.

An additional subgroup analysis by age was performed (based on the 4 age-categories) on a post-hoc basis for the cardiovascular safety trial 1245.25 to evaluate the influence of age using a larger dataset than was available for the pooled pivotal trials. As was the case for EFF-2, there was a reduction in the treatment effect of empagliflozin with increasing age. After 12 weeks, the adjusted mean treatment differences to placebo in patients under 50 years were -0.64% (95% CI: -0.83, -0.45) for the empagliflozin 10 mg group and -0.92% (95% CI: -1.11, -0.73) for the empagliflozin 25 mg group. In the category of patients aged 75 years or more, the adjusted mean treatment differences to placebo were -0.29% (95% CI: -0.45, -0.14) for the empagliflozin 10 mg group and -0.35% (95% CI: -0.51, -0.19) for the empagliflozin 25 mg group. The p-value for the treatment-by-age interaction term (p<0.0001) indicated that age had an influence on the treatment effect of empagliflozin. A similar pattern was evident for the analysis conducted at 28 weeks. As the subgroup analyses of EFF-2 and 1245.25 showed that the efficacy of empagliflozin

was reduced in patients aged 75 years or more, a further post-hoc subgroup analysis was conducted to address the impact of renal impairment on the HbA1c change from baseline in this age category. In this analysis, the treatment effect of empagliflozin on HbA1c in patients aged 75 years or more from trial 1245.25 was compared for subcategories of patients with eGFR cut-offs of 60 mL/min/1.73 m² and 45 mL/min/1.73 m². At 12 weeks, the difference to placebo in the adjusted mean change from baseline in HbA1c was lower for patients aged \geq 75 years with eGFR below 60 mL/min/1.73 m² (empagliflozin 10 mg: -0.20%; empagliflozin 25 mg: -0.13%) than for those with eGFR of 60 mL/min/1.73 m² or more (empagliflozin 10 mg: -0.38%; empagliflozin 25 mg: -0.55%). The corresponding p-value for the treatment-by-renal function interaction term was 0.0400, indicating that the degree of renal impairment (based on an eGFR cut-off of 60 mL/min/1.73 m²) had an influence on the efficacy of empagliflozin in patients aged 75 years or more. A similar pattern was evident at 28 weeks; the difference to placebo in the adjusted mean change from baseline in HbA1c was lower for patients aged \geq 75 years with eGFR below 60 mL/min/1.73 m² (empagliflozin 10 mg: -0.04%; empagliflozin 25 mg: -0.10%) than for those with eGFR of 60 mL/min/1.73 m² or more (empagliflozin 10 mg: -0.33%; empagliflozin 25 mg: -0.48%). The p-value for the treatment-by-renal function interaction term was 0.0857. When the subgroup analysis was performed using an eGFR cut-off of 45 mL/min/1.73 m², the difference to placebo in the adjusted mean change from baseline in HbA1c at 12 weeks was lower for the patients with eGFR below 45 mL/min/1.73 m² (empagliflozin 10 mg: -0.16%; empagliflozin 25 mg: -0.21%) than for those with eGFR of 45 mL/min/1.73 m² or more (empagliflozin 10 mg: -0.32%; empagliflozin 25 mg: -0.38%). The corresponding p-value for the treatment-by-renal function interaction term was 0.6637. At 28 weeks, the difference to placebo in the adjusted mean change from baseline in HbA1c in patients \geq 75 years with eGFR below 45 mL/min/1.73 m² was -0.23% for empagliflozin 10 mg and 0.00% for empagliflozin 25 mg. For patients with eGFR of 45 mL/min/1.73 m² or more, the treatment differences to placebo at 28 weeks were -0.28% for empagliflozin 10 mg and -0.37% for empagliflozin 25 mg. The corresponding p-value for the treatment-by-renal function interaction term was 0.0595. These analyses suggest that deteriorations in renal function with age contribute to the reduced efficacy.

In all 4 age categories, both doses of empagliflozin provided clinically meaningful FPG reductions from baseline compared with placebo. The adjusted mean treatment difference to placebo in the FPG change from baseline decreased with increasing age for both doses of empagliflozin (p-value= 0.0313 for the treatment-by-age interaction term).

In all 4 age categories, both doses of empagliflozin provided significant and clinically meaningful reductions from baseline in body weight compared with placebo. The adjusted mean treatment difference to placebo in the body weight change from baseline was similar across the categories of patients aged less than 75 years for both doses of empagliflozin. In the category of patients aged 75 years or more, the adjusted mean treatment difference to placebo was numerically higher for both empagliflozin doses (empagliflozin 10 mg: -3.66 kg; empagliflozin 25 mg: -3.72 kg) than in the other age categories. This result is partially attributable to an increase in body weight in the placebo group (adjusted mean change from baseline: 0.91 kg) in the category of patients aged 75 years or more; in the other 3 age categories there was either little change or a decrease in body weight with placebo treatment. However, the p-value for the treatment-by-age interaction term (p=0.1407) indicated that age had no overall influence on the treatment effect of empagliflozin with regard to body weight.

In all 4 age categories, both doses of empagliflozin provided significant and clinically meaningful reductions from baseline compared with placebo in SBP (p=0.5649) for treatment by age interaction and DBP (p=0.5489).

7.2.2.2. Gender

For both genders, empagliflozin provided significant and clinically meaningful reductions from baseline in HbA1c compared with placebo. The adjusted mean difference between empagliflozin (both doses) and placebo was numerically higher for male than for female patients; the p-value of 0.1597 for the treatment-by-gender interaction term indicated that there was no influence of

gender on the treatment effect of empagliflozin. For both genders, empagliflozin provided significant and clinically meaningful reductions from baseline compared with placebo in FPG (p-value of 0.7055 for treatment by gender interaction), body weight (p-value of 0.4241), SBP (p=0.9101) and DBP (p=0.8705).

7.2.2.3. Race

Both doses of empagliflozin provided significant and clinically meaningful reductions in HbA1c compared with placebo in White, Black, and Asian patients. The p-value for the treatment-by-race interaction term (p=0.5048) indicated that race did not have an influence on the treatment effect of empagliflozin. However, the overall number of Black patients was relatively small (46 patients). Both doses of empagliflozin provided significant and clinically meaningful reductions compared with placebo in White, Black, and Asian patients in FPG (p=0.8599 for treatment-by-race interaction term), body weight (p=0.8160), SBP (p=0.6461) and DBP (p=0.3154).

7.2.2.4. Geographical region

Both doses of empagliflozin provided significant and clinically meaningful reductions in HbA1c compared with placebo in patients in all regions: Europe, North America, Latin America, and Asia. The p-value for the treatment-by-region interaction term (p=0.7908) indicated that region did not have an influence on the treatment effect of empagliflozin. In all regions, compared with placebo, both doses of empagliflozin produced significant and clinically meaningful reductions in FPG (p= 0.858 for treatment-by-geographical region term), SBP (p=0.9104) and DBP (p=0.1387). The treatment difference to placebo for both doses of empagliflozin was higher for patients from North America and Latin America than for patients from Europe and Asia (p-value for the treatment-by geographical region term was 0.0809).

7.2.2.5. Baseline BMI

Treatment with both empagliflozin doses provided clinically meaningful HbA1c reductions from baseline after 24 weeks compared with placebo in all 4 BMI categories. The p-value for the treatment-by-baseline BMI term (p=0.6576) indicated that the treatment effect of empagliflozin was consistent across BMI categories. Both doses of empagliflozin provided significant and clinically meaningful reductions compared with placebo in all 4 BMI categories in FPG (p=0.4883 for treatment-by-BMI interaction term), body weight (p=0.1061), SBP (p=0.6248) and DBP (p=0.9473).

7.2.2.6. Baseline HbA1c

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. The p-value for the treatment-by-baseline HbA1c interaction term (<0.0001) also indicated that baseline HbA1c influenced the treatment effect of empagliflozin. The results for the analysis of changes in FPG by baseline HbA1c were in line with those reported above for HbA1c changes. Treatment with both doses of empagliflozin provided significant and clinically meaningful reductions in body weight in each of the individual baseline HbA1c categories. Although there was some variation between the subgroup categories, the p-value for the treatment-by-baseline HbA1c interaction term was 0.1437. Both doses of empagliflozin provided clinically meaningful reductions in SBP (p=0.4639 for treatment by baseline HbA1c interaction term) and DBP (p=0.1383) in each of the individual baseline HbA1c categories.

7.2.2.7. Baseline blood pressure

Two subgroup categories were defined based on BP values recorded at baseline: controlled BP (i.e. SBP below 130 mmHg and DBP below 80 mmHg) and uncontrolled BP (i.e. SBP of at least

130 mmHg or DBP of at least 80 mmHg). Both doses of empagliflozin provided clinically meaningful reductions in SBP in patients with uncontrolled BP at baseline. The treatment effect was greater in patients with uncontrolled BP at baseline (treatment difference to placebo was -4.6 and -5.5 mmHg for empagliflozin 10mg and 25mg, respectively) than in patients with controlled BP at baseline (-2.3 and -1.5 mmHg, respectively). The p-value for the treatment-by-BP control interaction term ($p=0.0038$) indicated that baseline BP had an influence on the treatment effect of empagliflozin with regard to the change from baseline in SBP. In the category of patients with uncontrolled BP, the adjusted mean changes from baseline in DBP were -1.9 mmHg in the placebo group, -3.8 mmHg in the empagliflozin 10 mg group, and -3.7 mmHg in the empagliflozin 25 mg group; the treatment difference to placebo was -1.9 mmHg for each of the empagliflozin doses. In the category of patients with controlled BP, reductions from baseline in DBP were not observed in any of the treatment groups; the adjusted mean changes from baseline in DBP were 1.8 mmHg in the placebo group, 1.2 mmHg in the empagliflozin 10 mg group, and 0.7 mmHg in the empagliflozin 25 mg group; the treatment difference to placebo was -0.7 mmHg for empagliflozin 10 mg and -1.1 mmHg for empagliflozin 25 mg. The p-value for the treatment-by-BP control interaction term was 0.2479.

7.2.2.8. Time since diagnosis of diabetes

The subgroup analysis by time since diagnosis of diabetes was performed for the HbA1c and FPG endpoints only. Treatment with empagliflozin (both doses) provided clinically meaningful HbA1c reductions compared with placebo in all 3 categories (i.e. ≤ 1 year, >1 to ≤ 5 years, and ≥ 5 years). The p-value for the treatment by-time since diagnosis term (0.7654) indicated that the treatment effect of empagliflozin was not influenced by the duration of diabetes. Treatment with empagliflozin (both doses) provided significant and clinically meaningful FPG reductions compared with placebo in all 3 categories of time since diagnosis of diabetes. The treatment difference was similar for patients across the subgroup categories, with a p-value for the interaction term of 0.9886.

7.2.2.9. Renal impairment

The subgroup analysis by renal impairment category showed a reduction in the efficacy of empagliflozin with increasing degree of renal impairment. The p-value for the treatment-by-renal impairment interaction term ($p=0.0009$) indicated that the degree of renal impairment influenced the treatment effect of empagliflozin. Nevertheless, in patients with mild or moderate renal impairment, treatment with empagliflozin (both doses) provided clinically meaningful reductions in HbA1c compared with placebo. An additional subgroup analysis was performed with the patients with moderate renal impairment further categorised into patients with chronic kidney disease stage 3A (moderate renal impairment A; eGFR 45 to <60 mL/min/1.73 m²) and chronic kidney disease stage 3B (moderate renal impairment B; eGFR 30 to <45 mL/min/1.73 m²). In patients with chronic kidney disease stage 3A, both doses of empagliflozin provided clinically meaningful reductions in HbA1c compared with placebo. In patients with chronic kidney disease stage 3B, the treatment difference to placebo was lower (for both empagliflozin doses) than in the other renal impairment categories; however, the number of patients in this category was too low (total 23 patients) to draw meaningful conclusions. A total of 2294 patients from the pivotal trials comprising EFF-2 had either normal renal function or mild renal impairment. The treatment difference to placebo in the change in HbA1c from baseline was -0.64% (95% CI: -0.71, -0.56) in the empagliflozin 10 mg group and -0.71% (95% CI: -0.78, -0.63) in the empagliflozin 25 mg group. Thus, in patients with normal renal function or mild renal impairment, empagliflozin at both tested doses provided clinically meaningful reductions in HbA1c from baseline. The results of the subgroup analysis of the change from baseline in FPG by renal impairment were consistent with the analysis of HbA1c changes described above. Treatment with both doses of empagliflozin provided clinically meaningful reductions in body weight in each of the renal impairment categories. The p-value for the treatment-by-renal impairment interaction term ($p=0.3288$). In the categories of patients with normal renal function, mild renal impairment, and moderate renal impairment, both doses of empagliflozin provided clinically meaningful reductions in SBP compared with

placebo. The magnitude of the BP reduction increased with increasing degree of renal impairment. For patients with normal renal function the treatment difference to placebo was -2.1 mmHg for empagliflozin 10 mg and -3.1 mmHg for empagliflozin 25 mg. For patients with moderate renal impairment the treatment difference was -5.4 mmHg for empagliflozin 10 mg and -9.6 mmHg for empagliflozin 25 mg. The p-value for the treatment-by-renal impairment interaction term ($p=0.0112$) indicated that the degree of renal impairment influenced the treatment effect of empagliflozin. The p-value for the treatment by renal impairment interaction term of 0.6069 indicated that the degree of renal impairment did not influence the effect of empagliflozin on the change from baseline in DBP.

7.2.2.10. Baseline HOMA-IR

The subgroup analysis by HOMA-IR category was performed for the HbA1c and FPG endpoints only. The HOMA-IR categories studied were ≤ 4 mU/L x mmol/L, >4 to 5.5 mU/L x mmol/L, >5.5 to ≤ 8.5 , and >8.5 mU/L x mmol/L. The subgroup analyses by baseline HOMA-IR showed that both doses of empagliflozin provided clinically meaningful reductions in HbA1c in each of the individual baseline HOMA-IR categories. The p-value for the treatment-by-baseline HOMA-IR interaction term was 0.0019, indicating that baseline HOMA had an influence on the treatment effect of empagliflozin with regard to HbA1c. The treatment difference was greatest for the patients in the highest baseline HOMA-IR category (>8.5 mU/L x mmol/L). Both doses of empagliflozin provided significant and clinically meaningful reductions in FPG in each of the individual baseline HOMA-IR categories. With increasing HOMA-IR, there was an increase in the treatment difference to placebo (p-value for the treatment-by-baseline HOMA-IR interaction term was 0.0150).

7.2.2.11. Baseline HOMA-IS

The subgroup analysis by HOMA-IS category was performed for the HbA1c and FPG endpoints only. The HOMA-IS categories studied were ≤ 25 mU/mmol, >25 to ≤ 40 mU/mmol, >40 to 70 mU/mmol, and >70 mU/mmol. Both doses of empagliflozin provided significant and clinically meaningful reductions in HbA1c in each of the individual baseline HOMA-IS categories. With increasing HOMA-IS category, there was a numerical trend towards a decrease in the treatment difference to placebo. The p-value for the treatment-by-baseline HOMA-IS interaction term was 0.1198. Both doses of empagliflozin provided significant and clinically meaningful reductions in FPG in each of the individual baseline HOMA-IS categories. The treatment difference to placebo with regard to the adjusted mean change from baseline in FPG was highest in the lowest HOMA-IS category (≤ 25 mU/mmol). Although there was no obvious trend across the other 3 HOMA-IS categories, the p-value for the treatment-by-baseline HOMA-IS interaction term of 0.0467, indicated that the level of insulin secretion at baseline influenced the treatment effect of empagliflozin.

7.2.3. Long term efficacy

The evidence of the persistence of the efficacy of empagliflozin is derived from analyses over at least 52 weeks in the efficacy pooling EFF-2 and the additional trials 1245.28, 1245.33, 1245.36, and 1245.25. The 52-week analysis of efficacy grouping EFF-2 comprises the 24-week duration pivotal trials (1245.19, 1245.20, 1245.23) and their extension trial 1245.31. Patients in the extension trial continued with the same double-blind trial medication that was assigned in the initial pivotal trial. All randomised patients in the pivotal trials were included in the analysis of EFF-2 irrespective of whether they continued in the extension trial or not. Because interim data from the extension trial are included, the numbers of patients with available efficacy data decreased over time due to some patients not having reached specific analysed timepoints at the time of the interim cut-off.

7.2.3.1. Long-term efficacy in the pooled pivotal studies (EFF-2 analysis)

The efficacy of empagliflozin in terms of reduction in HbA1c 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 timepoint 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 timepoint 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.

The pooled data from EFF-2 showed that of the patients with baseline HbA1c of >7.0% the proportion of patients achieving HbA1c <7.0% after 52 weeks was higher in the empagliflozin groups (empagliflozin 10 mg: 23.9%; empagliflozin 25 mg: 28.7%) than in the placebo group (8.4%). The odds of achieving HbA1c <7.0% after 52 weeks were higher for both empagliflozin dose groups than for placebo, with an odds ratio to placebo of 3.609 (95% CI: 2.633, 4.947) in the empagliflozin 10 mg group and 4.642 (95% CI: 3.402, 6.335) in the empagliflozin 25 mg group.

Changes in FPG were also maintained till 52 weeks in the pooled EFF-2 efficacy analysis. During the first 24 weeks of treatment there was a reduction in body weight from baseline in both empagliflozin treatment groups that was sustained up to 52 weeks. During the first 18 weeks of treatment there was a gradual reduction in SBP from baseline in both empagliflozin treatment groups that was sustained up to 52 weeks. In the empagliflozin 25 mg group the reduction in DBP occurred mostly during the first 12 weeks and was sustained until 52 weeks. Of the patients with high BP \geq 130/80 mmHg at baseline, the overall proportion of patients achieving BP <130/80 mmHg after 52 weeks was higher in the empagliflozin groups compared with placebo (24.0%, 21.1% and 9.2% in the empagliflozin 10mg, 25mg and placebo groups, respectively). The odds of achieving BP <130/80 mmHg after 52 weeks were higher for both empagliflozin dose groups than for placebo, with an odds ratio to placebo of 3.198 (95% CI: 2.213, 4.622) in the empagliflozin 10 mg group and 2.710 (95% CI: 1.864, 3.942) in the empagliflozin 25 mg group.

The pooled data from EFF-2 showed that fewer patients in the empagliflozin groups required rescue therapy up to 52 weeks compared to placebo (7.1%, 6.1% and 24.7% in the empagliflozin 10mg, 25mg and placebo groups, respectively). A logistic regression analysis showed that the odds of requiring rescue therapy were lower for patients in the empagliflozin treatment groups than for those in the placebo group in each of the pivotal trials. For the pooled analysis based on EFF-2 the odds ratios of using rescue medication for patients treated with empagliflozin compared with placebo were 0.211 (95% CI: 0.153, 0.292) for empagliflozin 10 mg and 0.180 (95% CI: 0.128, 0.253) for empagliflozin 25mg.

Results of the extension of the 4 pivotal studies (study 1245.31, section 7.1.2.1) showed that treatment with empagliflozin 10 mg or 25 mg resulted in a clinically meaningful improvement of glucose control, weight, and blood pressure in patients with type 2 diabetes mellitus who were either drug-naïve or on a background treatment with pioglitazone, metformin alone, or metformin and sulfonylurea, which was sustained over 52 weeks of treatment.

The persistence of the efficacy of empagliflozin is also supported by a combined analysis of the two 12 week dose-finding trials 1245.9 and 1245.10 with their 78 week open label extension trial 1245.24. The changes from baseline in HbA1c were analysed by an ANCOVA on the FAS (LOCF) after 90 weeks of treatment. For the patients in whom empagliflozin was investigated as monotherapy (from the preceding trial 1245.9), both doses of empagliflozin provided clinically meaningful reductions in HbA1c from baseline after 90 weeks; adjusted mean differences to metformin were 0.14% (95%: -0.08, 0.35) and 0.04% (95%: -0.18, 0.25) for the empagliflozin 10mg and 25mg groups, respectively. For the patients in whom empagliflozin was investigated as add-on to metformin (from the preceding trial 1245.10), both doses of empagliflozin provided clinically meaningful reductions in HbA1c from baseline after 90 weeks; the adjusted mean differences to sitagliptin were -0.16% (95%: -0.42, 0.10) and -0.29% (95%: -0.55, -0.03), respectively. Majority of the FPG-lowering response in the empagliflozin 10 mg and 25 mg groups was achieved at 6 weeks and maintained over time until the end of the study. After 78 weeks, the adjusted mean change from baseline in FPG was -10.51 mg/dL in the empagliflozin 10 mg group and -17.43 mg/dL in the empagliflozin 25 mg group, compared with -5.48 mg/dL in the placebo group.

Further evidence of long-term efficacy is derived from a 52-week interim analysis of the active-controlled (vs glimepiride) trial 1245.28; the difference from glimepiride in the adjusted mean HbA1c change from baseline at 52 weeks was -0.07% (95% CI: -0.15%, 0.01%). The p-value (based on a non-inferiority margin of 0.3%) was <0.0001 and therefore non-inferiority of empagliflozin 25 mg to glimepiride was demonstrated. Of the patients with baseline HbA1c of 7.0% or greater the overall proportion of patients achieving HbA1c <7.0% after 52 weeks was 38.7% in the empagliflozin 25 mg group and 39.0% in the glimepiride group. The odds of achieving HbA1c <7.0% after 52 weeks were almost identical for both treatment groups, with an odds ratio (empagliflozin 25 mg to glimepiride) of 1.027 (95% CI: 0.815, 1.295). Furthermore, the empagliflozin 25 mg group showed an initial reduction from baseline in adjusted mean FPG to -20.6 mg/dL after 28 weeks that was maintained over time (-20.0 mg/dL at 52 weeks). However, in the glimepiride group, there was a reduction in adjusted mean FPG from baseline to -20.0 mg/dL after 12 weeks but then a gradual return towards baseline (-8.9 mg/dL at 52 weeks).

Persistence of the efficacy of empagliflozin in patients taking basal insulin as background therapy was shown by data from the 78-week study duration of trial 1245.33 which has been discussed in detail in section 7.1.2.2. This includes an analysis of efficacy beyond the 18-week time point when adjustments of the basal insulin dose were permitted. The difference to placebo in the adjusted mean HbA1c change from baseline at 78 weeks was -0.46% (95% CI: -0.70, -0.23, p=0.0001) in the empagliflozin 10 mg group and -0.62% (95% CI: -0.87, -0.38, p<0.0001) in the empagliflozin 25 mg group. Of the patients with baseline HbA1c of 7.0% or greater (i.e. all patients in the FAS), the overall proportion of patients achieving HbA1c <7.0% after 78 weeks was 12.0% in the empagliflozin 10 mg group and 17.5% in the empagliflozin 25 mg group, compared with 6.7% in the placebo group. The odds of achieving HbA1c <7.0% after 52 weeks were higher for both empagliflozin groups than for placebo, with an odds ratio to placebo of 1.939 (95% CI: 0.884, 4.256) for the empagliflozin 10 mg group and 3.239 (95% CI: 1.518, 6.911) for the empagliflozin 25 mg group.

In study 1245.36, the HbA1c reductions that were observed at 24 weeks in trial 1245.36 in patients with mild or moderate renal impairment treated with empagliflozin were maintained until the end of the study at 52 weeks. Reductions in FPG, body weight, SBP and DBP were also maintained till 52 weeks (refer section 7.1.2.5 of this report).

[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]

Comments: The study report of the CV safety study 1245.25 was not provided in the dossier and the above results were only provided in the clinical efficacy summary.

In addition, a dose-finding study conducted in Japanese patients over 52 weeks demonstrates the persistence of efficacy. Trial 1245.38 was a Phase IIb dose finding trial conducted in Japanese patients. It comprised an initial 12-week treatment period in which 4 doses of empagliflozin (5 mg, 10 mg, 25 mg, and 50 mg) were investigated in comparison with placebo followed by a 40-week extension period in which patients in the empagliflozin 10 mg and 25 mg continued with the same treatment and patients in other groups were randomised to empagliflozin 10 mg and 25 mg. In the set of patients who were treated with empagliflozin 10 mg and 25 mg for the entire study duration, both empagliflozin doses provided clinically meaningful reductions in HbA1c, FPG, blood pressure, body weight compared with placebo that were sustained throughout the overall study duration.

7.2.4. Dose-comparison (efficacy of 10mg vs 25mg)

In each of the pivotal 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. For empagliflozin 25 mg, the treatment difference to empagliflozin 10 mg was -0.06% (95% CI: -0.13, 0.01). In each of the individual pivotal trials except for 1245.23 (met+SU), the reduction in

HbA1c from baseline was greater with empagliflozin 25 mg than with empagliflozin 10 mg. A similar pattern was evident for the analyses at 52 weeks. Similar results were observed for HbA1c responder rate and for the pooled analysis of the pivotal trials (EFF-2), the logistic regression analysis showed that the odds of achieving HbA1c <7.0% after 24 weeks were significantly higher for the empagliflozin 25 mg group than for the empagliflozin 10 mg group, with an odds ratio (25:10mg) of 1.302 (95% CI: 1.040, 1.629, p=0.0212). Similarly, after 52 weeks, the odds of achieving HbA1c <7.0% were significantly higher for the empagliflozin 25 mg group than for the empagliflozin 10 mg group, with an odds ratio of 1.286 (95% CI: 1.010, 1.638, p=0.0414).

In each of the individual pivotal trials (except for 1245.23 (met)) and for their pooling the reduction in FPG from baseline at 24 weeks was consistently higher with empagliflozin 25 mg than with empagliflozin 10 mg with similar results observed at 62 weeks.

In each of the individual pivotal trials, except 1245.19, and for their pooling, the reduction in body weight from baseline was higher with empagliflozin 25 mg than with empagliflozin 10 mg with similar results after 52 weeks.

In the individual pivotal trials, except 1245.23 (met+SU), and for their pooling, the reduction in SBP from baseline was higher with empagliflozin 25 mg than with empagliflozin 10 mg with a similar pattern evident after 52 weeks. However, the reduction in DBP from baseline was similar in both empagliflozin dose groups in each of the individual pivotal trials and for their pooling.

A formal statistical comparison was not performed to compare the use of rescue medication between the 10 mg and 25 mg dose groups. However, consistently across the pivotal trials the percentage of patients requiring rescue medication was lower in the empagliflozin 25 mg group than in the 10 mg group. In the EFF-2 pooling, the percentage of patients who required rescue medication was 4.1% in the empagliflozin 10 mg group and 2.4% in the empagliflozin 25 mg group.

7.3. Evaluator's conclusions on clinical efficacy for empagliflozin as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus

Regulatory guidelines²⁵ for the development of diabetes drugs were followed in designing and adapting the clinical development programme for empagliflozin. Overall, 13767 subjects were included and treated in the clinical trials constituting the development programme presented in this application. A total of 8506 patients with type 2 diabetes mellitus were treated with empagliflozin (empagliflozin 25 mg: 4563 patients, empagliflozin 10 mg: 3311 patients). Of these, 6808 patients were treated with empagliflozin for at least 24 weeks, 4415 patients for at least 52 weeks, and 1486 patients for at least 76 weeks. The clinical programme exceeds the requirements of relevant guidelines and provides adequate and sufficient information for the assessment of efficacy empagliflozin as treatment for type 2 diabetes in adults. Patient population studied was representative of the target patient population in which empagliflozin is proposed to be used.

Treatment with empagliflozin 10 mg or 25 mg once daily resulted in a robust improvement of glycaemic control with statistically significant and clinically meaningful reductions of HbA1c and FPG. The 4 pivotal trials demonstrated the superiority of both doses of empagliflozin to placebo after 24 weeks. In 3 of the 4 trials, the effects for the 25 mg dose were numerically

²⁵ These included EMA's draft "Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus" from 2010; EMA's final "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus" from 2012; FDA's "Draft Guidance for Industry - Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention" from 2008; and FDA's "Guidance for Industry - Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" from 2008.

larger than for the 10 mg dose. The effects were consistent across a range of different antidiabetic background regimens. Thus, empagliflozin improved glycaemic control as monotherapy and as add-on to metformin monotherapy, metformin plus sulphonylurea, and pioglitazone (with or without metformin). Almost maximal efficacy of empagliflozin on glycaemic control was established already 12 weeks after the start of treatment. Efficacy was sustained for at least 52 weeks, as shown in the double-blind extensions of the 4 pivotal trials. The proportions of patients reaching the target HbA1c (<7.0%) at Week 24 were significantly larger for both empagliflozin doses than for placebo in each trial; treatment with empagliflozin 25 mg led to higher responder rates than treatment with empagliflozin 10 mg. In addition, significantly fewer patients in the empagliflozin groups required rescue medication than patients in the placebo groups. The results for HbA1c and FPG were further supported by reductions in mean daily glucose and postprandial glucose, which were investigated in 2 of the pivotal trials.

Empagliflozin also provided significant and clinically meaningful reductions in HbA1c compared with placebo in all other Phase III placebo-controlled trials, i.e. in patients treated with basal insulin, in patients with type 2 diabetes and hypertension, in patients with mild and moderate renal impairment, and in patients with increased cardiovascular risk (including a subpopulation of patients with increased cardiovascular risk on a background of metformin and DPP-4 inhibitor, with or without 1 additional oral antidiabetic agent).

The HbA1c-lowering effect of empagliflozin was generally consistent across various subgroups based on demographic factors or baseline characteristics. These were gender, race (White, Asian, Black), ethnicity, geographical region, BMI, time since diagnosis of diabetes, and extent of insulin resistance (HOMA-IR) and insulin secretion (HOMA-IS). Higher baseline HbA1c values were associated with greater empagliflozin-mediated reductions in HbA1c. There is a high prevalence of chronic kidney disease in patients with type 2 diabetes, and only limited treatment options for patients with impaired renal function are available due to safety and tolerability concerns. As expected, given the mechanism of action of empagliflozin, a gradual reduction in efficacy of empagliflozin was observed with increasing degree of renal impairment. However, empagliflozin provided statistically significant and clinically meaningful reductions in HbA1c even in patients with moderate renal impairment (in a trial in patients with type 2 diabetes and renal impairment). Relevant reductions of HbA1c were achieved in both, patients with chronic kidney disease 3A and patients with chronic kidney disease 3B. Reduced efficacy of empagliflozin was seen with increasing age but HbA1c improvements compared with placebo were clinically meaningful in all subcategories of patients younger than 75 years. The reduced efficacy in patients aged 75 years or older appeared to be largely driven by the generally decreased renal function in these patients.

Body weight reduction and optimum control of BP are 2 important unmet needs in the management of patients with type 2 diabetes. Empagliflozin treatment led to statistically significant and clinically meaningful reductions in body weight in all pivotal trials. Furthermore, significant and clinically meaningful reductions of SBP compared with placebo were achieved for empagliflozin 25 mg in each of the pivotal trials. For DBP, reductions were also observed but were smaller and not always significant compared with placebo. In an ABPM trial in patients with type 2 diabetes and hypertension, both doses of empagliflozin were superior to placebo in reducing 24-h SBP and 24-h DBP after 12 weeks of treatment. Weight and blood pressure reductions of a magnitude similar to that in the pivotal trials were reached in the other supportive trials including the trials in patients with renal impairment or with high cardiovascular risk. Notably, in patients without hypertension, treatment with empagliflozin was not associated with an increased frequency of AEs indicative of hypotension. The weight and BP reductions were sustained throughout the short- and long-term trials. The effects of empagliflozin on body weight and BP are expected to modify cardiovascular risk factors and cardiovascular risk, and may translate into a benefit on the long-term micro- and macrovascular complications of diabetes that extend beyond the effect on glycaemic control. However effect of empagliflozin on morbidity and mortality has not yet been established.

Empagliflozin 25 mg was compared to the established antidiabetic drug glimepiride. In this double-blind trial (1245.28, Section 7.1.2.4), empagliflozin was shown to provide non-inferior glycaemic control to glimepiride (up to 4 mg daily) after 52 weeks of treatment. At the same time, empagliflozin was superior to glimepiride for several other clinically important endpoints, namely body weight reduction, a reduced occurrence of confirmed hypoglycaemic events, and for SBP and DBP reductions. Thus, similar glycaemic control was complemented by added benefits of empagliflozin 25 mg compared with glimepiride.

Metformin is the current standard first-line treatment for patients with type 2 diabetes. New antidiabetic drugs will therefore likely be employed as combination therapy, e.g. with metformin, or as monotherapy in patients for whom metformin is inappropriate. Sitagliptin is one of the few antidiabetic drugs with such a restricted monotherapy claim (in the EU). Therefore, empagliflozin (25 mg) efficacy was compared with that of sitagliptin (100 mg) in the pivotal monotherapy trial (1245.20) and its extension. For most endpoints, the exploratory comparison of both empagliflozin doses vs sitagliptin provided a larger treatment effect of empagliflozin. Treatment with empagliflozin 25 mg showed a numerically greater reduction in HbA1c than treatment with sitagliptin; the reduction in HbA1c for treatment with empagliflozin 10 mg was almost identical to that for sitagliptin. Treatment with both empagliflozin 10 mg and 25 mg reduced body weight and BP compared with sitagliptin treatment, although there was no direct statistical comparison between empagliflozin and sitagliptin. The usefulness of empagliflozin in the monotherapy setting was further substantiated in a 12-week, double-blind, placebo-controlled Phase IIb trial with an open label (immediate release) metformin group. Long-term data of up to 90 weeks from the open label extension of this trial showed sustained and similar improvements of glycaemic control with empagliflozin 25 mg and with metformin. These results suggest that empagliflozin may be an effective treatment option in patients for whom metformin is considered inappropriate. In this context, the added benefits of empagliflozin compared with the sulphonylurea glimepiride, which is also an alternative when metformin is inappropriate, are even more important.

In most of the trials, the 25 mg dose of empagliflozin showed better efficacy than the 10 mg dose. This was true for all endpoints (HbA1c, FPG, body weight, SBP, DBP). A higher proportion of patients reached the HbA1c target of <7% with empagliflozin 25 mg than with empagliflozin 10 mg. Fewer patients treated with the high empagliflozin dose required rescue medication than patients treated with the low empagliflozin dose.

7.3.1. Long term efficacy

In the Phase III, double-blind extension study 1245.31 (extension of the four 24-week pivotal studies for another 52 weeks), treatment with empagliflozin 10 mg or 25 mg resulted in a clinically meaningful improvement of glucose control, weight, and blood pressure in patients with type 2 diabetes mellitus who were either drug-naïve or on a background treatment with pioglitazone, metformin alone, or metformin and sulphonylurea, which was sustained over 52 weeks of treatment. For HbA1c, mean changes relative to placebo after 52 weeks across the studies were statistically significant and ranged from -0.54 to -0.76% in the empagliflozin 10 mg group and from -0.63 to -0.91 % in the empagliflozin 25 mg group. In drug-naïve patients, both doses showed a numerically larger decrease in mean HbA1c compared with sitagliptin (empagliflozin 10 mg: -0.10%; empagliflozin 25 mg -0.25%). In all studies, mean HbA1c levels decreased in both empagliflozin groups for up to 24 weeks and then remained stable until Week 52, while little change from baseline was seen for placebo patients. An important treatment target for patients with type 2 diabetes is adequate glycaemic control, which is defined as HbA1c <7.0% according to the American Diabetes Association and the European Association for the Study of Diabetes. In all 4 studies, the incidences of patients with glycaemic control were higher for the empagliflozin doses than for placebo, with exploratory odds ratios of empagliflozin over placebo ranging from 2.215 to 5.828 across the studies, and with empagliflozin 25 mg consistently showing the highest percent treatment response. These results are supported by a reduction in FPG sustained up to Week 52 in all studies. In addition, use of antidiabetic rescue medication was less common for the empagliflozin treatments than

for placebo (all studies) and sitagliptin (drug-naive). In summary, both empagliflozin doses led to a clinically meaningful and durable improvement of glycaemic control in patients who were drug-naive or received either pioglitazone, metformin, or metformin/SU as background therapy.

For body weight, mean changes relative to placebo after 52 weeks across the studies were statistically significant and ranged from -1.58 to -2.07 kg in the empagliflozin 10 mg group and from -1.83 to -2.19 kg in the empagliflozin 25 mg group. The treatment effect in comparison with sitagliptin in drug-naive patients was even more pronounced (empagliflozin 10 mg vs. sitagliptin: -2.21 kg; empagliflozin 25 mg vs. sitagliptin: -2.77 kg). Mean body weight in both empagliflozin groups decreased for up to 24 weeks and was then sustained until Week 52 in all studies. Of note, the reduction in body weight with empagliflozin was less pronounced in patients with baseline HbA1c \geq 8.5% than in those with baseline HbA1c $<$ 8.5% across studies. This is consistent with the observation that patients with poor glycaemic control, who tend to be in a catabolic state, are likely to gain weight when their glucose metabolism improves. Numerically more patients receiving empagliflozin (up to 20.3%) than receiving placebo (up to 6.8%) showed a $>$ 5% reduction in body weight after 52 weeks across the studies (and also when compared with sitagliptin treatment in drug-naive patients). These findings were supported by a sustained reduction in waist circumference relative to placebo in both empagliflozin groups across studies. For blood pressure, the mean changes relative to placebo in SBP at Week 52 were statistically significant and ranged from -2.8 to -4.6 mmHg in the empagliflozin 10 mg group and from -2.9 to -4.8 mmHg in the empagliflozin 25 mg group. In drug-naive patients, a significant decrease in mean SBP relative to sitagliptin was seen (empagliflozin 10 mg vs. sitagliptin: -2.7 mmHg; empagliflozin 25 mg vs. sitagliptin: -2.6 mmHg). These findings were supported by reductions in DBP relative to placebo in both empagliflozin groups across studies, albeit an only slight reduction seen for patients receiving metformin/SU.

When evaluating the combined benefits of empagliflozin (glucose control, reduced weight and BP) as a composite endpoint, it was found that more patients treated with either empagliflozin dose than treated with placebo (all studies) or sitagliptin (drug-naive) achieved a combined reduction in HbA1c by at least 0.5%, body weight by $>$ 2%, and SBP by $>$ 3 mmHg. Both empagliflozin groups showed changes in biomarkers for insulin resistance and secretion (assessed in 3 studies: drug-naive, metformin, and metformin/SU) that consistently suggest an improvement in beta-cell function and insulin resistance.

7.3.1.1. Limitations of data submitted and comments on proposed PI: Indications

The indication section of the proposed PI should specify the uses of empagliflozin as monotherapy and combination therapy. Patients on GLP-1 analogues were also excluded from all pivotal clinical trials. See also section 11.5 below.

8. Clinical safety

8.1. Studies providing evaluable safety data

Overall, 48 studies provided evaluable safety data for empagliflozin. For safety analyses, the studies were pooled into 6 groupings (SAFs-1 to 6) (Table 5 below).

Table 5: Study groupings for integrated safety analyses

Study grouping	Description	Studies included
SAF-1	Studies with empagliflozin monotherapy (in patients without background antidiabetic therapy)	Phase II: 1245.9, 1245.38 (only until 12 weeks) Phase III: 1245.20, 1245.31 monotherapy (only patients from 1245.20)
SAF-2 (= EFF-1)	Pivotal studies, excluding patients receiving an SU as background therapy	Phase III: 1245.19, 1245.20, 1245.23 _(met)
SAF-3 (= EFF-2)	Pivotal studies and their extension, including all patients	Phase III: 1245.19, 1245.20, 1245.23 _(met) , 1245.23 _(met+SU) , 1245.31
SAF-4	All studies in patients with type 2 diabetes and without special medical conditions (renal impairment or increased cardiovascular risk)	Phase I: 1245.2, 1245.4, 1245.44 Phase II: 1245.9, 1245.10, 1245.15, 1245.24, 1245.33, 1245.38 Phase III: 1245.19, 1245.20, 1245.23 _(met) , 1245.23 _(met+SU) , 1245.28, 1245.31, 1245.48
SAF-5	All studies in patients with type 2 diabetes ¹	Phase I: 1245.2, 1245.4, 1245.44 Phase II: 1245.9, 1245.10, 1245.15, 1245.24, 1245.33, 1245.38 Phase III: 1245.19, 1245.20, 1245.23 _(met) , 1245.23 _(met+SU) , 1245.25, 1245.28, 1245.31, 1245.36, 1245.48
SAF-6	All studies in healthy subjects ²	Phase I: 1245.1, 1245.3, 1245.5, 1245.6, 1245.7, 1245.8, 1245.16, 1245.17, 1245.18, 1245.27, 1245.30, 1245.40, 1245.41, 1245.43, 1245.45, 1245.50, 1245.51, 1245.58, 1245.63, 1245.79, 1275.3, 1275.5, 1276.9

Separate safety analyses were performed for study 1245.25 and presented in the dossier and in the cardiovascular safety meta-analysis report (U12-2463). ¹ Not including study 1245.42 (drug interaction with diuretics in patients with type 2 diabetes) because it was a cross-over design. ² Not including study 1245.83 because it was completed too late to be included.

SAF-1 pool was used for the safety assessment of empagliflozin administered as monotherapy. As the largest pool of patients, SAF-5 was used for safety subgroup analyses.

8.1.1. Pivotal efficacy studies

The on-treatment period was defined as the time between the first and the last intake of randomised (or open-label) study medication plus a washout period after the last intake. The washout periods were defined as 7 days for AEs, 3 days for laboratory measurements, and 1 day for vital sign measurements.

Details of the safety data collected and assessed in each of safety datasets is summarised in Table 6. AE analyses were based on the number of patients with AEs, not the number of AEs. AEs were coded with the MedDRA coding dictionary version 15.0. The types of the AEs analysed include all AEs, SAEs (non-fatal and with fatal outcome, both together and separately), AEs leading to discontinuation of study medication (including non-serious and serious events), all AEs by intensity, other significant AEs (based on the ICH E3 definition), investigator-defined drug-related AEs, and 8 categories of AEs of special interest²⁶ (decreased renal function, hepatic injury, urinary tract infection, genital infection, hypoglycaemic event, bone fracture, volume depletion, and malignancy).

²⁶ These adverse events were identified by standardised MedDRA queries (SMQs), BI-customised MedDRA queries (BICMQ; used only where no appropriate SMQ was available), and clinical laboratory results.

Table 6: Overview of integrated safety analyses

Safety analysis	SAF -1	SAF -2	SAF -3	SAF -4	SAF -5	SAF-5 subgroups ¹	SAF -6	1245.25
Disposition, demographics, baseline efficacy variables, exposure	Yes	Yes	Yes	Yes	Yes	Yes	Yes ²	Yes
Concomitant diagnoses and therapies	Yes	Yes	Yes	Yes	Yes	no	No	Yes
All adverse events, serious adverse events, adverse events leading to treatment discontinuation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
All adverse events by intensity	Yes	No	Yes	No	Yes	No	No	Yes
Investigator-defined drug-related adverse events, other significant adverse events (ICH E3)	No	No	Yes	No	Yes	No	No	Yes
Decreased renal function (SMQ) and hepatic injury (SMQ)	Yes	No	Yes	No	Yes	Yes	No	Yes
Renal laboratory parameters	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Elevated liver enzymes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Urinary tract infections (BICMQ) and genital infections (BICMQ)	Yes	No	Yes	No	Yes	Yes	No	Yes
Hypoglycaemic events	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Bone fractures (BICMQ)	No	No	Yes	Yes	Yes	Yes	No	Yes
Volume depletions (BICMQ)	Yes	No	Yes	No	Yes	Yes	No	Yes
Malignancies (BICMQ)	No	No	Yes	No	Yes	No	No	Yes
Safety laboratory parameters	Yes	Yes	Yes	No	Yes	No	No	Yes
Lipid laboratory parameters	No	No	Yes	No	Yes	No	No	No
Vital signs	No	No	Yes	No	Yes	No	No	Yes

In order to assess the cardiovascular risk of empagliflozin treatment compared with any control, a cardiovascular meta-analysis was planned. The primary endpoint 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 double-blind and controlled studies with a treatment duration of more than 12 weeks were included in the meta-analysis, and the analysis was based on the treated set. The cardiovascular risk ratio of empagliflozin treatment (the 2 test doses combined) against control treatment (all control treatments combined) and the associated confidence interval (CI) were calculated. The overall significance level for the meta-analysis was $\alpha = 2.5\%$, one-sided.

For all Phase III studies, all safety laboratory parameters were analysed by one central laboratory (Quintiles). For all Phase II studies (except study 1245.38), all safety laboratory parameters were analysed by another central laboratory (Covance). Safety laboratory parameters included (but were not restricted to) haematology, clinical chemistry, and urinalysis. Abnormal laboratory test results could also be recorded either as baseline conditions or as AEs. The protocols of all Phase III studies defined “significant AEs”, which are decreased renal function (creatinine shows a $\geq 2x$ increase from baseline and is above the upper limit of normal (ULN)) and hepatic injury (AST and/or ALT above $\geq 3x$ ULN, combined with bilirubin $\geq 2x$ ULN measured in the same sample). An independent DMC was formed to monitor patient safety across several Phase II and III studies (1245.19, 1245.20, 1245.23, 1245.25, 1245.28, 1245.31, 1245.36, 1245.48, 1245.49, 1245.39, 1245.46, 1245.38, and 1245.52). Based on

regular monitoring of safety data, the DMC²⁷ provided BI with advice regarding whether a study should continue as planned, be modified, or be discontinued.

8.2. Pivotal studies that assessed safety as a primary outcome

8.2.1. Study 1245.25

8.2.1.1. Study design, objectives, locations and dates

A Phase III, multicentre, international, randomised, parallel group, double blind cardiovascular safety study of BI 10773 (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk. The study will be conducted at multiple centres in 40 countries. The objective of the current study is to demonstrate non inferiority of two doses of BI 10773 (10 mg/daily and 25 mg/daily) compared to placebo with respect to first occurrence of any of the adjudicated components of the primary composite Major Adverse Cardiovascular Event endpoint (cardiovascular death, non-fatal stroke, nonfatal myocardial infarction) in patients with type 2 diabetes mellitus and increased cardiovascular risk. It was a randomised, double blind, parallel group, international, multicentre, add on to standard therapy, event driven study. The study started in Aug 2010 and was expected to be completed after 7-8 years. The interim data is available till Dec 2011.

8.2.1.2. Inclusion and exclusion criteria

The main inclusion criteria were: Type 2 diabetes mellitus patients with increased cardiovascular risk and insufficient glycaemic control despite current antidiabetic treatment at screening. Male and female patients on diet and exercise regimen who are drug-naive or pre-treated with any background therapy. HbA1c of $\geq 7.0\%$ and $\leq 10\%$ for patients on background therapy or HbA1c $\geq 7.0\%$ and $\leq 9.0\%$ for drug-naive patients; Age ≥ 18 years; BMI ≤ 45 kg/m²; Signed and dated written informed consent ; patients must have high cardiovascular risk, defined as at least one of the following:

- Confirmed history of myocardial infarction (>2 months prior to informed consent).
- Evidence of multivessel coronary artery disease, in 2 or more major coronary arteries, irrespective of the revascularization status, i.e. a) Either the presence of a significant stenosis (imaging evidence of at least 50% narrowing of the luminal diameter measured during a coronary angiography or a multi-sliced computed tomography angiography), in 2 or more major coronary arteries, b) Or a previous revascularisation (percutaneous transluminal coronary angioplasty with or without stent, or coronary artery bypass grafting) at least 2 months ago, in 2 or more major coronary arteries, c) Or the combination of previous revascularisation in one major coronary artery at least 2 months ago (percutaneous transluminal coronary angioplasty with or without stent, or coronary artery bypass grafting), and the presence of a significant stenosis in another major coronary artery²⁸ (imaging evidence of at least 50% narrowing of the luminal diameter measured during a coronary angiography or a multisliced computed tomography angiography). Evidence of a single vessel coronary artery disease with: a) The presence of a significant stenosis i.e. the imaging evidence of at least 50% narrowing of the luminal diameter of one major coronary artery in patients not subsequently successfully revascularised (measured during a coronary angiography or a multi-sliced computed tomography angiography) b) And at least one of the following (either (i) or (ii)): (i). A positive non invasive stress test²⁹,

²⁷ The DMC was composed of 3 members independent of the sponsor (2 physicians and 1 statistician); further support was provided by a statistician independent of the sponsor.

²⁸ Note: A disease affecting the left main coronary artery is considered as a 2-vessel disease.

²⁹ A positive non invasive stress test, confirmed by either: 1. A positive exercise tolerance test in patients without a complete left bundle branch block, Wolff-Parkinson-White syndrome, or paced ventricular rhythm or 2. A positive stress echocardiography showing regional systolic wall motion abnormalities, or

(ii) Or patient discharged from hospital with a documented diagnosis of unstable angina within 12 months prior to selection.

- Last episode of unstable angina >2 months prior informed consent with confirmed evidence of coronary multivessel or single vessel disease as defined above.
- History of ischemic or haemorrhagic stroke (>2 months prior to informed consent).
- Presence of peripheral artery disease (symptomatic or not) documented by either: previous limb angioplasty, stenting or bypass surgery; or previous limb or foot amputation due to circulatory insufficiency; or angiographic evidence of significant (> 50%) peripheral artery stenosis in at least one limb; or evidence from a non-invasive measurement of significant (>50% or as reported as hemodynamically significant) peripheral artery stenosis in at least one limb; or ankle brachial index of < 0.9 in at least one limb. The exclusion criteria were similar to those described for the pivotal Phase III studies.

8.2.1.3. Study treatments

After a 1-week screening period, patients will have a 2 week placebo run-in. Eligible patients will be randomly assigned to BI 10773 10 mg, BI 10773 25 mg or placebo in a balanced randomisation ratio e.g.1:1:1. Patients will then be treated with either BI 10773 or placebo in addition to their background medication, until the required number of events is reached. There will be a 4 week follow up period. Study will continue until enough cardiovascular events have occurred to be able to comply with the objective of the trial.

8.2.1.4. Safety variables and outcomes

Primary endpoint: The primary endpoint used is time to the first occurrence of any of the following adjudicated components of the composite endpoint: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI) and nonfatal stroke.

Key secondary cardiovascular endpoints were:

- The time to the first occurrence of the following adjudicated events (treated as a composite): CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), non-fatal stroke and hospitalization for unstable angina pectoris.

Further secondary endpoints are the occurrence of and time to each of the following events:

- Silent MI
- Heart failure requiring hospitalization
- New onset albuminuria defined as ACR \geq 30 mg/g
- New onset macroalbuminuria \geq 300 mg/g
- Composite microvascular outcome defined as: 1) Need for retinal photocoagulation, 2) Vitreous haemorrhage, 3) Diabetes-related blindness, 4) New or worsening nephropathy defined as: 4a) New onset of macroalbuminuria; or 4b) Doubling of serum creatinine level accompanied by an eGFR (based on modification of diet in renal disease (MDRD) formula) \leq 45 mL/min/1.73m²; or 4c) Need for continuous renal replacement therapy; or d) death due to renal disease.

Tertiary cardiovascular endpoints: occurrence of and time to each of the following adjudicated events:

- CV death (including fatal stroke and fatal MI)
- Non-fatal MI

3. A positive scintigraphic test showing stress-induced ischemia, i.e. the development of transient perfusion defects during myocardial perfusion imaging.

- Non-fatal stroke
- Hospitalisation for unstable angina
- All cause mortality
- TIA
- Coronary revascularization procedures.

Other tertiary endpoints included:

- Individual components of the composite microvascular outcome
- Changes from baseline in ECG, physical examination, vital signs (blood pressure and pulse rate) and laboratory parameters
- AEs
- Hypoglycaemic events
- Protocol-specified significant adverse events
- Use of rescue medication.

The efficacy outcomes included: Change from baseline in: HbA1c, Fasting Plasma Glucose (FPG), weight, waist circumference and blood pressure at Weeks 12, 52, once a year and at end of study.

8.2.1.5. Randomisation and blinding methods

Randomisation will be stratified in a balanced ratio e.g. 1:1:1 for the following factors: HbA1c < or \geq to 8.5% at screening, BMI < or \geq to 30 kg/m² at randomisation, geographical regions (North America, Latin America, Europe, Africa and Asia) and renal function at screening (normal: eGFR \geq 90 mL/min, mild impairment: 60 mL/min \leq eGFR \leq 89 mL/min and moderate impairment: 30 mL/min \leq eGFR \leq 59 mL/min). Treatment assignment will be by means of a third-party phone/web-based randomisation at Visit 3 involving use of an Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). After randomisation at Visit 3, patients, investigators and individuals involved with the trial conduct or analysis for the clinical trial report will remain blinded with regard to the randomised treatment assignments until after database lock.

8.2.1.6. Analysis populations

There will be an interim analysis of this trial to support the New Drug Application (NDA). These interim data will also be used in a cardiovascular meta-analysis. It is projected that approximately 80 confirmed primary events will have been observed from this trial at that time. The interim analysis and the cardiovascular meta-analysis will be performed by a team independent from the 1245.25 trial team, so that the trial team remains blinded to the results.

8.2.1.7. Sample size

Assuming a non-inferiority margin of 1.3 and power 90% with a significance level of 0.025 (one-sided), with the BI 10773 and placebo patients in 2:1 ratio, 691 events are required to achieve the primary aim of the trial (using a Haybittle-Peto boundary that preserves 0.0249 of the alpha for the last look). To obtain the 691 events, based on 7000 patients, assuming an accrual period of 24 months, yearly event rate of 1.5% and randomization rate of 3500 patients/year, the trial duration will be just under 8 years. So planned treatment duration of the patients will be between 6 and 8 years with approximately 8 years as the planned total duration of trial. With 691 events, the trial will have 80% power to detect a hazard ratio of 0.785 (corresponding to a 21.5% risk reduction in CV outcome events) for the primary endpoint.

8.2.1.8. Statistical methods

For the primary analysis a Cox proportional hazards regression model of time to the first event of CV death, non-fatal MI or non-fatal stroke with factors treatment, baseline categories of HbA1c (< or > 8.5%), age, gender, baseline categories of BMI (less than or greater than and equal to 30), geographical regions (North America, Latin America, Europe, Africa and Asia) and renal function at baseline (normal: eGFR \geq 90 mL/min, mild impairment: 60 mL/min \leq eGFR \leq 89 mL/min and moderate impairment: 30 mL/min \leq eGFR \leq 59 mL/min) will be conducted. The primary analysis will be performed on the treated set. The non-inferiority margin will be 1.3 and the hypotheses will be one-sided with a significance level of $\alpha=0.025$. If noninferiority will be established for this margin, non-inferiority will be tested on the key secondary endpoint based on the margin of 1.3. The 10mg and 25mg treatment arms will be combined for these analyses.

However, as this is an event driven trial and the trial will be stopped when the 691 patients have experienced an adjudicated primary outcome events are reached (which can be before or after 8 years). The trial will not be stopped if 691 patients have experienced an adjudicated outcome event for the key secondary endpoint but will continue until 691 patients have experienced an adjudicated primary outcome event. If the given assumptions are not met during the trial and more patients need to be recruited or the accrual period needs to be changed because of a slower randomization rate, a protocol amendment has to be done to incorporate the new calculations.

8.2.1.9. Participant flow

[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]

8.2.1.10. Major protocol violations/deviations

[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]

8.2.1.11. Baseline data

[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]

8.2.1.12. Interim CV safety results

[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]

8.2.1.13. Other interim safety results

[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]

[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]

8.3. Patient exposure

A total of 13183 patients with type 2 diabetes were treated in the clinical studies; of these, 3311 patients were treated with empagliflozin 10 mg, 4563 were treated with empagliflozin 25 mg, and 4697 were treated with comparator medications (placebo, metformin, sitagliptin and glimepiride). The number of treated subjects in all clinical studies and the numbers of treated subjects in all safety groupings and study 1245.25 are summarised in the table below.

Table 7: Number of treated subjects in safety groups

Grouping Study	Placebo	Empa <10 mg	Empa 10 mg	Empa 25 mg	Empa >25 mg	All (randomised) empa	All comparators ¹	Total randomised ²	Open-label empa 25 mg
SAF-1	420	191	414	414	110	1129	723	1852	87
1245.9	82	81	81	82	--	244	162	406	--
1245.20	229	--	224	223	--	447	452	899	87
1245.31 ³	136 ³	--	165 ³	159 ³	--	324 ³	291 ³	615 ³	--
1245.38	109	110	109	109	110	438	109	547	--
SAF-2	600	--	606	605	--	1211	823	2034	156
1245.19	165	--	165	168	--	333	165	498	--
1245.20	229	--	224	223	--	447	452	899	87
1245.23 _(MET)	206	--	217	214	--	431	206	637	69
SAF-3	825	--	830	822	--	1652	1048	2700	257
1245.19	165	--	165	168	--	333	165	498	--
1245.20	229	--	224	223	--	447	452	899	87
1245.23 _(MET)	206	--	217	214	--	431	206	637	69
1245.23 _(MET+STZ)	225	--	224	217	--	441	225	666	101
1245.31 ⁴	512 ⁴	--	607 ⁴	582 ⁴	--	1189	667	1856 ⁴	--
SAF-4	1584	382	1590	2332	219	4523	2738	7261	--
SAF-5	3522	382	3311	4285	219	8197	4676	12873	--
SAF-6	59	24	52	194	169	393 ⁵	246 ⁶	521	--
1245.25	1619	--	1623	1632	--	3255	1619	4874	--

¹ Including all active comparators and placebo except for SAF-6. For SAF-1 all comparators includes placebo, metformin, and sitagliptin; for SAF-2 and SAF-3 all comparators includes placebo and sitagliptin; for SAF-4 and SAF-5 all comparators includes placebo, metformin, sitagliptin, and glimepiride; for 1245.25 all comparators corresponds to placebo.

² Only randomised patients, not including open-label empagliflozin 25 mg.

³ Only patients who had completed the preceding study 1245.20; these patients had no background antidiabetic medication.

⁴ Patients could only enter the extension study 1245.31 if they completed one of the preceding studies (1245.19, 1245.20, 1245.23_(MET), and 1245.23_(MET+STZ)).

⁵ Subjects treated with empagliflozin alone in at least 1 treatment period; some of these subjects were co-administered empagliflozin and other active drugs in other treatment periods in the same study.

⁶ Subjects treated with any active comparator drug alone in at least 1 treatment period; some of these subjects were co-administered empagliflozin and other active drugs in other treatment periods in the same study.

Study grouping SAF-5 included 12873 patients treated with randomised study medication; 3311 patients (25.7%) were treated with empagliflozin 10 mg, 4285 patients (33.3%) with empagliflozin 25 mg, and 3522 patients (27.4%) with placebo; 601 patients (4.7%) were treated with other empagliflozin doses and 1154 patients (9.0%) were treated with active comparator medications (sitagliptin, metformin, and glimepiride). The percentage of patients who prematurely discontinued study medication was lower in the empagliflozin groups (9.5% for 10 mg and 9.8% for 25 mg) than in the placebo group (12.8%) and the most common reason for premature discontinuation was AEs (overall 3.9%). In SAF-5, 4261 patients (51.8%) were treated with empagliflozin 10 mg or 25 mg for 52 weeks or more and 1482 patients (18.0%) for 76 weeks or more. Due to the lack of a placebo arm in some studies and the different premature discontinuation rates, the mean exposure was higher to empagliflozin (327.8 days for empagliflozin 10 mg and 353.0 days for empagliflozin 25 mg) than to placebo (286.0 days). In SAF-5, the mean age was 59.6 years and the majority were male (63%), White (62.0%) or Asian (33.8%)³⁰; diagnosed with type 2 diabetes for over 5 years (64.8%). SAF-5 included a dedicated efficacy and safety study in patients with renal impairment, as well as a dedicated cardiovascular outcome study. Demographic and baseline data were generally similar across randomised groups. In the SAF-5 group, the mean and median exposure to study medication was lower in the placebo group than in the other groups. The reason for the lower exposure could be explained by the fact that not all studies in this grouping included the placebo treatment. Furthermore, there was a higher rate of patients who did not continue in the extension study in the placebo group (7.0%) than in the empagliflozin groups (6.2% for 10 mg and 4.9% for 25 mg) and a higher rate of patients who discontinued due to reasons other than not continuing in the extension study in the placebo group (12.8%) than in the empagliflozin groups (9.5% for 10 mg and 9.8% for 25 mg)³¹.

³⁰ 3.6% were Black or African American.

³¹ As groupings SAF-5 (all patients) and SAF-4 (all studies with patients with type 2 diabetes and without special medical conditions) included studies 1245.24 (extension of 1245.9 and 1245.10; patients could be re-randomised) and 1245.38 (during which patients could be re-randomised), according to the rules of treatment assignment, a patient is shown in 2 treatment groups if he/she was re-randomised to a different study drug/dose. Consequently, the numbers of patients for empagliflozin 10 mg, empagliflozin

Study grouping SAF-1 included 1852 patients treated with randomised study medication and 87 patients treated with open-label empagliflozin 25 mg. Of the randomised and treated patients, the majority (80.0%) either completed the treatment period or were still on treatment in study 1245.31 at the time of interim database lock. Overall for randomised and treated patients, 10.2% completed the preceding study and decided not to continue in the extension study (1245.31). The most common reasons (other than not continuing in extension) for premature discontinuation were refusal to continue study medication (3.0%) and AEs (2.6%). The mean and median exposure to study medication was lower in the placebo group than in the other groups.

Study grouping SAF-2 included 2034 patients treated with randomised study medication and 156 patients treated with open-label empagliflozin 25 mg. The extension study (1245.31) is not included in this study grouping and the number of premature discontinuations was lower in the active treatment groups compared with the placebo group. In the SAF-2 group, the mean exposure to the study medication was similar across treatment groups.

Study grouping SAF-3 included 2700 patients treated with randomised study medication and 257 patients treated with open-label empagliflozin 25 mg. Of the randomised and treated patients, the majority (64.2%) was still on treatment in the extension study (1245.31). Overall, 22.3% completed the preceding study and decided not to continue in the extension study. The percentage of patients who did not continue in the extension study was only slightly lower in the empagliflozin groups (20.5% for 10 mg and 21.0% for 25 mg) than in the placebo group (25.3%) and the sitagliptin group (22.9%). The percentage of patients who prematurely discontinued study medication due to reasons other than not continuing in extension was lower in the empagliflozin groups (10.8% for 10 mg and 12.8% for 25 mg) and in the sitagliptin group (12.1%) than in the placebo group (17.1%). The most common reasons (other than not continuing in extension) for premature discontinuation were: refusal to continue study medication (3.9%) and AEs (3.7%). The patients treated in the open-label empagliflozin 25 mg group in the preceding studies (1245.20, 1245.23 (met), and 1245.23 (met+SU)) were not eligible for continuation in the extension study (1245.31); 14.0% discontinued prematurely in the preceding studies. The mean exposure to the study medication was similar across randomised treatment groups.

Study grouping SAF-4 included 7261 patients treated with randomised study medication and majority of these (77.2%) completed the treatment period or were still on treatment at the time of the interim database lock. Overall for randomised and treated patients, 11.0% completed the preceding study and decided not to continue in the extension study. The percentage of patients who did not continue in the extension study was lower in the empagliflozin groups (12.8% for 10 mg and 9.0% for 25 mg) than in the placebo group (15.7%). The percentage of patients who prematurely discontinued study medication due to reasons other than not continuing in extension was lower in the empagliflozin groups (10.3% for 10 mg, 10.6% for 25 mg, and 10.4% for the all randomised) than in the placebo group (15.5%) and the all comparators group (14.1%). The most common reasons (other than not continuing in extension) for premature discontinuation were: AEs (3.9%) and refusal to continue study medication (2.8%). The mean and median exposure to study medication was lower in the placebo group than in the other groups. Due to the lack of an empagliflozin 10 mg treatment arm in study 1245.28, the exposure to empagliflozin 10 mg was lower than to empagliflozin 25 mg.

A total of 521 healthy subjects were treated in the study grouping SAF-6; 501 of them completed treatment(s) as planned, whereas 20 subjects prematurely discontinued from the study, mostly due to AEs (9 subjects, 1.7%) or withdrawal of consent (6 subjects, 1.2%). Disposition was not analysed by treatment in this grouping because almost all of the studies were of crossover design and the subjects received multiple treatments. The median exposure

25 mg, and all randomised empagliflozin groups are higher in the exposure and adverse event sections than those in the disposition, demographics, baseline characteristics, and laboratory evaluation sections, where only the first treatment assignment was used.

for all treatments ranged from 1.0 to 4.0 days as this grouping included studies with single-dose treatment and multiple-dose treatment of a few days. The highest single dose of empagliflozin was 800 mg in study 1245.1.

The total (randomised) patients from each SAF (except SAF-6, the healthy subjects) and study 1245.25 and all patients treated with open-label empagliflozin 25 mg are summarised in the dossier. In all groupings and in study 1245.25, more than half of the patients were male. Most patients were White or Asian and were from Europe, North America, or Asia. About half of the patients were 50 to <65 years of age. The average BMI was about 30 kg/m² and indicated an overweight population. The majority was diagnosed with type 2 diabetes for over 1 year and most patients had a history of hypertension. The majority of the patients had normal renal function or mild renal impairment at baseline. Demographic data were generally balanced across groups in each SAF and in study 1245.25. Baseline efficacy variables for the total (randomised) patients from each SAF (except SAF-6, the healthy subjects grouping), study 1245.25, and all patients treated with open-label empagliflozin 25 mg are summarised in the dossier. The values were generally similar across groups in each SAF and in study 1245.25. The most common relevant medical history reported for the randomised and treated patients in SAF-1 to SAF-5 was hypertension, which was reported for more than half of all patients; the frequencies were similar for all groups in each SAF.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal studies

In the SAF-3 group (pivotal studies and their extension), the frequency of patients with any AE was lower in the empagliflozin groups and the sitagliptin group than in the placebo group. The frequencies of patients with genital infection (BICMQ) or confirmed hypoglycaemic AEs were higher in the empagliflozin groups than in the comparator groups. The frequencies of patients with decreased renal function (SMQ) or volume depletion (BICMQ) were overall low ($\leq 1\%$) in all groups. The frequencies of patients with other types of AEs analysed for this grouping were similar in all groups (Table 8 below). The most common AE at SOC level was infections and infestations, with a lower frequency in the sitagliptin group than in the other groups. At PT level, the most frequently reported adverse events were hyperglycaemia, nasopharyngitis, and urinary tract infection. Hyperglycaemia was reported more frequently by patients in the placebo group than in the other groups. In the open-label empagliflozin 25 mg group, the most frequent AE at SOC level was metabolism and nutrition disorders (hyperglycemia). Of the randomised and treated patients in SAF-3, most patients who had any AE reported having mild or moderate events; within each intensity category, the frequencies were comparable for the placebo and the empagliflozin groups (mild: 42.9% for placebo, 44.1% for empagliflozin 10 mg, 43.6% for empagliflozin 25 mg, and 45.3% for sitagliptin; moderate: 24.8% for placebo, 23.6% for empagliflozin 10 mg, 22.0% for empagliflozin 25 mg, and 16.6% for sitagliptin; severe: 6.3% for placebo, 4.1% for empagliflozin 10 mg, 4.5% for empagliflozin 25 mg, and 3.1% for sitagliptin). For AE of severe intensity at PT level, hyperglycaemia was reported for 4 patients (0.5%) in the placebo group only; myocardial infarction was reported for 3 patients (0.4%) in the placebo group only; back pain was reported for no patient in the placebo group, 4 in the empagliflozin 10 mg group, 1 in the empagliflozin 25 mg group, and 2 in the sitagliptin group; acute renal failure was reported for 1 patient in the empagliflozin 10 mg group, 3 in the empagliflozin 25 mg group, and none in the placebo or sitagliptin group. No other severe event was reported by more than 2 patients per group. Of the treated patients in the open-label empagliflozin 25 mg group in SAF-3, 39.3% were reported to have had AEs of mild intensity, 21.8% of moderate intensity, and 1.9% of severe intensity.

Table 8: Overview of frequency of patients with adverse events in SAF-3-TS, OLS

	Placebo	Empa 10	Empa 25	Sitagliptin	OL empa 25 mg
	N (%)				
Number of patients	825 (100.0)	830 (100.0)	822 (100.0)	223 (100.0)	257 (100.0)
Patients with any adverse event	611 (74.1)	596 (71.8)	576 (70.1)	145 (65.0)	162 (63.0)
Patients with AEs leading to discontinuation of study medication	35 (4.2)	25 (3.0)	34 (4.1)	5 (2.2)	9 (3.5)
Patients with serious adverse events	61 (7.4)	59 (7.1)	48 (5.8)	9 (4.0)	9 (3.5)
Patients with decreased renal function (SMQ)	2 (0.2)	8 (1.0)	7 (0.9)	0	2 (0.8)
Patients with hepatic injury (SMQ)	19 (2.3)	8 (1.0)	18 (2.2)	5 (2.2)	2 (0.8)
Patients with urinary tract infection (BicMQ)	102 (12.4)	105 (12.7)	82 (10.0)	16 (7.2)	11 (4.3)
Patients with genital infection (BicMQ)	9 (1.1)	48 (5.8)	42 (5.1)	2 (0.9)	4 (1.6)
Patients with confirmed hypoglycaemic AEs ¹	36 (4.4)	56 (6.7)	44 (5.4)	1 (0.4)	9 (3.5)
Patients with bone fracture (BicMQ)	13 (1.6)	11 (1.3)	6 (0.7)	2 (0.9)	3 (1.2)
Patients with volume depletion (BicMQ)	2 (0.2)	8 (1.0)	5 (0.6)	1 (0.4)	2 (0.8)
Patients with malignancy (BicMQ)	6 (0.7)	3 (0.4)	8 (1.0)	1 (0.4)	1 (0.4)

SMQ = Standardised MedDRA Query; BicMQ = BI-customised MedDRA query

¹ Any adverse event (not restricted to the PT hypoglycaemia) assessed by the investigator to be a hypoglycaemic adverse event and with documented plasma glucose of ≤ 70 mg/dL or required assistance of another person

In the SAF-2 group (which included pivotal studies, but excluded patients receiving an SU as background therapy), the frequencies of patients with confirmed hypoglycaemic AEs were overall low and comparable across treatment groups. The frequencies of patients with other types of AEs analysed for this grouping were similar in all groups. The most common AE at SOC level was infections and infestations, with similar frequencies in the placebo and the empagliflozin groups (placebo 24.7%, empagliflozin 10 mg 25.4%, empagliflozin 25 mg 25.5%) but with a lower frequency in the sitagliptin group (20.2%). At PT level, the most frequently reported AE was urinary tract infection. Hyperglycaemia was reported by a higher proportion of patients in the placebo group (14.0%) than in the other groups (empagliflozin 10 mg 3.0%, empagliflozin 25 mg 1.7%, sitagliptin 5.8%). Other AEs with a frequency of >5% in any group (nasopharyngitis and dyslipidaemia) were reported with similar frequencies for all groups.

8.4.1.2. Other studies

In the SAF-5 group (all studies in T2DM patients), the frequency of patients with genital infection (based on BicMQ) was higher in the empagliflozin groups than in the comparator groups. The frequencies of patients with other types of AEs were similar in all groups. At PT level, the most frequently reported AE was hypoglycaemia. Hyperglycaemia was reported more frequently by patients in the comparator groups than in the empagliflozin groups (incidence rates per 100 patient-years: 14.12 for placebo, 4.86 for empagliflozin 10 mg, 4.95 for empagliflozin 25 mg, 4.86 for all randomised empagliflozin, and 13.45 for all comparators). Other AE with a frequency of >5% in any group were reported with similar frequencies for all groups. The majority of the patients who had any AE reported having mild or moderate events. The frequencies of patients with AEs of mild intensity were slightly higher in the empagliflozin groups (37.2% for 10 mg, 38.0% for 25 mg, and 37.7% for all randomised) than in the comparator groups (34.4% for placebo and 35.5% for all comparators). The frequency of patients with AEs of moderate intensity was slightly higher in the all comparators group (27.1%) than in the other groups (range: 24.6% to 25.9%). The frequency of patients with AEs of severe intensity was slightly lower in the empagliflozin groups (6.1% for 10 mg, 6.5% for 25 mg, and 6.2% for all randomised) than in the comparator groups (8.3% for placebo and 7.8% for all comparators). The most frequent AE of severe intensity at SOC level was cardiac disorders, which was reported less frequently in the empagliflozin groups than in the placebo group and the all comparators group. Other SOCs showed similar frequencies of severe AEs for all groups. For adverse event of severe intensity at PT level, all PTs reported in the SOC cardiac disorders,

as well as hyperglycaemia and chest pain were reported less often in the empagliflozin groups than in the comparator groups.

In the SAF-1 group (empagliflozin monotherapy studies), the frequencies of patients with any AE or AEs leading to discontinuation of study medication were lower in the empagliflozin groups than in the comparator groups. The frequency of patients with decreased renal function (SMQ) was overall low in the empagliflozin groups; no event was reported in the comparator groups. The frequency of patients with hepatic injury (SMQ) was low and similar in all groups. The frequency of patients with genital infection (BICMQ) was higher in the empagliflozin groups than in the comparator groups and that of all other types of AEs analysed for this grouping were similar in all groups. At PT level, the most frequently reported AE was nasopharyngitis, reported with similar frequencies in all groups. Hyperglycaemia was reported more frequently by patients in the comparator groups than in the empagliflozin groups (incidence rates per 100 patient years: 27.49 for placebo, 4.47 for empagliflozin 10 mg, 2.85 for empagliflozin 25 mg, 3.39 for all randomised empagliflozin, and 20.15 for all comparators). Of the randomised and treated patients in SAF-1, most patients who had any AE reported having mild or moderate events. The frequencies of patients with AEs of mild intensity were similar in all 4 groups (38.3% for placebo, 35.5% for empagliflozin 10 mg, 37.9% for empagliflozin 25 mg, and 39.0% for all comparators). The frequencies of patients with AEs of moderate intensity were lower in the empagliflozin groups (13.3% for 10 mg and 12.1% for 25 mg) than in the comparator groups (16.0% for placebo and 15.4% for all comparators). AEs of severe intensity were reported for 7 patients in the placebo group (1.7%), 11 patients in the empagliflozin 10 mg group (2.7%), 12 patients in the empagliflozin 25 mg group (2.9%), and 18 patients in the all comparators group (2.5%). At PT level, other than back pain and muscle spasms (each reported for 2 patients (0.3%) in the all comparators group only), no severe event was reported by more than 1 patient per group.

In the SAF-4 group (all studies in patients with T2DM and without special medical conditions), the frequency of patients with any AE was higher in the empagliflozin groups than in the placebo group, but comparable to the frequency in the all comparators group. The frequencies of patients with other types of AEs analysed for this grouping were similar in all groups.

In SAF-6 group (healthy subjects), the frequency of subjects with any AE was higher in the all empagliflozin group than in the placebo group, but lower than in the all active comparators group and the empagliflozin + other group. Four subjects reported AEs leading to discontinuation of study medication and 2 subjects reported SAEs. The most common events at PT level were headache, nasopharyngitis, and oropharyngeal pain. Headache was reported more frequently in the all empagliflozin group (12.0%) and the all active comparators group (11.4%) than in the placebo group (6.8%) and the empagliflozin + other group (8.3%). Other PTs showed comparable frequencies across groups.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal studies

Comments: The sponsors have not provided information on drug-related AEs in the SAF-3 dataset (refer section 11.4).

8.4.2.2. Other studies

Investigator-defined drug-related AEs were higher in the empagliflozin groups (10 mg, 25 mg, and all randomised empagliflozin) than in the comparator groups (placebo and all comparators). The most common drug-related AE at SOC level was metabolism and nutrition disorders. The SOCs metabolism and nutrition disorders, investigations, and nervous system disorders showed similar frequencies for all groups. The SOCs infections and infestations, renal and urinary disorders, gastrointestinal disorders, general disorders and administration site conditions, reproductive system and breast disorders, and skin and subcutaneous tissue disorders were more frequently reported as drug-related AEs in the empagliflozin groups than in the comparator groups. At PT level, pollakiuria, polyuria, dysuria, dry mouth, thirst, and a few

PTs that represent genital infection (such as vulvovaginal mycotic infection and fungal genital infection) were reported more frequently in the empagliflozin groups than in the comparator groups. Hyperglycaemia was less frequent in the empagliflozin groups than in the comparator groups. The other most frequent investigator-defined drug-related events were reported with similar frequencies in all groups.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal studies

In the SAF-5 safety dataset, a total of 74 patients were known to have fatal AEs starting on treatment; in addition, 1 healthy subject died of a road traffic accident in a Phase I study (1245.16). For the 74 patients who died, both absolute frequencies and the incidence rates per 100 patient-years were lower in the empagliflozin groups than in the comparator groups. No death was reported in the open-label empagliflozin 25 mg group. A total of 9 patients were known to have fatal AEs during the screening or the run-in period. A total of 14 patients were known to have fatal AEs in the post-treatment period (3 patients in placebo, 4 patients in empagliflozin 10 mg, and 7 patients in empagliflozin 25 mg group). A total of 5 patients were known to have fatal AEs in the post-study period (3 patients in placebo, 1 patient in empagliflozin 10 mg, and 1 patient in empagliflozin 25 mg group). The most frequent fatal AEs at SOC level were general disorders and administration site conditions (reported with similar frequencies and incidence rates per 100 patient-years in all groups) and cardiac disorders. Fatal cardiac disorders were reported at lower incidence rates per 100 patient-years in the empagliflozin groups (all randomised: 0.11 (absolute frequency 0.1%)) than in the comparator groups (all comparators: 0.28 (0.3%)). The most frequent fatal AEs at PT level were sudden death, death, and acute myocardial infarction.

Of the randomised and treated patients in SAF-3, the frequency of patients who reported SAEs (including fatal events) was lower in the sitagliptin and OL-25mg groups than in the other groups (7.4%, 7.1%, 5.8%, 3.5% and 4% in placebo, empagliflozin 10 mg, 25 mg, OL 25mg and sitagliptin groups, respectively). The highest frequency of SAEs at SOC level was cardiac disorders, reported with a higher frequency in the placebo group than in the other groups. The most frequent SAE at PT level was osteoarthritis. Most of the PTs were only reported for only 1 patient per treatment group.

Of the randomised and treated patients in SAF-2, the frequency of patients who reported SAEs (including fatal events) was low and similar in each treatment group (3.3% for placebo, 3.6% for empagliflozin 10 mg, 2.6% for empagliflozin 25 mg, and 2.7% for sitagliptin). The highest frequency of SAEs at SOC level was cardiac disorders, reported with comparable frequencies in all groups (range: 0.3% to 0.7%). The majority of the events at PT level were reported for no more than one patient per treatment group. Events reported for at least 2 patients in any treatment group were myocardial infarction (2 patients in the placebo group (0.3%) only), acute cholecystitis (2 patients in the placebo group (0.3%) and 1 in the sitagliptin group (0.4%)), and breast cancer (2 patients in the empagliflozin 25 mg group (0.3%) only). Both patients reported with breast cancer (1 subject each in study 1245.19 and study 1245.23 (met)) had an onset day of less than 6 months after the start of empagliflozin treatment.

8.4.3.2. Other studies

Of the randomised and treated patients in SAF-5, the absolute frequencies and the incidence rates per 100 patient-years of patients who reported SAEs (including fatal events) were lower in the empagliflozin groups (10 mg, 25 mg, and all randomised) than in the comparator groups (placebo and all comparators). The highest frequency of SAEs at SOC level was cardiac disorders, reported with lower frequencies in the empagliflozin groups than in the comparator groups. Frequencies of patients with vascular disorders, renal and urinary disorders, and respiratory, thoracic and mediastinal disorders were also lower in the empagliflozin groups than in the comparator groups. At PT level, acute myocardial infarction, cardiac failure, coronary artery disease, myocardial infarction, and ischaemic stroke showed lower frequencies in the empagliflozin groups than in the comparator groups; cerebrovascular accident showed

higher frequencies in the empagliflozin groups than in the comparator groups. No PT was reported with a frequency of above 0.5% in the all randomised empagliflozin group. Other SAEs, including acute renal failure, were reported with similar frequencies in all groups.

In the SAF-4 group, the incidence rate per 100 patient-years of patients who reported SAEs (including fatal events) was higher in the placebo group (incidence rate per 100 patient-years 10.10 (absolute frequency 6.4%)) than in the other groups (7.07 (6.2%) for empagliflozin 10 mg, 7.27 (7.2%) for empagliflozin 25 mg, 7.20 (6.7%) for all randomised empagliflozin, and 7.74 (6.7%) for all comparators). The highest frequency of SAEs at SOC level was cardiac disorders, reported with lower frequencies in the empagliflozin groups (range: 0.8% to 0.9%) than in the comparator groups (1.3% for both placebo and all comparators). Frequencies of injury, poisoning and procedural complications, and reproductive system and breast disorders were higher in the empagliflozin groups than in the comparator groups; frequencies of 'neoplasm benign, malignant and unspecified' and 'general disorders and administration site conditions' were higher in the empagliflozin 25 mg group than in the other groups. At PT level, for patients with SAEs with a frequency of $\geq 0.2\%$ in any group, myocardial infarction, angina pectoris, myocardial ischaemia, acute myocardial infarction, prostate cancer, acute cholecystitis, and nephrolithiasis showed higher frequencies in the comparator groups than in the empagliflozin groups. Cellulitis and fall showed higher frequencies in the empagliflozin groups than in the comparator groups. Other events with a frequency of $\geq 0.2\%$ in any group were reported with similar frequencies in all groups.

In the SAF-6 group, two subjects had SAEs: 1 subject in the empagliflozin 25 mg group (severe migraine with aura requiring hospitalisation; study 1245.51) and 1 in the all active comparator group (fatal road traffic accident after administration of moxifloxacin; study 1245.16); both events were deemed by the investigator to be not related to the study medication.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

In the SAF-3 group, the frequency of patients who reported AEs leading to discontinuation of study medication was low and similar in each treatment group. At PT level, most of the AEs leading to discontinuation of study medication were only reported for at most 1 patient per treatment group. Of the treated patients in the open-label empagliflozin 25 mg group, 3.5% reported AEs leading to discontinuation of study medication; only nausea was reported for more than 1 patient.

In the SAF-2 group, the frequency of patients who reported AE leading to premature discontinuation of study medication was similar in all groups (3.2% for placebo, 1.0% for empagliflozin 10 mg, 2.3% for empagliflozin 25 mg, and 2.2% for sitagliptin). At PT level, increased beta-N-acetyl-D-glucosaminidase³² and decreased weight were reported each for 2 patients (0.3%) in the empagliflozin 25 mg group only. Beta-N-acetyl-D glucosaminidase was only measured in Chinese patients as requested by the local authority. Myocardial infarction was reported for 2 patients (0.3%) in the placebo group only. All other AEs leading to discontinuation of study medication were only reported for at most 1 patient per treatment group.

³² N-acetyl-beta-D-glucosaminidase is a high molecular-weight lysosomal enzyme found in many tissues of the body. It cannot pass into glomerular ultrafiltrate due to its high molecular weight. However, this enzyme shows high activity in renal proximal tubular cells, and leaks into the tubular fluid as the ultrafiltrate passes through proximal tubules. When proximal tubular cells are injured due to any disease process including glomerular proteinuria, nephrolithiasis, hyperglycemia, interstitial nephritis, transplant rejection or nephrotoxic agents such as antibiotics, antiepileptics, or radiocontrast agents, its urine level increases and thus is used as a reflection of proximal tubular cell necrosis.

8.4.4.2. Other studies

In the SAF-5 group, the absolute frequency and the incidence rate per 100 patient-years of patients who reported AEs leading to discontinuation of study medication was similar in each group. The most frequent AE leading to discontinuation of study medication at SOC level was cardiac disorders, reported more frequently in the placebo and the all comparators group than in the empagliflozin groups. At PT level, more patients in the empagliflozin groups than in the comparator groups discontinued study medication due to urinary tract infections, dizziness and weight decrease. More patients in the placebo group and the all comparators group than in the empagliflozin groups discontinued study medication due to myocardial infarction, acute myocardial infarction, and hypoglycaemia.

In the SAF-1 monotherapy group, unadjusted frequencies and the incidence rates per 100 patient-years of patients who reported AEs leading to discontinuation of study medication were lower in the empagliflozin groups (incidence rate per 100 patient-years 2.79 (unadjusted frequency 1.7%) for 10 mg and 4.43 (2.7%) for 25 mg) than in the comparator groups (7.89 (4.3%) for placebo and 5.79 (3.6%) for all comparators). The most common AE at SOC level was cardiac disorders, reported by 5 patients in the all comparators group and 1 patient in the empagliflozin 10 mg group. At PT level, myocardial infarction, diabetes mellitus, and diarrhoea were each reported as leading to premature discontinuation for 2 patients in the all comparators group and by no patient in the empagliflozin groups. All other events leading to discontinuation of study medication were only reported for at most 1 patient per group.

In the SAF-4 group, the most frequent AE leading to premature discontinuation of study medication at SOC level was investigations, with similar frequencies in all groups. At PT level, more patients in the placebo group and the all comparators group than in the empagliflozin groups discontinued study medication due to myocardial infarction, constipation, and diarrhoea. A few patients in the empagliflozin groups discontinued study medication due to balanitis (2 patients for 10 mg and 4 for 25 mg) and no patient in the placebo group or the all comparators group discontinued study medication due to balanitis.

In the SAF-6 group (in healthy subjects), 4 subjects had events leading to premature discontinuation of study medication: 3 subjects (1.2%) in the all active comparator group (1 subject with nausea and vomiting, 1 each with increased blood creatine phosphokinase and road traffic accident) and 1 in the group of subjects receiving combination of empagliflozin (any dose) and other active drugs (0.3%; with gastroenteritis).

8.5. Laboratory tests

8.5.1. Liver function

The analysis of the frequency of patients with hepatic injury (as reported as AEs) was analysed based on selected sub-categories from the SMQ 20000006 “Drug related hepatic disorders” narrow versions (SMQ 20000008 “Signs and symptoms of liver related investigations”, 20000009 “Cholestasis and jaundice of hepatic origin”, 20000010 “Hepatitis, non-infectious”, and 20000013 “Hepatic failure, fibrosis, and other liver damage-related conditions”). These SMQ analyses were performed for SAF-1, 3, 5, and study 1245.25. In addition, elevated liver enzymes were assessed in the clinical laboratory evaluation for all SAFs (except SAF-4) and study 1245.25.

8.5.1.1. Pivotal studies

In the SAF-3 group, the frequency of the randomised and treated patients with hepatic events (based on SMQ) was low and similar for all treatment groups: 2.3% for placebo (19 patients), 1.0% for empagliflozin 10 mg (8 patients), 2.2% for empagliflozin 25 mg (18 patients), and 2.2% for sitagliptin (5 patients). The most frequent events at PT level were hepatic steatosis (similar for all groups; range: 0.4% to 0.7%), increased ALT (0.7% in the placebo, 0.2% in the empagliflozin 10 mg, 0.4% in the empagliflozin 25 mg, and 0.4% in the sitagliptin group), and hyperbilirubinaemia (0.6% in the empagliflozin 25 mg group, none in the other 3 groups). All

other events were reported for no more than 2 patients per group. Two patients in the open-label empagliflozin 25 mg group (0.8%) were reported with hepatic events (1 with chronic hepatitis and 1 with increased hepatic enzyme), but none was reported with laboratory values consistent with biochemical Hy's law constellation³³ (one patient was reported with ALT or AST $\geq 5x$ ULN).

8.5.1.2. Other studies

In the SAF-5 group, hepatic events based on SMQs were reported at frequencies of less than 2% for all groups; after exposure adjustment, the incidence rate per 100 patient-years was lower for the empagliflozin groups than the comparator groups. The most common PTs were hepatic steatosis, increased ALT, and increased AST. Hyperbilirubinaemia was reported with higher frequency in the empagliflozin 25 mg group (0, 1 (<0.01%) and 7 (0.2%) in placebo, empagliflozin 10mg and 25mg groups, respectively); all other events were generally balanced across the groups. Overall, although the frequency of patients with liver enzyme elevation on treatment (ALT/AST $\geq 3x$ ULN with total bilirubin $\geq 2x$ ULN or ALT/AST $\geq 10x$ ULN) was higher in the empagliflozin groups (11 patients) than in the comparator groups (1 patient), the liver enzyme elevation of each of the patients described above could be explained by plausible alternative causalities; there has been no evidence in favour of a causal relationship between empagliflozin treatment and elevated liver enzymes. The frequency of patients with ALT and/or AST $\geq 3x$ ULN was lower in the empagliflozin groups (0.4% for 10 mg, 0.5% for 25 mg, and 0.5% for all randomised) than in the placebo (0.8%) and the all comparators group (0.8%).

In the SAF-6 (healthy subjects) group, no subject was reported with laboratory values consistent with biochemical Hy's law constellation. One subject in the empagliflozin >25 mg group was reported with ALT or AST $\geq 3x$ ULN and 1 subject in the all comparators group with ALT or AST $\geq 5x$ ULN.

8.5.2. Kidney function

The analysis of the frequency of patients with decreased renal function reported as AEs was based on the narrow SMQ 20000003 "Acute renal failure". In addition, the frequency of patients with serum creatinine $\geq 2x$ baseline and above the ULN during treatment was calculated. These analyses were performed for SAF-1, 3, 5, and study 1245.25. Renal laboratory parameters (serum creatinine, eGFR, eCcr, urine albumin, urine albumin to creatinine ratio) were summarised descriptively for all SAFs (except SAF-6) and study 1245.25. Data for serum cystatin C (available for SAF-1, 2, 3, 5, and study 1245.25) was also evaluated.

8.5.2.1. Pivotal studies

In the SAF-3 group, of the randomised and treated patients, 2 patients in the placebo group (0.2%), 8 in the empagliflozin 10 mg group (1.0%), 7 in the empagliflozin 25 mg group (0.9%), and none in the sitagliptin group were reported with events of the SMQ "Acute renal failure". The most frequent PT was renal impairment, which was only reported for patients in the 2 empagliflozin groups. One patient in the placebo group (0.1%), 3 in the empagliflozin 10 mg group (0.4%), and none in the empagliflozin 25 mg or sitagliptin group were reported with serum creatinine $\geq 2x$ baseline and above the ULN. Two patients in the open-label empagliflozin 25 mg group (0.8%) were reported with the SMQ (both with the PT renal impairment); none was reported with serum creatinine $\geq 2x$ baseline and above the ULN.

³³ Briefly, Hy's Law cases have the following three components: 1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo 2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP) 3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

Of the randomised and treated patients, the baseline median (Q1, Q3) serum creatinine values were similar across all treatment groups: 72.0 (61.0, 86.0) $\mu\text{mol/L}$ for placebo (N=825), 74.0 (63.0, 86.0) $\mu\text{mol/L}$ for empagliflozin 10 mg (N=830), 73.0 (63.0, 85.0) $\mu\text{mol/L}$ for empagliflozin 25 mg (N=822), and 75.0 (64.0, 85.0) $\mu\text{mol/L}$ for sitagliptin (N=223). The change from baseline was small and similar across all groups at Week 24: 0 (-4.0, 5.0) $\mu\text{mol/L}$ for placebo (N=708), 0 (-5.0, 6.0) $\mu\text{mol/L}$ for empagliflozin 10 mg (N=769), 1.0 (-4.0, 6.0) $\mu\text{mol/L}$ for empagliflozin 25 mg (N=754), and 0 (-4.0, 7.0) $\mu\text{mol/L}$ for sitagliptin group (N=205). Few patients with values at Week 76 were available, as the extension study was ongoing when the database for SAF-3 analyses was locked and most patients had not yet been treated for 76 weeks; at this time point, the change from baseline was also small and similar across all groups. Of the randomised and treated patients, the baseline median (Q1, Q3) eGFR values were similar across all treatment groups: 85.4 (73.3, 100.1) mL/min/1.73m² for placebo (N=825), 85.0 (73.0, 101.2) mL/min/1.73m² for empagliflozin 10 mg (N=830), 86.0 (73.5, 99.7) mL/min/1.73m² for empagliflozin 25 mg (N=822), and 86.7 (74.9, 97.2) mL/min/1.73m² for sitagliptin (N=223). At Week 24, the change from baseline was small and similar for all groups: -0.2 (-7.0, 6.0) mL/min/1.73m² for placebo (N=708), -0.2 (-6.9, 6.1) mL/min/1.73m² for empagliflozin 10 mg (N=769), -1.0 (-7.8, 6.1) mL/min/1.73m² for empagliflozin 25 mg (N=754), and -0.2 (-8.1, 4.4) mL/min/1.73m² for sitagliptin (N=205) and few patients with values at Week 76 were available.

When the shifts in UACR categories from baseline to last value on treatment were analysed, lower proportions of patients from the empagliflozin groups (2.1% for 10 mg and 2.0% for 25 mg) showed shifts from micro- to macroalbuminuria than those from the comparator groups (5.4% for placebo and 9.8% for sitagliptin); moreover, only patients in the empagliflozin groups showed shifts from macroalbuminuria to normal (18.5%, 5 of 27 patients for 10 mg; 10.5%, 2 of 19 for 25 mg; none for placebo or sitagliptin). Shifts to other categories were similar for all 4 groups: 6.5% to 8.6% shifted from normal to microalbuminuria and 0 to 0.6% from normal to macroalbuminuria; 24.4% to 44.0% shifted from microalbuminuria to normal and 29.6% to 36.8% from macro- to microalbuminuria. The proportion of patients in the open-label group whose last value on treatment shifted from normal at baseline to microalbuminuria was 5.5% (9 of 164 patients), from micro- to macroalbuminuria 1.6% (1 of 61), and from normal to macroalbuminuria 0.6% (1 of 164). The proportion whose last value on treatment shifted from microalbuminuria at baseline to normal was 31.1% (19 of 61) and from macro- to microalbuminuria 40.0% (6 of 15).

8.5.2.2. Other studies

In the SAF-5 group, events of the SMQ “acute renal failure” were reported at low frequencies for all 5 groups (placebo, empagliflozin 10 mg, empagliflozin 25 mg, all randomised empagliflozin, and all comparators). After adjustment for exposure, the incidence rate per 100 patient-years was similar for all groups. No patients treated with empagliflozin doses other than 10 and 25 mg were reported with these events. The most frequent PT was renal impairment, reported more frequently in the empagliflozin groups (rate per 100 patient-years: 0.73 for 10 mg, 0.76 for 25 mg, 0.74 for all randomised) than in the placebo (0.61) and the all comparators group (0.48). The exposure-adjusted rates of other events in the SMQ “acute renal failure” were similar for all groups. A similar percentage of patients in all groups were reported with serum creatinine $\geq 2x$ baseline and above the ULN: 8 patients (0.2%) in the placebo, 11 (0.3%) in the empagliflozin 10 mg, 13 (0.3%) in the empagliflozin 25 mg, 24 (0.3%; all were from 10 mg and 25 mg groups) in the all randomised empagliflozin, and 11 (0.2%) in the all comparators group. The median (Q1, Q3) of baseline and last value on treatment were similar for all 5 groups and there was hardly any difference between baseline and last value on treatment in all groups. The median (Q1, Q3) of baseline and last value on treatment were similar for all 5 groups and there were only small changes in eGFR values over time in all groups.

Descriptive statistics for baseline and last on-treatment values of urine albumin by baseline urine albumin category were calculated. The majority of the patients in SAF-5 had baseline values of <20 mg/L or between 20 mg/L and <200 mg/L; only about 10% of the patients had baseline values of ≥ 200 mg/L. For the patients with baseline values of <20 mg/L, median values

at baseline and last observation on treatment were similar for all 5 groups; in fact, for the all empagliflozin group and the all comparators group, there was no change in median values.

For the analysis of urine-albumin-to-creatinine ratio, categories of normal (a UACR of <30 mg/g), microalbuminuria (30 to <300 mg/g), and macroalbuminuria (\geq 300 mg/g) were used. For all groupings and study 1245.25, the majority of the patients had baseline values in the normal or microalbuminuria ranges. For the patients with normal UACR at baseline, only very small changes at last value on treatment from baseline were seen in all 5 groups. For those with microalbuminuria at baseline, greater decreases in UACR (median (Q1, Q3)) were seen in patients in the empagliflozin groups (10 mg: -21.9 (-47.7, 0.0) mg/g; 25 mg: -23.0 (-55.7, 2.8) mg/g; all randomised: -23.0 (-52.2, 0.9) mg/g) than in the placebo group (-8.8 (-34.7, 32.0) mg/g) and the all comparators group (-10.6 (-36.2, 27.4) mg/g). For those with macroalbuminuria at baseline, again greater decreases in UACR were seen in patients in the empagliflozin groups (10 mg: -286.2 (-591.4, -55.7) mg/g, N=218; 25 mg: -330.6 (-704.5, -80.4) mg/g, N=277; all randomised: -310.3 (-674.5, -61.0) mg/g, N=504) than in the placebo group (-118.0 (-436.9, 303.2) mg/g, N=273) and the all comparators group (-117.3 (-448.3, 292.2) mg/g, N=296).

When the shifts in UACR categories from baseline to last value on treatment were analysed, lower proportion of patients from the empagliflozin groups (3.5% for 10 mg, 3.2% for 25 mg, and 3.3% for all randomised) showed shifts from micro- to macroalbuminuria than those from the placebo (9.2%) and the all comparators group (8.2%); higher proportion of patients from the empagliflozin groups showed shifts from macro- to microalbuminuria (35.3% for 10 mg, 36.8% for 25 mg, and 35.5% for all randomised) than those from the placebo (23.4%) and the all comparators group (24.0%).

Serum cystatin C was analysed as a safety laboratory parameter in all studies. Descriptive statistics for SAF-5 showed that while there were small decreases in "cystatin C" last value on treatment from baseline in the comparator groups (median (Q1, Q3) for both placebo and all comparators groups: -0.03 (-0.11, 0.06) mg/L), there were small increases in the empagliflozin groups (0.03 (-0.08, 0.11) mg/L for 10 mg; 0.03 (-0.08, 0.13) mg/L for both 25 mg and all randomised). There were also slightly more patients showing shifts from normal range at baseline to >ULN at last value on treatment in the empagliflozin groups (range: 6.8% to 7.7%) than in the comparator groups (2.6% for placebo and 2.2% for all comparators). To investigate whether the small increase in serum cystatin C on treatment was reversible after the stop of study medication, follow-up data for cystatin C were analysed and presented in the study report 1245.48. In this 12-week study, the last value on treatment for the empagliflozin groups increased slightly from baseline (mean change 0.04 mg/L for 10 mg and 0.05 mg/L for 25 mg); no change of last value on treatment from baseline was seen for the placebo group. However, after a 2-week follow-up period, cystatin C values for the empagliflozin groups returned toward baseline and were similar to the placebo group (mean change from baseline at follow-up 0.02 mg/L for both placebo and empagliflozin 10 mg, 0.01 mg/L for empagliflozin 25 mg).

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal studies

In the SAF-3 group, for all electrolyte parameters investigated (sodium, potassium, calcium, magnesium, chloride, phosphate, bicarbonate), normalised median values for the randomised and treated patients at last value on treatment were similar among all 4 groups (placebo, empagliflozin 10 mg, empagliflozin 25 mg, and sitagliptin) and similar to those seen at baseline in all groups. Shifts with respect to the reference ranges occurred at similar frequencies for all groups. Possibly clinically significant abnormal high values were rare and also occurred at similar frequencies for all groups. In the open-label group empagliflozin 25 mg, changes from baseline in all parameters were minor; shifts from normal to >ULN values and possibly clinically significant abnormal high values were rare.

The normalised median values for enzymes (AST, ALT, alkaline phosphatase, LDH, creatine kinase, and lipase) at last value on treatment were similar among all 4 groups (placebo,

empagliflozin 10 mg, empagliflozin 25 mg, and sitagliptin) and similar to those seen at baseline in all groups. Shifts with respect to the reference ranges occurred at similar frequencies for all groups. Possibly clinically significant abnormal values were rare and also occurred at similar frequencies for all groups, except those for lipase (higher for empagliflozin). In the open-label empagliflozin 25 mg group, changes from baseline in all parameters were minor and shifts to higher values were rare; possibly clinically significant abnormal values were rare as well.

For the randomised and treated patients, normalised uric acid values decreased from baseline to last value on treatment in the empagliflozin groups (median change (Q1, Q3): -45 (-105, 8) $\mu\text{mol/L}$ for 10 mg and -49 (-103, 0) $\mu\text{mol/L}$ for 25 mg); it did not change for placebo (0 (-49, 45) $\mu\text{mol/L}$) and it increased for sitagliptin (18 (-27, 60) $\mu\text{mol/L}$). Notably more patients with values >ULN at baseline showed shifts into the normal range at last value on treatment in the empagliflozin groups (89.7% for 10 mg and 86.7% for 25 mg) than in the comparator groups (45.7% for placebo and 38.5% for sitagliptin). Additionally, slightly more patients showed shifts from normal values to <LLN in the empagliflozin groups (2.8% for 10 mg and 3.2% for 25 mg) than in the comparator groups (1.2% for placebo and 1.5% for sitagliptin). There were only minor and comparable changes in median urea values across groups.

8.5.3.2. Other studies

In the SAF-5 group, normalised median electrolyte values were comparable in the 5 groups (placebo, empagliflozin 10 mg, empagliflozin 25 mg, all randomised empagliflozin, all comparators) both at baseline and at last observation on treatment. The proportions of patients with shifts in values from the normal range at baseline to >ULN at last observation on treatment were overall similar across groups. The only minor differences were seen for bicarbonate (higher proportions in the comparator groups than in the empagliflozin groups) and for phosphate (slightly higher proportions in the empagliflozin groups, with a dose-dependent increase, than in the comparator groups). The proportion of patients with shifts in electrolyte values from the normal range at baseline to <LLN at last observation on treatment were comparable between groups, except for magnesium (notably lower proportions in the empagliflozin groups than in the comparator groups), for phosphate (slightly lower proportions in the empagliflozin groups than in the comparator groups), and for bicarbonate (slightly higher proportion in the empagliflozin groups than in the comparator groups). The proportion of patients with possibly clinically significant abnormal values was also comparable between groups, with the exception of phosphate (higher proportion in the empagliflozin groups than in the comparator groups).

The enzymes (AST, ALT, alkaline phosphatase, LDH, creatine kinase, and lipase) did not show any notable changes from baseline across groups. The proportion of patients with shifts from normal values at baseline to >ULN at last value on treatment was similar across groups and the proportions of patients with possibly clinically significant abnormal high values were also comparable across groups for all enzyme parameters.

Comparable decreases in uric acid values were noticed in both empagliflozin groups. A small increase in uric acid was found for the all comparators group. No overall median change from baseline was found in the placebo group. Slightly more patients showed shifts from normal uric acid values at baseline to less than LLN values at last observation on treatment in the empagliflozin groups (56 patients (2.1%) for 10 mg, 65 patients (1.9%) for 25 mg, and 133 patients (2.0%) for all randomised groups) than in the comparator groups (37 patients (1.4%) for placebo and 42 patients (1.1%) for all comparators). Shifts from >ULN values at baseline to normal values occurred with higher frequencies in the empagliflozin groups (61.6% for 10 mg, 58.9% for 25 mg, and 60.8% for all randomised groups) than in the comparator groups (36.5% for placebo and 37.4% for all comparators). Changes in urea were overall negligible and comparable across groups; shifts from normal baseline values to either <LLN or >ULN values at last observation on treatment as well as the frequencies of possibly clinically significant abnormal values were comparable and overall rare in all groups.

8.5.4. Haematology

8.5.4.1. Pivotal studies

In the SAF-3 group, the normalised haematocrit value increased in the empagliflozin groups to last value on treatment from baseline (median change (Q1, Q3): 2.8% (0.0%, 4.3%) for 10 mg and 2.8% (0 %, 5.7%) for 25 mg), whereas it decreased in the comparator groups (-1.3% (-2.8%, 1.4%) for both placebo and sitagliptin). Additionally, more patients with haematocrit values in the normal range at baseline showed shifts to >ULN at last value on treatment in the empagliflozin groups (20 patients (2.7%) for 10 mg and 25 patients (3.5%) for 25 mg) than in the comparator groups (4 patients (0.6%) for placebo and none for sitagliptin). Nevertheless, possibly clinically significant abnormal high values were reported for fewer patients in the empagliflozin groups (1 patient for 25 mg (0.1%) and no patient for 10 mg) than in the comparator groups (2 patients for placebo (0.3%) and 1 patient for sitagliptin (0.5%). A similar trend in changes from baseline and shifts as for haematocrit was noticed for haemoglobin. In other haematology parameters, only minor changes in median values were overall noted and differences among groups were small.

8.5.4.2. Other studies

In the SAF-5 group, a small increase in haematocrit levels between baseline and last value on treatment was noticed in all empagliflozin groups. However, the increase was reversible after the discontinuation of empagliflozin treatment. Higher proportion of patients showed shifts in haematocrit from the normal range at baseline to >ULN at last value on treatment in the empagliflozin groups (103 patients (3.8%) for 10 mg, 154 patients (4.4%) for 25 mg, 293 patients (4.3%) for all randomised) than in the comparator groups (14 patients (0.5%) for placebo, 18 patients (0.5%) for all comparators). Possibly clinically significant abnormal high values were reported for more patients in the empagliflozin groups (14 patients (0.5%) for 10 mg, 31 patients (0.8%) for 25 mg, 50 patients (0.7%) for all randomised) than in the comparator groups (6 patients (0.2%) for placebo, 10 patients (0.2%) for all comparators). A similar trend in changes from baseline and shifts as for haematocrit was noticed for haemoglobin. In other haematology parameters, only minor changes in median values and small differences between groups were noted. Moreover, the incidence rate per 100 patient-years of thromboembolic AEs was overall low and lower in the empagliflozin groups than in the placebo and the all comparators groups.

8.5.5. Serum lipids and apolipoproteins

8.5.5.1. Pivotal studies

In the SAF-3 group, small treatment differences to placebo (increases that were generally dose-dependent) were seen for total cholesterol, HDL cholesterol, and LDL cholesterol in the empagliflozin groups. No obvious difference to placebo was seen for LDL/HDL cholesterol ratio. For triglycerides, a treatment difference to placebo (decrease) was seen in the empagliflozin 10 mg group, whereas no obvious treatment difference to placebo was seen in the empagliflozin 25 mg group. Changes in apolipoproteins A-I and B, were overall negligible and comparable across groups; shifts from normal baseline values to either <LLN or >ULN values at last observation on treatment were comparable and overall infrequent in all groups. For total cholesterol, more patients showed shifts from normal baseline to >ULN at end of treatment in the empagliflozin 25 mg than in the other 3 groups. However, for HDL cholesterol and LDL cholesterol, the highest frequency was found in the sitagliptin group, followed by the empagliflozin groups (25 mg and 10 mg) and by placebo. For triglycerides, fewer patients showed shifts to >ULN values in the empagliflozin groups than in the comparator groups. The number of randomised patients with possibly clinically significant abnormal high values for total cholesterol was the highest in the sitagliptin group (11.9%) followed by the empagliflozin groups (7.7% for 10 mg and 7.2% for 25 mg) and placebo (5.7%). For triglycerides, fewer randomised patients had possibly clinically significant abnormal high values in the empagliflozin groups (16.1% for 10 mg and 17.8% for 25 mg) than in the comparator groups (19.6% for placebo and 22.3% for sitagliptin). In the open-label 25 mg group, mean changes (SD) from baseline in lipid parameters to last value on

treatment, evaluated by descriptive statistics, were: -0.06 (1.42) mmol/L for total cholesterol, 0.01 (0.11) mmol/L for HDL cholesterol, -0.05 (0.64) mmol/L for LDL cholesterol, and 0.0 (1.9) mmol/L for triglycerides. The frequencies of shifts from normal to >ULN were 18.5% (24 patients) for total cholesterol, 0.6% (1 patient) for HDL cholesterol, 14.5% (23 patients) for LDL cholesterol, and 10.1% (20 patients) for triglycerides. Possibly clinically significant abnormal high values were observed for 17 patients (7.5%) for total cholesterol and 38 patients (21.0%) for triglycerides.

8.5.5.2. Other studies

In the SAF-5 group, compared with placebo, small increases were seen with empagliflozin treatment in total cholesterol, HDL cholesterol, and LDL cholesterol, both at Week 24 and at Week 52, without notable changes between Week 24 and Week 52. Compared with placebo, no obvious change was seen for empagliflozin treatment for the LDL/HDL cholesterol ratio. For non-HDL cholesterol, dose-dependent increases were seen in the empagliflozin groups compared with the placebo group. For triglycerides, small treatment differences vs. placebo (decreases) were seen at Week 24 for both empagliflozin groups; at Week 52, no obvious change from baseline was seen in the empagliflozin groups compared with placebo, while there were absolute increases from baseline values for all groups. For all parameters except triglycerides, the proportions of patients with shifts from normal values at baseline to >ULN at last value on treatment were higher in the empagliflozin groups than in the comparator groups. More patients in the empagliflozin groups had possibly clinically significant abnormal high values of total cholesterol in the empagliflozin groups (7.0% for 10 mg, 7.2% for 25 mg, and 7.4% for all randomised) than in the comparator groups (5.6% for placebo and 6.1% for all comparators). Possibly clinically significant abnormal high values of triglycerides were lower in the empagliflozin groups (17.7% for 10 mg, 18.8% for 25 mg, and 18.1% for all randomised) than in the comparator groups (21.4% for placebo and 21.9% for all comparators). There were no clear changes in apolipoprotein A-I and B, comparably across groups; shifts from normal baseline values to either <LLN or >ULN values at last observation on treatment were comparable and overall rare in all groups.

8.5.6. Electrocardiograph

8.5.6.1. Pivotal studies

There is no data on ECG provided in the safety summary in module 2 or in the individual study reports. In the pivotal studies, 12-lead ECGs were taken at baseline and at end of study.

8.5.6.2. Other studies

Study 1245.16 tested the effect of empagliflozin treatment (single dose) on the QT(c) interval in 30 healthy subjects. The randomised, placebo-controlled, double-blind, cross-over study included moxifloxacin as a positive control. The study showed that single oral doses of empagliflozin 25 mg (therapeutic dose) and 200 mg (supra-therapeutic dose) were not associated with a QT(c) interval prolongation and that these doses were safe and well tolerated.

8.5.7. Vital signs

In the SAF-3 group (equivalent to the EFF-2 efficacy dataset), changes in BP were analysed as efficacy endpoint. Despite the decrease in blood pressure in the empagliflozin groups, the frequency of patients with hypotension, syncope, or orthostatic hypotension was similar in all groups. Despite the reduction in BP, there were no significant changes in pulse rate in the empagliflozin or other treatment groups.

8.6. AEs of special interest

AEs of renal function and hepatic function have already been discussed in section 8.5.1 and 8.5.2 above. Other AEs of special interest included urinary tract infections.

8.6.1. Urinary tract infections

The PTs genitourinary tract infection, fungal urogenital infection, and bacterial urogenital infection were included in the search for both urinary tract infections and genital infections.

In the SAF-3 group, the frequencies of urinary tract infection (BICMQ) were similar in the 4 groups: 12.4% for placebo, 12.7% for empagliflozin 10 mg, 10.0% for empagliflozin 25 mg, and 7.2% for sitagliptin. The most frequent events at PT level were urinary tract infection (with similar frequencies for all groups; range: 6.3% to 10.8%) and asymptomatic bacteriuria (with similar frequencies for all groups: 0.4% to 1.3%). All other events were reported for less than 1% of the patients per group.

Most patients reported with urinary tract infections (BICMQ) had either 1 or 2 episodes; 3 or 4 episodes were reported for 0.2% to 0.6% of the patients; only 1 patient (0.1%) in the empagliflozin 10 mg group reported ≥ 5 episodes. Most of the patients reported mild or moderate intensity for their worst episodes; very few patients reported severe intensity for their worst episodes (0.6% in the placebo group, 0.2% in the empagliflozin 10 mg group, and none in the other 2 groups). Very few patients reported events (worst episodes) that required or prolonged hospitalisation (0.6% in the placebo group, 0.2% in the empagliflozin 10 mg group, and none in the other 2 groups). Very few patients reported events (worst episodes) that led to the discontinuation of study medication (0.2% in the placebo group, 0.5% in the empagliflozin 10 mg group, 0.2% in the empagliflozin 25 mg group, and none in the sitagliptin group). The frequency of urinary tract infection (BICMQ) was higher for female (range for the 4 groups: 12.2% to 24.3%) than male (2.2% to 5.0%) patients. The frequency was higher for patients with chronic or recurrent urinary tract infections (range for the 4 groups: 0 to 40.5%, N=10 to 53) than those without (range for the 4 groups: 7.5% to 11.3%, N=213 to 788).

One patient in the placebo group and 2 in the empagliflozin 10 mg group reported urosepsis; 1 patient in the placebo group reported acute pyelonephritis.

For the treated patients in the open-label empagliflozin 25 mg group, the frequency of urinary tract infection (BICMQ) was 4.3%, with the only PT reported being urinary tract infection. No patient reported events that were severe, required or prolonged hospitalisation, or lead to discontinuation of study medication; no patient reported more than 2 episodes.

In the SAF-5 group, the incidence rates per 100 patient-years of urinary tract infections based on BICMQ were similar for all 5 groups. The most common PTs were urinary tract infection, cystitis, and asymptomatic bacteriuria, all of which were reported with similar incidence rates per 100 patient-years for all groups. All other events were reported for no more than 0.2% of patients per group. The frequencies of patients with pyelonephritis, acute pyelonephritis, or urosepsis were low and similar for all groups ($<0.1\%$ for all groups). For all groups, most of the events were mild or moderate in intensity; very few patients ($\leq 0.3\%$ per group) were reported with severe events. Very few patients ($\leq 0.4\%$ per group) were reported with events requiring or prolonging hospitalisation; patients with urosepsis or acute pyelonephritis all required hospitalisation. Premature discontinuations of study medication due to urinary tract infection (BICMQ) were infrequent ($\leq 0.4\%$ per group). The proportion of patients who had urinary tract infections was higher for women (range for all groups: 16.0% to 18.4%) than for men (3.1% to 4.1%). The proportion of patients who had urinary tract infections was higher in the group of patients with chronic or recurrent urinary tract infections than in those without. These characteristics of the events or patients were all balanced among the 5 groups. For the 4 cases of PT septic shock, there were no data suggesting that the source of infections was the urinary tract. In 5 of the 14 PT sepsis cases the urinary tract was possibly the source of infection. The frequency of patients with pyelonephritis was similar for all groups: 3 patients in the placebo group (0.09%), none in the empagliflozin 10 mg group, 4 in the empagliflozin 25 mg group (0.09%), 5 in the all randomised empagliflozin group (0.06%), and 4 in the all comparators group (0.09%). None of these events were serious.

8.6.2. Genital infections

The PTs genitourinary tract infection, fungal urogenital infection, and bacterial urogenital infection were included in the search for both urinary tract infections and genital infections.

In the pivotal SAF-3 group, the frequencies of genital infections (BICMQ) were higher in the empagliflozin groups (5.8% for 10 mg and 5.1% for 25 mg) than in the comparator groups (1.1% for placebo and 0.9% for sitagliptin). The most frequent event at PT level was balanoposthitis (1.0% in the empagliflozin 10 mg group, 0.2% in the empagliflozin 25 mg group, and none in the other 2 groups). All other events were reported for less than 1% of the patients per group. Most of the patients with genital infection had 1 or 2 episodes; 2 patients in the empagliflozin 10 mg group (0.2%) reported 3 or 4 episodes; only 1 patient (0.1%) in the empagliflozin 25 mg group reported ≥ 5 episodes. Most of the patients reported events (worst episodes) of mild or moderate intensity; no patient reported any severe event. Only 2 patients in the empagliflozin 10 mg group (0.2%) reported an event (worst episode) that required or prolonged hospitalisation. Very few patients reported events (worst episodes) that led to the discontinuation of study medication (0.5% in the empagliflozin 10 mg group, 0.2% in the empagliflozin 25 mg group, and none in the other groups). For the comparator groups, the frequency of genital infections was similar for female patients (1.2% for both placebo and sitagliptin) and male patients (0.9% for placebo and 0.7% for sitagliptin); whereas for the empagliflozin groups, the frequency was higher for female patients (8.7% for 10 mg and 9.2% for 25 mg) than male (3.5% for 10 mg and 1.9% for 25 mg). Four patients in the open-label empagliflozin 25 mg group (1.6%) reported genital infection (2 with balanoposthitis and 1 each with vaginal infection and vulvovaginal candidiasis).

In the SAF-5 group, the incidence rates per 100 patient-years of genital infections (BICMQ) were higher in the empagliflozin groups than the comparator groups. The most common PTs were balanitis, vulvovaginal mycotic infection, and vulvovaginal candidiasis; almost all PTs were reported more frequently in the empagliflozin groups. For all groups, most of the events were mild or moderate in intensity; very few patients (1 in the placebo, 1 in the empagliflozin 10 mg, and 2 in the empagliflozin 25 mg group) were reported with severe events. Very few patients (2 in the placebo and 4 in the empagliflozin 10 mg group) were reported with events requiring or prolonging hospitalisation. The majority of the patients who had genital infections continued study medication; premature discontinuations of study medication due to genital infection were infrequent (1 patient in the placebo ($<0.1\%$), 14 in the empagliflozin 10 mg (0.4%), and 15 in the empagliflozin 25 mg group (0.3%)). The majority of the patients with genital infections had 1 or 2 episodes; 4 patients in the empagliflozin 25 mg group had ≥ 4 episodes. In all groups, the proportion of patients who had genital infections was about twice as high for women (for all randomised empagliflozin: 6.9%) as for men (for all randomised empagliflozin: 3.3%); regardless of gender, the frequencies of patients with genital infection were higher in the empagliflozin groups than in the comparator groups. The proportion of patients who had genital infections was higher in the group of patients with chronic or recurrent genital infections (for all randomised empagliflozin: 18.4%, 19 of 103 patients) than those without (for all randomised empagliflozin: 4.4%, 311 of 7077 patients); regardless of a history of chronic or recurrent genital infections, the frequencies of patients with genital infection were higher in the empagliflozin groups than in the comparator groups.

8.6.3. Hypoglycaemic events

Hypoglycaemic adverse event was considered 'confirmed' if it was associated with measured plasma glucose of ≤ 70 mg/dL or required the assistance of another person.

8.6.3.1. In individual Phase III studies

The frequency of patients with confirmed hypoglycaemic AEs for empagliflozin monotherapy (study 1245.20 and extension) was low and similar to placebo; no patient had any confirmed hypoglycaemic AE with plasma glucose of <54 mg/dL or where assistance of another person was required. For patients with metformin alone (study 1245.23 (met) and extension) or pioglitazone with or without metformin (study 1245.19) background medication, the

frequencies of patients with confirmed hypoglycaemic AEs were low and comparable in all groups. No patient had any confirmed hypoglycaemic AEs where assistance of another person was required. For patients with metformin+SU background medication (study 1245.23 (met+SU) and extension), the frequencies of patients with confirmed hypoglycaemic AEs were higher in the empagliflozin groups than in the placebo group; the frequency was higher in the empagliflozin 10 mg group than in the 25 mg group. The frequencies of patients with confirmed hypoglycaemic AEs where minimum plasma glucose was <54 mg/dL were similar in the empagliflozin 25 mg group and the placebo group; the frequency was slightly higher in the empagliflozin 10 mg group. No patient had any confirmed hypoglycaemic AEs where assistance of another person was required. In study 1245.28, the frequency of patients with confirmed hypoglycaemic AEs was lower in the empagliflozin 25 mg group (2.0%) than in the glimepiride group (21.2%). The frequency of patients with confirmed hypoglycaemic AEs where minimum plasma glucose was <54 mg/dL was also lower in the empagliflozin 25 mg group (1.3%) than in the glimepiride group (7.9%). Moreover, in this study the occurrence of confirmed hypoglycaemic AEs up to Week 52 was a key secondary endpoint and showed a significantly lower incidence in the empagliflozin 25 mg group (1.6%) compared with the glimepiride group (20.4%). The adjusted risk ratio of empagliflozin vs. glimepiride was 0.077 (97.5% confidence interval: 0.040 to 0.148; $p < 0.0001$; Cochran-Mantel-Haenszel test). For patients with basal insulin background therapy (study 1245.33), the frequencies of patients with confirmed hypoglycaemic AEs in the empagliflozin groups were similar to placebo during the 78 weeks of treatment. However, in this study, the dose of basal insulin was not to be adjusted in the first 18 weeks and could be adjusted thereafter at the discretion of the investigator; the frequency of patients with confirmed hypoglycaemic AEs at Week 18 was higher in the empagliflozin 25 mg group (28.4%) than in the empagliflozin 10 mg (19.5%) and the placebo group (20.6%). For patients with "any" background antidiabetic medication, the frequencies of patients with confirmed hypoglycaemic AEs in the empagliflozin groups were similar to placebo; the frequencies of patients with confirmed hypoglycaemic AEs where minimum plasma glucose was <54 mg/dL were also similar in all groups. The frequencies of patient with confirmed hypoglycaemic AEs where assistance of another person was required were low and similar in all groups. In study 1245.36 (patients with renal impairment), 52.7% of the patients had insulin background therapy.

8.6.3.2. Placebo-controlled studies

Analyses of confirmed hypoglycaemic AEs based on a grouping of only placebo controlled studies (all studies in SAF-5 except study 1245.24, the extension part of 1245.38, and 1245.28) were performed.

The frequency of confirmed hypoglycaemic AEs in placebo-controlled studies (12.6% for placebo, 13.7% for empagliflozin 10 mg, and 13.6% for empagliflozin 25 mg) was compared with a Cochran-Mantel-Haenszel (CMH) analysis, which was stratified by study of origin. The adjusted risk ratio of empagliflozin 10 mg to placebo was 1.174 (95% CI: 1.040 to 1.324; $p = 0.0090$); the adjusted risk ratio of empagliflozin 25 mg to placebo was 1.092 (0.972 to 1.226; $p = 0.1373$). However, a modified analysis in studies with at least 1 confirmed hypoglycemic AE³⁴ showed that the adjusted rates of empagliflozin groups were similar to placebo (adjusted rate 0.883, 95% CI: 0.726 to 1.076, $p = 0.2172$ for 10 mg; 0.955, 95% CI: 0.790 to 1.154, $p = 0.6345$ for 25 mg). Only patients in studies 1245.25, 1245.33, and 1245.36 had hypoglycaemic AE which required assistance of another person in placebo-controlled studies. The frequency (0.4% for placebo, 0.4% for empagliflozin 10 mg, and 0.5% for empagliflozin 25 mg) was also compared with a CMH analysis. Compared with placebo, the adjusted risk ratio of both empagliflozin 10 mg (1.156; 0.508 to 2.630; $p = 0.7299$) and 25 mg was similar (1.142; 0.560 to 2.326; $p = 0.7152$). However, when only studies with at least 1 event were included in the analysis (studies 1245.25, 1245.33, and 1245.36), the adjusted rate of empagliflozin was higher than placebo

³⁴ These were studies 1245.19 and extension, 1245.20 and extension, 1245.23 (met) and extension, 1245.23 (met+SU) and extension, 1245.25, 1245.33, 1245.36, 1245.38, and 1245.48.

(1.624; 95% CI: 0.522 to 5.049, p=0.4021 for 10 mg and 1.847; 95% CI: 0.622 to 5.487, p=0.2695 for 25 mg).

8.6.3.3. SAF-3 pivotal studies group

Of the randomised and treated patients in SAF-3, which included patients with sulphonylurea background medication, the frequencies of confirmed hypoglycaemic AEs were higher in the empagliflozin groups (6.7% for 10 mg and 5.4% for 25 mg) than the comparator groups (4.4% for placebo and 0.4% for sitagliptin). Most of the patients had 1 or 2 confirmed symptomatic or asymptomatic episodes. Most of the patients were reported with symptomatic events. No patient required the assistance of another person. Most of confirmed episodes were mild in intensity. No event required or prolonged hospitalisation. Three patients in the empagliflozin 10 mg group discontinued study medication due to the events. The frequencies of patients who had a recorded plasma level of <54 mg/dL during their worst hypoglycaemic episode were similar for the empagliflozin and the placebo group. The majority of the patients had their first episodes after having taken study medication for more than 84 days. The frequencies of confirmed hypoglycaemic AEs were similar in all age groups. The frequencies of confirmed hypoglycaemic AEs were higher for patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73m²) than those with normal renal function or mild impairment (eGFR ≥ 60 mL/min/1.73m²).

8.6.3.4. SAF-2 (Pivotal studies, excluding patients receiving an SU as background therapy)

Of the randomised and treated patients, the frequencies of confirmed hypoglycaemic AEs were similar in the empagliflozin groups (1.2% 10 mg and 1.3% for 25 mg) and the comparator groups (0.8% for placebo and 0.4% for sitagliptin). Most of the patients had 1 or 2 confirmed symptomatic or asymptomatic episodes; 5 to 9 confirmed symptomatic episodes were reported for 1 patient each in the placebo (0.2%), empagliflozin 10 mg (0.2%), and empagliflozin 25 mg group (0.2%). Most of these patients were reported with symptomatic events. No patient required the assistance of another person.

Almost all confirmed episodes were mild in intensity. No event led to the discontinuation of study medication or required/prolonged hospitalisation. Two patients in the placebo group (0.3%) had events which led to the discontinuation of or decrease in dose in antidiabetic background medication within 14 days of the events. Only 2 patients in the placebo (0.3%), 5 in the empagliflozin 10 mg (0.8%), and 2 in the empagliflozin 25 mg group (0.3%) had a recorded plasma level of <54 mg/dL during their worst hypoglycaemic episode. Two patients in the empagliflozin 10 mg group (0.3%) had their first episodes after having taken study medication for >7 and ≤ 28 days; all other patients had their first episodes after having taken study medication for more than 28 days.

8.6.3.5. SAF-1 monotherapy studies

The frequencies of confirmed hypoglycaemic AEs were low and similar for all groups, taken into account the differences in exposure (incidence rates per 100 patient-years were not calculated for hypoglycaemic AEs). Most events were symptomatic. All events were mild and none required the assistance of another person. No event required or prolonged hospitalisation, or lead to the discontinuation of study medication and no patient in the empagliflozin groups had any episode with plasma glucose of <54 mg/dL. All episodes occurred after 28 days after the start of study medication. No patient had 10 or more confirmed episodes.

8.6.4. Bone fracture

In the pivotal SAF-3 group, the frequency of the randomised and treated patients with bone fracture (BicMQ) was low and similar for all treatment groups: 1.6% for placebo, 1.3% for empagliflozin 10 mg, 0.7% for empagliflozin 25 mg, and 0.9% for sitagliptin. The most frequent events at PT level were traumatic fracture (0.5% in the placebo, 0.1% in the empagliflozin 10 mg, 0.2% in the empagliflozin 25 mg, and none in the sitagliptin group), foot fracture (0.4% in the placebo group only), facial bones fracture (0.2% in the empagliflozin 10 mg group only), and

tibia fracture (0.2% in the placebo and 0.1% in the empagliflozin 25 mg group only). All other events were reported for no more than 1 patient per group. Three patients in the open-label empagliflozin 25 mg group (1.2%) were reported with bone fracture (1 each with lumbar vertebral fracture, pathological fracture, and wrist fracture).

In the SAF-5 group, frequency of bone fractures was low and the incidence rate per 100 patient-years was lower in the empagliflozin 25 mg group than the other groups. The most common PT was traumatic fracture, also reported with a lower incidence rate per 100 patient-years in the empagliflozin 25 mg group than the other groups. All other events were reported for no more than 0.2% of the patients per group. Laboratory markers related to bone health (calcium, phosphate, and alkaline phosphatase) were assessed in all studies; vitamin D (25-OH-cholecalciferol), intact parathyroid hormone (iPTH), and urine N-terminal telopeptide (NTx) were assessed in studies 1245.20, 1245.28, 1245.33, and 1245.38 only. There were only minor changes in all groups in the median values for 25-OH vitamin D, and iPTH. There were no changes in calcium, phosphate, or alkaline phosphatase median values. Urine NTx to creatinine ratio slightly increased in the empagliflozin groups, where as it slightly decreased in the comparator groups.

8.6.5. Volume depletion

In the SAF-3 group, the frequencies of the randomised and treated patients with volume depletion were low and comparable in all groups. In the empagliflozin 10 mg group, each PT was only reported by 2 patients; in the empagliflozin 25 mg group, syncope was reported by 3 patients, other PTs were reported each by only 1 patient. Two patients in the open-label empagliflozin 25 mg group were reported with volume depletion (1 each with hypotension and syncope). In the SAF-5 group, the incidence rates per 100 patient-years were similar for all groups. The most common PTs were hypotension and syncope, reported with similar incidence rates per 100 patient-years in all groups. All other events were reported for no more than 0.2% of patients per group. For patients taking diuretics at baseline, the frequencies and incidence rates per 100 patient-year of patients with volume depletion were about twice as high as those not taking diuretics at baseline; however, the incidence rates per 100 patient-years were similar for all treatment groups regardless of diuretics use at baseline. This was especially noted for patients taking loop diuretics.

8.6.6. Malignancy

The overall incidence rates per 100 patient-years for malignancy were similar for all groups: 1.16 for placebo, 1.13 for empagliflozin 10 mg, 1.14 for empagliflozin 25 mg, 1.13 for all randomised empagliflozin, and 1.00 for all comparators. High level terms (HLT) reported more often in the all randomised empagliflozin group (and reported for at least 2 patients) were: skin melanomas (6 patients in the all randomised empagliflozin group and none in the all comparators group, respiratory tract and pleural neoplasms malignant cell type unspecified NEC (5 and none), bladder neoplasms malignant (2 and none), bile duct neoplasms malignant (2 and none), oropharyngeal, nasopharyngeal and tonsillar neoplasms malignant and unspecified (2 and none), and thyroid neoplasms malignant (2 and none). On the other hand, HLTs reported more often in the all comparators group (and reported for at least 2 patients) were: prostatic neoplasms malignant (2 patients in the all randomised empagliflozin group and 4 patients in the all comparators group), breast and nipple neoplasms malignant (1 and 2), hepatobiliary neoplasms malignancy unspecified (1 and 2), renal neoplasms malignant (none and 2). For the treated patients in the open-label empagliflozin 25 mg group in SAF-3, only 1 patient (0.4%) was reported with a malignancy (prostate cancer) For malignancies with an onset of >6 months after the start of treatment, the frequencies of patients with breast cancer were similar in the all randomised empagliflozin group and the all comparators group. No renal cancer was reported in the empagliflozin groups. Although the PT bladder cancer was reported for 2 patients (incidence rate 0.05 per 100 patient-years) in the all randomised empagliflozin group and none in the all comparators group, the PT transitional cell carcinoma (consistent with clinical assessment of bladder cancer) was reported for 1 patient (incidence rate 0.04 per 100 patient-

years) in the all comparators group and none in the all randomised empagliflozin group. Therefore the incidence for bladder cancer was similar for empagliflozin and comparators.

Considering the time frame for the development of malignancy, patients treated for >6 months and reported malignant events after 6 months were also analysed. The incidence rates per 100 patient-years for patients with malignancy in this analysis were also similar for all groups. There was no plausible mechanism of action to support a causal relationship between empagliflozin treatment and skin melanoma; the imbalance could be due to random fluctuation. Similarly there was no obvious explanation for the lung cancer cases in the empagliflozin group; there was a lack of uniform malignancy cell type, which suggested that these occurrences were not based on similar mechanisms of tumour growth.

8.7. Post-marketing experience

No post-marketing data are available.

8.8. Safety issues with the potential for major regulatory impact

8.8.1. Liver toxicity

The incidence of elevated ALT/AST was low and similar in empagliflozin and comparator groups. Furthermore, there were no reports of Hy's law cases in the large database of subjects treated with empagliflozin.

8.8.2. Haematological toxicity

Empagliflozin treatment slightly increased haematocrit values (absolute change from baseline around 3%), but the increase in haematocrit was reversible after the discontinuation of empagliflozin treatment; the frequencies of patients with thromboembolic AEs did not increase with empagliflozin treatment (0.08% for 10 mg and 0.09% for 25 mg; 0.23% for placebo).

8.8.3. Serious skin reactions

None.

8.8.4. Cardiovascular safety

In order to assess the cardiovascular risk of empagliflozin treatment compared with any control, a cardiovascular meta-analysis was planned. The primary endpoint 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.

[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]

The primary endpoint was the 4-point Major Adverse Cardiovascular Events (4-point MACE) composite endpoint. Time to first occurrence of any component was calculated, as based on adjudicated results.

- CV death (including fatal stroke and fatal MI);
- Non-fatal MI;
- Non-fatal stroke: ischaemic and haemorrhagic stroke ;
- Hospitalisation due to unstable angina.

The cardiovascular risk ratio of empagliflozin treatment (the 2 test doses combined) against control treatment (all control treatments combined) and the associated confidence interval (CI) were calculated. The overall significance level for the meta-analysis was $\alpha = 2.5\%$, one-sided. An interim analysis was planned and an α -spending approach was used to compensate for the repeated testing.

Secondary endpoints were the 3-point MACE³⁵, 5-point MACE³⁶, and 7-point MACE³⁷ composite endpoints. For each, time to first occurrence of any component was calculated (based on adjudicated results). Tertiary endpoints were the time to first occurrence of each individual component of the 7-point MACE endpoint and of all-cause mortality. Additional endpoints were time to first MI (fatal and non-fatal) and stroke (fatal and nonfatal).

The primary model was a Cox proportional hazards model; sensitivity analyses were based on a Poisson regression model and stratified analysis of incidences (calculation of odds-ratio based on exact test for stratified 2x2 contingency tables and risk ratio based on stratified Cochran-Mantel-Haenszel test). The time to event was also presented using Kaplan-Meier estimates. The primary analysis was performed based on the treated set, consisting of all randomised patients who had received at least one dose of study drug. A sensitivity analysis was performed based on the on-treatment set. For the interim analysis, non-inferiority based on the 1.8 margin for the hazard ratio for combined empagliflozin vs. all comparators was addressed. At the same time, non-inferiority based on the 1.3 margin and superiority was assessed, with testing performed in hierarchical order. The interim analysis had been planned to be performed after about 118 patients had a confirmed 4-point MACE event.

[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]

[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]

[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]

8.8.5. Unwanted immunological events

None.

8.9. Other safety issues

8.9.1. Safety in special populations

Based on SAF-5, subgroup analyses of the following were performed: patient disposition, demographic and other characteristics of study population, drug exposure, any AE, AEs leading to discontinuation of study medication, SAEs, decreased renal function, hepatic injury, urinary tract infection, genital infection, hypoglycaemic events, bone fracture, and volume depletion.

8.9.1.1. Intrinsic factors

8.9.1.1.1. Age

Of all randomised patients, around half were between the age of 50 and <65 years. A substantial number of patients (755) were ≥ 75 years of age. Only 29 patients were ≥ 85 years and so this age category was included in the ≥ 75 years category for subgroup analyses.

The proportion of patients who prematurely discontinued study medication (including not continuing in extension) was higher with patients <50 years (25.0%) than with older patients (range: 14.0% to 17.9%). The proportion of patients who prematurely discontinued due to AEs

³⁵ Three-point MACE: CV death (including fatal stroke and fatal MI); Non-fatal MI; Non-fatal stroke: ischaemic and haemorrhagic stroke.

³⁶ Five-point MACE: CV death (including fatal stroke and fatal MI); Non-fatal MI; Non-fatal stroke: ischaemic and haemorrhagic stroke; Hospitalisation due to unstable angina; Hospitalisation due to congestive heart failure.

³⁷ Seven-point MACE: CV death (including fatal stroke and fatal MI); Non-fatal MI; Non-fatal stroke: ischaemic and haemorrhagic stroke; Hospitalisation for unstable angina; Hospitalisation due to congestive heart failure; Transient ischaemic attack (TIA); Coronary revascularisation procedures.

increased with age (from 2.0% for patients <50 years to 7.4% for patients ≥ 75 years). For all groups in any age category, the frequencies for premature discontinuation were generally consistent with those of the overall population in SAF-5. Generally, the frequency of AEs (all types) increased with age. The frequency of patients with SAEs was lower in the empagliflozin groups than in the placebo group for all age categories. On the other hand, the frequency of patients with genital infection (BICMQ) was higher in the empagliflozin groups than in the placebo group for all age categories. For patients <50 years and between 50 and <65 years, the frequencies of AEs (other than SAEs and genital infections) were comparable across the groups. For patients between 65 and <75 years, the frequency of patients with urinary tract infection was higher in the empagliflozin groups than in the placebo group. The frequencies of the other types of AEs (except SAEs, genital infections and urinary tract infections) were comparable across the groups. For patients ≥ 75 years, the frequency of patients with AEs leading to discontinuation of study medication was lower in the empagliflozin groups than in the placebo group. On the other hand, the frequency of patients with urinary tract infections was higher in the empagliflozin groups than in the placebo group; the further increase in the frequency of urinary tract infections from the age group 65 to <75 years to the age group ≥ 75 years appeared to be proportional for placebo and empagliflozin 25 mg. Moreover, the frequency of patients with volume depletion was higher in the empagliflozin 25 mg group than in the empagliflozin 10 mg and the placebo group; the most common PTs were syncope (empagliflozin 25 mg: 1.5%) and hypotension (empagliflozin 25mg: 1.1%), which were reported more frequently in the empagliflozin 25 mg group than in the other groups. The frequencies of other types of AEs (except SAEs, genital infections and AEs described above) were comparable across the groups.

Additionally, post-hoc analyses were conducted to investigate whether the observed imbalances in AEs frequencies for volume depletion and urinary tract infection in patients ≥ 75 years of age were associated with decreased renal function. The frequencies of these events in patients ≥ 75 years of age were analysed in subgroups of eGFR categories (3 subgroup analyses with 2 categories each: patients ≥ 75 years by eGFR <30 or ≥ 30 mL/min/1.73 m², by eGFR <45 or ≥ 45 mL/min/1.73m², and by eGFR <60 or ≥60 mL/min/1.73 m²). The number of patients in the lowest eGFR subgroup (eGFR <30 or ≥ 30 mL/min/1.73 m²) was very low, therefore results were inconclusive. Results for the other 2 subgroups showed that 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. It was therefore concluded that renal function does not seem to be a predictor of the increased risk for volume depletion in elderly patients treated with empagliflozin. On the other hand, 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.

8.9.1.1.2. Gender

The frequency of patients with any AE, with urinary tract infection, or with genital infection was higher for women than for men. The frequency of patients with genital infection was higher in the all randomised empagliflozin group than in the all comparators group for both genders. The frequency of patients with urinary tract infection was slightly higher in the all randomised empagliflozin group than in the all comparators group for women but not for men. All other AEs occurred at similar frequencies for both groups for either gender.

8.9.1.1.3. Race and ethnicity

The frequency of patients with AEs leading to discontinuation of study medication for Black/African American patients was higher in the all randomised empagliflozin group than in the all comparators group. The frequency of patients with SAEs for Black/African American patients was lower in the all randomised empagliflozin group than in the all comparators group. The frequency of patients with genital infection (BICMQ) was higher in the all randomised

empagliflozin group for all races. Demographic data were balanced between non-Hispanic/Latino patients and Hispanic/Latino patients. The mean exposure was higher for non-Hispanic/Latino patients than for Hispanic/Latino; for either ethnicity, the exposure was comparable for the all randomised empagliflozin group and the all comparators group. The frequency of patients with genital infection was higher in the all randomised empagliflozin group than in the all comparators group for both ethnicity categories. The frequency of patients with SAEs or hepatic injury (SMQ) was lower in the all randomised empagliflozin group than in the all comparators group for Hispanic/Latino patients.

8.9.1.1.4. BMI

Majority of the Asian patients were in the lowest BMI category (<25 kg/m²). The proportion of patients with a history of hypertension increased with BMI. Any AE, any SAEs, urinary tract infection, and genital infection increased in frequency with BMI. The frequency of patients with genital infection was higher in the all randomised empagliflozin group than in the all comparators group for all baseline BMI categories; other types of AEs were balanced between the 2 groups.

8.9.1.1.5. Renal function

Renal function was categorised as normal (eGFR ≥90 mL/min/1.73m²), mild impairment (60 to <90 mL/min/1.73m²), moderate impairment (30 to <60 mL/min/1.73m²), and severe impairment (<30 mL/min/1.73m²). The moderate renal impairment category was further divided into moderate A (eGFR 45 to <60 mL/min/1.73m²) and moderate B (30 to <45 mL/min/1.73m²).

The proportion of patients who prematurely discontinued study medication due to AEs increased with the severity of renal impairment. The age, the proportion of patients with history of hypertension, and the time since diagnosis of diabetes increased with the severity of renal impairment. There were few patients in the severe impairment category (52 patients in the placebo, 7 in the empagliflozin 10 mg, and 56 in the empagliflozin 25 mg group) and the mean exposure for this category was shorter than for the other categories. The frequencies of almost all types of AEs (except hepatic injury based on SMQ and genital infection) increased with the severity of renal impairment.

For all baseline renal function categories (except severe impairment), the frequency of patients with SAEs was lower in the empagliflozin groups than in the placebo group. On the other hand, the frequency of patients with genital infection was higher in the empagliflozin groups than in the placebo group; in the severe impairment category, no genital infection was reported. For patients with normal renal function at baseline, the frequency of patients with any AE was higher in the empagliflozin groups than in the placebo group. The frequencies of the other types of AEs (except SAEs and genital infections) were comparable across the groups. For patients with mild renal impairment at baseline, the frequencies of adverse events (other than SAEs and genital infections) were comparable across the groups. For patients with moderate renal impairment, the frequency of patients with any AE was lower in the empagliflozin groups than in the placebo group; the frequency of patients with decreased renal function or urinary tract infection was higher in the empagliflozin groups than in the placebo group.

8.9.1.1.6. Hypertension at baseline

Three quarters of the patients in SAF-5 (74.5%) had a history of hypertension at baseline; study 1245.48 also evaluated safety in T2DM patients with hypertension treated for 12 weeks. Overall, empagliflozin 10 mg or 25 mg daily treatment was well tolerated and showed similar safety profiles (except higher genital infection) compared with placebo treatment.

8.9.1.2. Extrinsic factors

8.9.1.2.1. Geographical region

From the patient demographic data, patients in Asia were slightly younger, lower in BMI, less likely to have history of hypertension, and had shorter duration of diabetes than those in other

geographical regions. The frequency of any AE, decreased renal function (SMQ), genital infection (BICMQ), and confirmed hypoglycaemic AEs in Africa/Middle East was higher than in the other regions. The frequency of patients with genital infection (BICMQ) was lower in Asia than in other regions; for all regions, the frequencies were higher in the all randomised empagliflozin group than in the all comparators group. The frequency of patients with decreased renal function (SMQ) in North America was higher in the all randomised empagliflozin group than in the all comparators group. The frequency of patients with SAEs was lower in the all randomised empagliflozin group than in the all comparators group in the regions Africa/Middle East, Europe, and Latin America.

8.9.2. Safety related to drug-drug interactions and other interactions

In all of the Phase I-II drug interaction studies, co-administration of both drugs resulted in a comparable safety profile in terms of AE frequencies and laboratory and vital sign assessments compared with separate administrations of empagliflozin and the drug tested. In studies investigating the effect of a high-fat, high-calorie meal on empagliflozin treatment (empagliflozin 25 mg as a single dose in study 1245.79 and empagliflozin 50 mg as a single dose in 1245.3), no safety signals were seen.

In addition to drug interaction studies with sitagliptin and linagliptin in healthy subjects, based on study 1245.25, analyses in a subpopulation of patients with metformin and a DPP-4 inhibitor with or without one additional oral antidiabetic medication as background medication were performed for the following: patient disposition, demographic and other characteristics of study population, drug exposure, any adverse event, adverse events leading to discontinuation of study medication, SAEs, decreased renal function (SMQ), hepatic injury (SMQ), urinary tract infection (BICMQ), genital infection (BICMQ), hypoglycaemic events, volume depletion (BICMQ), safety laboratory parameters, and vital signs. All safety analyses for this subpopulation are summarised in the dossier. The frequencies of patients with any AE or confirmed hypoglycaemic AE were lower in the empagliflozin groups than in the placebo group. The frequency of patients with AE leading to discontinuation of study medication was similar in the placebo and empagliflozin 25 mg groups but higher in the empagliflozin 10 mg group. The frequency of patients with genital infection (BICMQ) was higher in the empagliflozin groups than in the placebo group. Other types of AE were balanced in all 3 groups. Hence, there was no evidence of drug interactions when empagliflozin was administered to patients on treatment with metformin+DPP4-inhibitors.

8.9.3. Use in pregnancy/lactation

Empagliflozin is not expected to impact fertility, implantation, and embryo-foetal development based on the reproductive and developmental toxicology studies. Pregnant or nursing women were excluded from any study in the clinical development programme; women of child-bearing potential were to undergo pregnancy testing and to use an acceptable method of contraception during the study. However, if a woman became pregnant, the study medication was to be stopped. The woman was to be followed-up until birth or termination of the pregnancy. In finished studies and in unfinished studies up to the interim database locks, 8 patients became pregnant while treated with study medication. Four of them were treated with empagliflozin; of these patients, 1 had an induced abortion, 1 had a miscarriage, and 2 delivered healthy babies.

8.9.4. Overdose, drug abuse, withdrawal and rebound and effect on ability to drive or operate machinery

There have been clinical studies using doses higher than the therapeutic doses (10 mg and 25 mg) of empagliflozin: 800 mg as a single dose was administered to 6 healthy subjects in study 1245.1, 100 mg daily for 8 days was administered to 9 patients in study 1245.2, and 50 mg daily for 12 weeks was to be administered to 70 patients in study 1245.10 and to 110 patients in study 1245.38. In all of these studies, empagliflozin treatment was well tolerated and there was no specific safety concern. Furthermore, the thorough QT study (1245.16) showed that a single suprathreshold dose of 200mg empagliflozin was not associated with a QT(c) interval prolongation. Three cases of overdose recorded as AEs were found in SAF-5 in a search of any

PT that contains the word “overdose”; none was an overdose of empagliflozin. The BI global drug safety database was also searched for reported cases of overdose; no additional cases were found.

Since pharmacological properties, non-clinical data, and clinical data do not indicate an impact on the central nervous system suggestive for stimulant, depressant, hallucinogenic or mood-elevating effects, the potential for abuse is believed to be minimal. No clinical or nonclinical study investigating the potential of drug abuse was carried out. No drug-seeking behaviour was reported in clinical studies; treatment compliance as calculated by tablet count did not indicate drug abuse.

The sponsor’s global drug safety database was searched for the PTs withdrawal syndrome and rebound effect; no case was found. As the pharmacodynamic effect of empagliflozin only extends to about 3 days after the last dose, a follow-up period of 1 week was planned for most studies. However, a 4-week follow-up period was planned for long-term (>52 weeks) studies. The results of these studies showed a return toward baseline at the follow-up visit for the parameters of FPG, BP, body weight, basal insulin dose, haematocrit and hemoglobin, serum creatinine and uric acid.

No study investigating the effects on the ability to drive and use machines was performed. The frequency of hypoglycaemic events was generally similar for empagliflozin and placebo treatment in patients with or without background antidiabetic therapy, except for patients with metformin plus a sulphonylurea background therapy or a fixed dose basal insulin background therapy (the frequency was increased with empagliflozin treatment in these patients).

8.10. Evaluator’s overall conclusions on clinical safety

To support an integrated analysis of safety, the 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 (pool of pivotal trials with extensions, 2957 patients in total) as this pooling corresponds to the efficacy pooling EFF-2. 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).

In SAF-5, 63.0% of the patients were male. The mean age was 59.6 years. The majority (64.8%) was diagnosed with type 2 diabetes for over 5 years. Most patients were White (62.0%) or Asian (33.8%); 3.6% were Black or African American. SAF-5 included a dedicated efficacy and safety study in patients with renal impairment, as well as a dedicated cardiovascular outcome study. Demographic and baseline data were generally similar across randomised groups. The frequencies of patients with treatment-emergent AEs in the empagliflozin groups (68.1% for 10 mg and 69.5% for 25 mg) were similar to the frequency in the placebo group (68.6%) in SAF-5. The MedDRA preferred terms reported most often were hypoglycaemia, hyperglycaemia, nasopharyngitis, and urinary tract infection. Apart from hyperglycaemia, which was reported with a substantially lower frequency in the empagliflozin groups (4.3% for 10 mg and 4.7% for 25 mg) than in the placebo group (10.3%), the frequencies of most of these preferred terms were similar across the groups.

The frequencies of patients with AEs assessed by the investigator as drug-related were higher in the empagliflozin groups (20.6% for 10 mg and 19.9% for 25 mg) than in the placebo group (15.2%). Genital infections were reported as drug-related AEs more frequently in the empagliflozin groups than in the placebo group.

The frequencies of patients with AEs leading to discontinuation of study medication were similar for all groups (4.8% for empagliflozin 10 mg, 4.9% for empagliflozin 25 mg, and 5.3% for placebo). The MedDRA preferred term urinary tract infection was reported for higher proportions of patients in the empagliflozin groups than in the placebo group as AEs leading to discontinuation. The frequency of patients with AEs of severe intensity was slightly lower in the empagliflozin groups (6.1% for 10 mg and 6.5% for 25 mg) than in the placebo group (8.3%).

The frequencies of patients with SAEs (including fatal events) were lower in the empagliflozin groups (9.6% for 10 mg and 10.3% for 25 mg) than in the placebo group (12.7%) in SAF-5. Cardiac disorders were reported as SAEs with lower frequencies in the empagliflozin groups (2.1% for 10 mg and 2.3% for 25 mg) than in the placebo group (4.0%). The incidence rate per 100 patient-years of patients with fatal AEs was lower with empagliflozin treatment (0.52; 41 deaths; including all doses) than with comparator treatments (0.78; 33 deaths; including placebo).

In pre-specified standardised MedDRA queries regarding hepatic injury, the frequencies were similar for all groups (1.2% for empagliflozin 10 mg, 1.4% for empagliflozin 25 mg, and 1.5% for placebo). There were more patients with liver enzyme elevation (ALT/AST \geq 3x ULN with total bilirubin \geq 2x ULN or ALT/AST \geq 10x ULN) in the empagliflozin groups (11 patients) than in the comparator groups (1 patient). However, no cases satisfied Hy's law and all cases could be explained by plausible causalities alternative to drug-induced liver injury.

Effects on renal function were in general similar for all groups, based on the evaluation of renal AEs (with a pre-specified standardised MedDRA query) and laboratory parameters. For patients receiving empagliflozin, there was a small decrease in eGFR after the start of treatment (lowered by 2 to 3 mL/min/1.73 m² from baseline after 12 weeks); thereafter, eGFR value gradually returned to baseline over time (lowered by around 1 mL/min/1.73 m² from baseline after 1 year). This minimal change in eGFR was judged not to be of clinical relevance and was reversible after discontinuation of empagliflozin treatment. For patients with micro- or macroalbuminuria, empagliflozin treatment led to a greater reduction in albuminuria than placebo.

Empagliflozin treatment slightly increased haematocrit values (absolute change from baseline around 3%). Nevertheless, the increase in haematocrit was reversible after the discontinuation of empagliflozin treatment; the frequencies of patients with thromboembolic adverse events did not increase with empagliflozin treatment (0.08% for 10 mg and 0.09% for 25 mg; 0.23% for placebo).

Empagliflozin treatment led to small dose-dependent increases (around 0.1 mmol/L) in total cholesterol, HDL cholesterol, and LDL cholesterol but no change in LDL/HDL cholesterol ratio. Empagliflozin treatment did not change electrolyte levels and there were no other significant changes in other laboratory parameters.

[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]

Safety of empagliflozin was demonstrated in a very large set (12873 patients) and a representative sample of patients with type 2 diabetes using a variety of antidiabetic background medications. Empagliflozin 10 mg or 25 mg once daily demonstrated similar and favourable safety profiles.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of empagliflozin in the proposed usage are:

- Simple once daily oral dosing.
- The sponsor has conducted a comprehensive program of pharmacokinetic interaction studies with drugs which are most likely to be co-administered with empagliflozin and these have revealed no evidence of significant interference by these drugs with empagliflozin PKs such as to necessitate any recommendations regarding dosage adjustment.

- 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 which was confirmed in the study comparing empagliflozin with glimepiride (study 1245.28).
- In addition to reduction of HbA1c, empagliflozin treatment also helps reduce FPG and MDG levels.
- Statistically and clinically relevant reduction in body weight.
- Statistically and clinically relevant reduction in blood pressure.
- Efficacy was shown in treatment-naïve T2DM patients and when used in combination with metformin, combination with metformin+sulphonylurea, combination with basal insulins.
- Empagliflozin was also non-inferior to sitagliptin and glimepiride in terms of glycaemic control.
- Efficacy was also shown in T2DM patients with renal impairment, hypertension and CV risk factors.
- Of the patients with high HbA1c (>10%) who received open-label treatment with empagliflozin 25mg od for 24 weeks, 15.2% showed HbA1c<7% after 24 weeks of treatment.
- Long-term efficacy was adequately evaluated in patients and reduction in HbA1c, FPG, body weight and BP was maintained for up to 52 weeks.
- Empagliflozin was devoid of serious hypoglycaemic AEs usually associated with other OADs.
- **[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]**
- In a randomised, placebo-controlled, active-comparator, crossover study of 30 healthy subjects no increase in QTc was observed with either 25 mg or 200 mg empagliflozin.
- Empagliflozin demonstrated a favourable safety profile in a very large set of patients with type 2 diabetes using a variety of antidiabetic background medications.

9.2. First round assessment of risks

The risks of empagliflozin in the proposed usage are:

- Efficacy was not shown in patients with moderate renal impairment (grade 3B with EGFR<45ml/kg/m²) and in patients with severe renal impairment.
- As efficacy of the drug is dependent on renal function, it is essential to monitor renal function in the T2DM patients during administration of empagliflozin and it would be prudent to have set guidelines to monitor renal function during long-term treatment with empagliflozin (similar to that included in the PI for the other approved SGLT2 inhibitor-dapagliflozin).
- Genital infections, increased urination, urinary tract infections, hypoglycaemia, and volume depletion were identified as listed side effects. Those events were mostly reported as mild in intensity and did not lead to discontinuation of trial drug.
- Potential safety concerns about use of empagliflozin with pioglitazone due to inconsistent results in the PK drug interaction studies between pioglitazone and empagliflozin.

9.3. First round assessment of benefit-risk balance

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 benefits 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 mild diuretic effect.

Overall, 13767 subjects were included and treated in the clinical trials constituting the development programme presented in this application. A total of 8506 patients with type 2 diabetes mellitus were treated with empagliflozin (empagliflozin 25 mg: 4563 patients, empagliflozin 10 mg: 3311 patients). Of these, 6808 patients were treated with empagliflozin for at least 24 weeks, 4415 patients for at least 52 weeks, and 1486 patients for at least 76 weeks. With this number of patients and extent of exposure, the clinical programme exceeds the requirements of relevant guidelines and provides adequate and sufficient safety and efficacy information for the assessment of empagliflozin as treatment for type 2 diabetes in adults.

Treatment with empagliflozin 10 mg or 25 mg once daily resulted in a robust improvement of glycaemic control with statistically significant and clinically meaningful reductions of HbA1c and FPG. The 4 pivotal trials demonstrated the superiority of both doses of empagliflozin to placebo after 24 weeks. In 3 of the 4 trials, the effects for the 25 mg dose were numerically larger than for the 10 mg dose. The effects were consistent across a range of different antidiabetic background regimens. Thus, empagliflozin improved glycaemic control as monotherapy and as add-on to metformin monotherapy, metformin plus sulphonylurea, and pioglitazone (with or without metformin).

Maximal efficacy of empagliflozin on glycaemic control was established 12 weeks after the start of treatment. Efficacy was sustained for at least 52 weeks, as shown in the double-blind extensions of the 4 pivotal trials. The proportions of patients reaching the target HbA1c (<7.0%) at Week 24 were significantly larger for both empagliflozin doses than for placebo in each trial; treatment with empagliflozin 25 mg led to higher responder rates than treatment with empagliflozin 10 mg. In addition, significantly fewer patients in the empagliflozin groups required rescue medication than patients in the placebo groups. The results for HbA1c and FPG were further supported by reductions in mean daily glucose and postprandial glucose, which were investigated in 2 of the pivotal trials.

Empagliflozin also provided significant and clinically meaningful reductions in HbA1c compared with placebo in all other Phase III placebo-controlled trials, i.e. in patients treated with basal insulin, in patients with type 2 diabetes and hypertension, in patients with mild and moderate renal impairment, and in patients with increased cardiovascular risk (including a subpopulation of patients with increased cardiovascular risk on a background of metformin and DPP-4 inhibitor, with or without 1 additional oral antidiabetic agent). The HbA1c-lowering effect of empagliflozin was generally consistent across various subgroups based on demographic factors or baseline characteristics.

Body weight reduction and optimum control of blood pressure are 2 important unmet needs in the management of patients with type 2 diabetes. Empagliflozin treatment led to statistically significant and clinically meaningful reductions in body weight in all pivotal trials. Furthermore, significant and clinically meaningful reductions of SBP compared with placebo were achieved for empagliflozin 25 mg in each of the pivotal trials. For DBP, reductions were also observed but were smaller and not always significant compared with placebo. In an ABPM trial in patients with type 2 diabetes and hypertension, both doses of empagliflozin were superior to placebo in reducing 24-h SBP and 24-h DBP after 12 weeks of treatment. Weight and blood pressure reductions of a magnitude similar to that in the pivotal trials were reached in the other supportive trials including the trials in patients with renal impairment or with high cardiovascular risk. Notably, in patients without hypertension, treatment with empagliflozin was not associated with an increased frequency of AEs indicative of hypotension. The weight and blood pressure reductions were sustained throughout the short- and long-term trials. The effects of empagliflozin on body weight and blood pressure are expected to modify cardiovascular risk factors and cardiovascular risk, and may translate into a benefit on the long-

term micro- and macrovascular complications of diabetes that extend beyond the effect on glycaemic control. This is being evaluated in the ongoing study in T2DM patients with CV risk factors (study 1245.25) **[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]**

Empagliflozin 25 mg was compared to the established antidiabetic drug glimepiride. In this double-blind trial, empagliflozin was shown to provide non-inferior glycaemic control to glimepiride (up to 4 mg daily) after 52 weeks of treatment. At the same time, empagliflozin was superior to glimepiride for several other clinically important endpoints, namely body weight reduction, a reduced occurrence of confirmed hypoglycaemic events, and for SBP and DBP reductions.

Metformin is the current standard first-line treatment for patients with type 2 diabetes. New antidiabetic drugs will therefore likely be employed as combination therapy, e.g. with metformin, or as monotherapy in patients for whom metformin is inappropriate. Sitagliptin is one of the few antidiabetic drugs with such a restricted monotherapy claim (in the EU). Therefore, empagliflozin efficacy was compared with that of sitagliptin in the pivotal monotherapy trial (1245.20) and its extension. Empagliflozin 25 mg once daily showed significantly greater reductions in HbA1c, weight and blood pressure than sitagliptin at Week 52. The usefulness of empagliflozin in the monotherapy setting was further substantiated in a 12-week, double-blind, placebo-controlled Phase IIb trial with an open-label (immediate release) metformin group. Long-term data of up to 90 weeks from the open-label extension of this trial showed sustained and similar improvements of glycaemic control with empagliflozin 25 mg and with metformin. These results suggest that empagliflozin may be an efficacious treatment option in patients for whom metformin is considered inappropriate. In this context, the added benefits of empagliflozin compared with the sulphonylurea glimepiride, which is also an alternative when metformin is inappropriate, are even more important.

In most of the trials, the 25 mg dose of empagliflozin showed better efficacy than the 10 mg dose. This was true for all endpoints (HbA1c, FPG, body weight, SBP, DBP). A higher proportion of patients reached the HbA1c target of <7% with empagliflozin 25 mg than with empagliflozin 10 mg. Fewer patients treated with the high empagliflozin dose required rescue medication than patients treated with the low empagliflozin dose.

To support an integrated analysis of safety, the 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 (pool of pivotal trials with extensions, 2957 patients in total) as this pooling corresponds to the efficacy pooling EFF-2. 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%). This was consistently observed across the different poolings, trials, and subgroup analyses, indicating that treatment with empagliflozin was generally satisfactory for patients. The overall frequency of treatment-emergent AEs 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 AEs 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 incidence of fatal AEs was lower with empagliflozin treatment (SAF-5: 41 deaths, 0.5%, incidence rate 0.52 per 100 patient years) than with comparator treatments (including placebo; 33 deaths, 0.7%, 0.78 per 100 patient years). **[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]**

MedDRA preferred terms reported most frequently as AEs were nasopharyngitis, urinary tract infection, hyperglycaemia, and hypoglycaemia; the frequency of most of these events were similar across the treatment groups. Hyperglycaemia was reported with a substantially lower frequency in the empagliflozin groups (SAF-3: 5.5% for 10 mg and 4.5% for 25 mg) than in the placebo group (21.7%).

With regard to subgroups, there was no clear evidence for a major influence of any intrinsic or extrinsic factor on adverse event frequencies. The safety laboratory data revealed no clear trends of clinical relevance in relation to the use of empagliflozin. Small increases of haematocrit were observed, but did not lead to an increased frequency of thromboembolic events. Small increases in lipid parameters (total cholesterol, HDL cholesterol, and LDL cholesterol) were seen for the empagliflozin groups (with differences to placebo ranging from 0.06 mmol/L to 0.13 mmol/L). But as no meaningful changes were seen for the LDL/HDL ratio and no safety signal was observed in the cardiovascular meta-analysis, the changes in lipid parameters are not considered clinically meaningful. Across all AE and laboratory analyses, differences between the 2 doses of empagliflozin investigated in Phase III trials (10 mg and 25 mg) were small and not always consistently observed across trials and poolings. Therefore, both doses are considered equally safe for the treatment of type 2 diabetes.

Overall, empagliflozin demonstrated a favourable safety profile in a very large set of patients with type 2 diabetes using a variety of antidiabetic background medications.

Empagliflozin was safe and efficacious in patients with type 2 diabetes as a monotherapy and in combination with other oral antidiabetic medications or insulin. Empagliflozin was also safe and efficacious in patients with type 2 diabetes and further co-morbidities like mild or moderate renal impairment, hypertension, or high cardiovascular risk. Empagliflozin 25 mg generally showed numerically better efficacy results than empagliflozin 10 mg, and both doses showed a good safety profile.

Hence, the overall benefit-risk profile for empagliflozin 25mg od for the proposed indication is favourable.

10. First round recommendation regarding authorisation

It is recommended that empagliflozin 25mg od be approved for the proposed indication of “as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.” However, the approval is subject to a satisfactory response to the clinical questions (refer section 11).

11. Clinical questions

11.1. Pharmacokinetics

None.

11.2. Pharmacodynamics

None.

11.3. Efficacy

The sponsors have not clarified if the dataset submitted to the USA and Canada was similar to that submitted to Australia and EU. Could the sponsors please clarify?

11.4. Safety

1. Module 2 (Clinical summary of safety) states that analysis of drug-related adverse events was performed for SAF-3 (pivotal study with extension), SAF-5 (all patients), and study 1245.25. However, the results of drug-related AEs were only provided for the SAF-5 and study 1245.25; results for the pivotal studies SAF-3 group were not provided. Could the sponsors provide the results of drug-related AEs in the pivotal studies group (SAF-3)?
2. In the pivotal studies, 12-lead ECGs were taken at baseline and at end of study. There is no data on ECG provided in the safety summary in module 2 or in the individual study reports. Could the sponsors please clarify this?

11.5. Product Information: indications

The indications should provide details of how empagliflozin should be used in the different T2DM patients (as monotherapy, in combination with other OADs and with basal insulin).

- **Monotherapy**
Empagliflozin is indicated as an adjunct to diet and exercise in patients with type 2 diabetes mellitus for whom metformin is otherwise indicated but was not tolerated.
- **Initial combination**
Empagliflozin is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus when diet and exercise have failed to provide adequate glycemic control and there are poor prospects for response to metformin monotherapy (for example, high initial HbA1c levels).
- **Add-on combination**
Empagliflozin is indicated in patients with type 2 diabetes mellitus to improve glycemic control:
 - in combination with metformin, when metformin alone with diet and exercise does not provide adequate glycemic control;
 - in combination with a sulfonylurea (SU), when a SU alone with diet and exercise does not provide adequate glycemic control;
 - in combination with insulin (alone or with one or both of metformin or a sulfonylurea [SU]) when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.

Could the sponsors please comment.

12. Second round evaluation of clinical data submitted in response to questions

12.1. Pharmacokinetics

None.

12.2. Pharmacodynamics

None.

12.3. Efficacy

The sponsors have not clarified if the dataset submitted to the USA and Canada was similar to that submitted to Australia and EU. Could the sponsors please clarify?

Sponsor's response:

In the original submission, the applicant stated that the data set submitted to Australia was similar to the data set submitted to the EU. The applicant confirms that the data set submitted to Australia was also similar to the data set submitted to the USA and Canada in the original submission.

However, in the subsequent interactions with the health authorities in the EU and USA, the applicant proposed new dose recommendation and target population according to the feedback from the authorities, and following further assessment of clinical data. The applicant now recommends that *"The recommended starting dose of empagliflozin is 10 mg once daily. In patients tolerating empagliflozin 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily. Empagliflozin is not recommended for use in patients with eGFR <45 ml/min/1.73 m². The therapeutic experience in patients aged 85 years and older is limited; initiation of empagliflozin therapy in this population is not recommended."*, as reflected in the modified PI and CMI.

The rationale for the above changes is detailed in the revised Clinical Overview, dated 31 Oct 2013 and is summarised below:

Both empagliflozin 10 mg and 25 mg consistently demonstrate sustained, clinically meaningful, and statistically significant efficacy. Since empagliflozin 10 mg provides substantial efficacy with lower exposure, 10 mg is recommended as a starting dose. In patients tolerating empagliflozin 10 mg once daily and requiring additional glycaemic control, the dose can be increased to the maximum once daily dose of 25 mg. The clinical findings show that, on average, empagliflozin 25 mg promotes better HbA1c reduction than empagliflozin 10 mg. This is also reflected by the higher proportion of patients who reached the HbA1c target of <7% with empagliflozin 25 mg (37.2%) than with empagliflozin 10 mg (31.5%) in the pooled pivotal trials at 24 weeks. Additionally, a lower proportion of patients in the 25 mg dose group (2.4%) than in the 10 mg group (4.1%) required rescue medication in the pooled pivotal trials. Therefore, the Applicant believes that patients who do not have adequate glycaemic control on empagliflozin 10 mg will benefit by increasing the dose to 25 mg once daily. In general, both doses were well tolerated and there were no meaningful differences between the overall safety profiles of both doses. In regard to the frequency of any adverse event, severe adverse events, serious adverse events, adverse events leading to treatment discontinuation, or fatal adverse event, similar proportions of patients were noted with such events for both doses.

The Applicant proposes empagliflozin 10 mg as a starting dose, as 10 mg provides substantial efficacy with lower exposure. In patients tolerating 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily. This approach represents a simple dosing recommendation consistent with other anti-diabetic agents, allowing individualised dose adjustment.

The therapeutic experience in patients aged 85 years and older is limited; initiation of empagliflozin therapy in this population is not recommended.

Evaluator's comments on sponsor's response:

The evaluators agree with the sponsor's request for proposed new dose recommendation and target population. The modified dosing regimen ensures that the lowest effective dose is used in patients.

12.4. Safety

Question 1: Module 2 (Clinical summary of safety) states that analysis of drug-related adverse events was performed for SAF-3 (pivotal study with extension), SAF-5 (all patients), and study 1245.25. However, the results of drug-related AEs were only provided for the SAF-5 and study 1245.25; results for the pivotal studies SAF-3 group were not provided. Could the sponsors provide the results of drug-related AEs in the pivotal studies group (SAF-3)?

Sponsor's response:

Of the randomised and treated patients in SAF-3, the frequencies of patients with investigator-defined drug-related AEs were higher in the empagliflozin groups (10 mg and 25 mg) than in the placebo group, and lower in the sitagliptin group than in the placebo group.

The frequencies of the most common investigator-defined drug-related AEs at system organ class (SOC) level were in general higher in the empagliflozin groups than in the placebo group, and lower in the sitagliptin group than in the placebo group. At preferred term (PT) level, pollakiuria, polyuria, dysuria, thirst, vulvovaginal mycotic infection, vulvovaginal pruritus, and balanoposthitis were reported more frequently in the empagliflozin groups than in the other groups. Urinary tract infection was less frequent in the empagliflozin groups and the sitagliptin group than in the placebo group. Hyperglycaemia was less frequent in empagliflozin groups than in the other groups. Weight decrease and dry mouth were reported more frequently in the empagliflozin 25 mg group than in the other groups. Hypoglycaemia was more frequent in the empagliflozin 10 mg group than in the other groups. The other most frequent investigator-defined drug-related events (with a frequency of >0.5% in any group) were reported with similar frequencies in all groups. In the open-label empagliflozin 25 mg group, the most frequent investigator-defined drug-related AE at SOC level was metabolism and nutrition disorders (hypoglycaemia most common).

Evaluator's comments on sponsor's response:

Results of drug-related AEs in the SAF-3 (pivotal study with extension) dataset was similar to that observed in the SAF-5 dataset and no new safety concerns were raised following review of this data.

Question 2: In the pivotal studies, 12-lead ECGs were taken at baseline and at end of study. There is no data on ECG provided in the safety summary in module 2 or in the individual study reports. Could the sponsors please clarify this?

Sponsor's response:

According to the protocol of all Phase III studies, 12-lead ECGs were taken at Visits 3 (randomisation) and Visit 7 (end of treatment) and as required. Clinically significant findings at the screening or randomisation visits were to be regarded as baseline conditions; new findings thereafter were to be recorded as AEs, if: they were not associated with an already-reported adverse event, symptom or diagnosis, and the investigational drug was discontinued, reduced, or increased, or additional treatment was required.

Although no ECG data were provided in the study reports or in the summary documents submitted, the important and significant ECG findings were carefully captured and sent for independent adjudication. Summary of these ECG findings was provided in an interim cardiovascular meta-analysis report (U12-2463). The ECG source documents were to be stored at the investigational sites. Copies of ECGs for patients who had ECG findings recorded as AEs were to be digitised and archived at Boehringer Ingelheim.

To systematically address the cardiovascular (CV) safety of empagliflozin treatment, an independent clinical event committee (CEC) was established for the central adjudication of potential CV endpoint events. For all Phase III trials, the CEC reviewed all reported trigger events. The criteria for a trigger event to be sent for adjudication were defined in the CEC charter. Among the trigger events defined in the charter, those related to ECG findings are: cardiac fibrillation, ECG electrically inactive area, ECG signs of myocardial ischaemia,

electrocardiogram Q wave abnormal, electrocardiogram QT interval abnormal, electrocardiogram QT prolonged, electrocardiogram repolarisation abnormality, electrocardiogram ST segment abnormal, electrocardiogram ST segment depression, electrocardiogram ST segment elevation, electrocardiogram ST-T segment abnormal, electrocardiogram ST-T segment depression, electrocardiogram ST-T segment elevation, electrocardiogram T wave abnormal, electrocardiogram T wave inversion, electrocardiogram U-wave abnormality, electrocardiogram U-wave biphasic, exercise electrocardiogram abnormal, long QT syndrome, long QT syndrome congenital, torsade de pointes, ventricular arrhythmia, ventricular fibrillation, ventricular flutter, and ventricular tachyarrhythmia.

Adjudication was performed without knowledge of the treatment assignment of any patient; if confirmed by the CEC, patients with trigger events were adjudicated to have CV endpoint events as defined in the CEC charter.

The CEC-confirmed CV endpoint events were summarised in the CV meta-analysis (interim report see (U12-2463)), which included data from completed trials (randomised double-blind Phase II and Phase III trials with a treatment duration of longer than 12 weeks) and on-going trials (randomised double-blind Phase III trials that had pre-planned interim database locks). The primary endpoint of the meta-analysis is the 4-point MACE (a composite of cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization due to unstable angina); the secondary endpoint is the 3-point MACE (cardiovascular death, non-fatal MI, and non-fatal stroke).

The Applicant is also conducting a long-term CV outcome study (1245.25), which is placebo-controlled and includes patients with type 2 diabetes and high CV risk. The primary endpoint was the 3-point MACE; the secondary endpoint was the 4-point MACE. The interim CV data of this trial were included in the interim meta-analysis report, both as part of the meta-analysis and analysed exclusively at the study level. Additionally, silent myocardial infarction is defined as a further secondary endpoint in the 1245.25 study protocol. By the end of the study, all available ECGs will be assessed for silent myocardial infarctions and this secondary endpoint will be reported in the final report.

Furthermore, a Phase I study (1245.16 (U11-1908)) tested the effect of empagliflozin treatment (single dose) on the QT(c) interval in 30 healthy subjects. The randomised, placebo-controlled, double-blind, cross-over study included moxifloxacin as a positive control. The study showed that single oral doses of empagliflozin 25 mg (therapeutic dose) and 200 mg (supra-therapeutic dose) were not associated with a QT(c) interval prolongation and that these doses were safe and well tolerated. Furthermore, 12-lead ECGs were regularly performed in all Phase I studies in the empagliflozin clinical development programme; no clinically relevant findings in the ECGs were observed.

In summary, ECGs data were carefully collected throughout the clinical development programme. Clinically significant ECG findings were properly captured and were recorded as AEs. All CV events, including ECG findings, were adjudicated centrally and independently, and summarized in a CV meta-analysis across the Phase II and III trials. Therefore, the Applicant believes that the analyses of 12-lead ECGs data in the empagliflozin clinical development programme have been adequate; **[Information redacted to protect the integrity of the ongoing cardiovascular outcomes trial (1245.25)]**

Evaluator's comments on sponsor's response:

The sponsor's response is acceptable. The final results of the long-term CV outcome study 1245.25 should be submitted on completion.

12.5. Product Information: indications

Could the sponsors please respond to the comments made in relation to suggested changes in the proposed PI [Indications] for empagliflozin.

The indications should provide details of how empagliflozin should be used in the different T2DM patients (as monotherapy, in combination with other OADs and with basal insulin).

Sponsor's response:

Boehringer Ingelheim proposes the following alternative wording to the proposed indication:

JARDIANCE 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 for patients in 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 CLINICAL TRIALS).

The PI has been amended to include this revised wording.

Evaluator's comments on sponsor's response:

The above proposed indication is acceptable.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of empagliflozin in the proposed usage are unchanged from those identified in section 9.1.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of empagliflozin in the proposed usage are unchanged from those identified in section 9.2.

13.3. Second round assessment of benefit-risk balance

After consideration of the responses to clinical questions, the benefit-risk balance of empagliflozin in the proposed usage is favourable.

14. Second round recommendation regarding authorisation

It is recommended that empagliflozin be approved for the following modified indication proposed by the sponsors in their S31 response:

"JARDIANCE 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 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 CLINICAL TRIALS)."

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605

<http://www.tga.gov.au>