Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	**c20771668-04**
BI Study Number:	1245.171
BI Investigational Product:	Empagliflozin
Title:	A Meta-Analysis of Amputation Risk in empagliflozin studies (1245.25, 1245.110, 1245.121)
Brief lay title	This study combines data from 3 other studies testing empagliflozin in patients with diabetes or with chronic heart failure. The study looks at the numbers of patients who had lower limb amputations
Protocol version identifier:	4.0
Date of last version of protocol:	10 April 2019
PASS:	Yes
EU PAS register number:	Study not yet registered and will be registered following protocol regulatory endorsement
Active substance:	Empagliflozin
Medicinal product:	Jardiance®
Product reference:	Not applicable
Procedure number:	Jardiance: EMEA/H/C/002677/MEA Synjardy: EMEA/H/C/003770/MEA Glyxambi: EMEA/H/C/003833/MEA
Marketing authorisation holder:	Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein Germany
Joint PASS:	No
Research question and objectives:	The primary objective of this exploratory meta-analysis is to evaluate the frequencies, incidence rates, and hazard ratios of lower-limb amputation (LLA) events (primary outcome) and of adverse events (AEs) related to amputation (secondary outcome) in patients treated with empagliflozin compared with placebo in the pooled population of the long-term studies 1245.25, 1245.110, and 1245.121 (SAF-M1), in the pooled population of studies 1245.110 and 1245.121 (SAF-M2), and in each of the 3 studies separately.

	The exploratory objectives are to evaluate the frequencies of recurrent LLA events and of AEs related to recurrent LLA events and to assess the frequencies and incidence rates of patients with AEs related to amputation preceding the amputation for empagliflozin compared with placebo in SAF-M1, SAF-M2, and in each of the 3 studies separately. Further exploratory objectives are to evaluate the frequencies, incidence rates, and hazard ratios of the primary and secondary outcomes by subgroup and of the secondary outcome by grouped PTs for SAF-M1 and SAF-M2 as well as to assess details on LLA events for SAF-M2 in patients treated with empagliflozin compared with placebo.
Countries of study:	Study 1245.25 (completed): multinational trial in 42 countries worldwide Study 1245.110 (ongoing): multinational trial in approx. 22 countries Study 1245.121(ongoing): multinational trial in approx. 15 countries
Author:	[redacted]
MAH contact person:	[redacted]
EU-QPPV:	[redacted]
Signature of EU-QPPV:	The signature of the EU-QPPV is provided electronically
Date:	10 April 2019

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ASA	Acetylsalicylic acid
ATC	Anatomical-Therapeutic-Chemical classification
BI	Boehringer Ingelheim
BMI	Body mass index
CANVAS	Canagliflozin cardiovascular assessment study
CI	Confidence interval
CKD-EPIcr	Chronic Kidney Disease Epidemiology Collaboration Equation (based on serum creatinine value)
CRO	Contract research organisation
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
DBP	Diastolic blood pressure
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EF	Ejection fraction
EMPEROR	**EMP**agliflozin outcom**E** t**R**ial in patients with chr**O**nic hea**R**t failure (study 1245.110, EMPEROR-Preserved, and 1245.121, EMPEROR-Reduced)
GCP	Good clinical practice
HbA_{1c}	Glycated haemoglobin
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
ICH	International Conference on Harmonization
IEC	Independent ethics committee
ITT	Intent to treat
IRB	Institutional review board
KM	Kaplan-Meier
LLA	Lower-limb amputation
LVEF	Left ventricular ejection fraction
MAH	Marketing authorisation holder
MDRD	Modification of diet in renal disease
MedDRA	Medical dictionary for regulatory activities
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
NYHA	New York Heart Association
PASS	Post-authorization safety study
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred term
QD/qd	Once daily
SAE	Serious adverse event
SAF	Safety analysis grouping
SAP	Statistical analysis plan

SBP	Systolic blood pressure
SD	Standard deviation
SGLT2	Sodium-glucose cotransporter 2
SmPC	Summary of product characteristics
SoC	Standard of care
SOP	Standard operating procedure
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

3. RESPONSIBLE PARTIES

This meta-analysis will be conducted by Boehringer Ingelheim (BI). The MAH contact person is:

[redacted]

Tel.: [redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance®			
Name of active ingredient: empagliflozin			
Protocol date: 12 January 2018	**Study number:** 1245.171	**Version/Revision:** 4.0	**Version/Revision date:** 10 April 2019
Title of study:	A Meta-Analysis of Amputation Risk in empagliflozin studies (1245.25, 1245.110, 1245.121)		
Rationale and background:	As an outcome of the Article 20 referral on the risk of lower-limb amputation (LLA) in the EU, Boehringer Ingelheim was requested to conduct a meta-analysis of the 2 chronic heart failure studies (1245.110 and 1245.121) together with the EMPA-REG OUTCOME trial (1245.25) as an additional pharmacovigilance activity. To further investigate the risk for LLA, in ongoing and future long-term clinical trials with empagliflozin (including 1245.110 and 1245.121), LLA and events related to LLA are to be systematically captured. This protocol specifies that a meta-analysis of 3 large and long-term studies (1245.25: completed; 1245.110 and 1245.121: ongoing) will be carried out to evaluate the risk for LLA.		
Research question and objectives:	The primary objective of this exploratory meta-analysis is to evaluate the frequencies, incidence rates, and hazard ratios of lower-limb amputation (LLA) events (primary outcome) and of adverse events (AEs) related to amputation (secondary outcome) in patients treated with empagliflozin compared with placebo in the pooled population of the long-term studies 1245.25, 1245.110, and 1245.121 (SAF-M1), in the pooled population of studies 1245.110 and 1245.121 (SAF-M2), and in each of the 3 studies separately. The exploratory objectives are to evaluate the frequencies of recurrent LLA events and of AEs related to recurrent LLA events and to assess the frequencies and incidence rates of patients with AEs related to amputation preceding the amputation for empagliflozin compared with placebo in SAF-M1, SAF-M2, and in each of the 3 studies separately. Further exploratory objectives are to evaluate the frequencies, incidence rates, and hazard ratios of the primary and secondary outcomes by subgroup and of the secondary outcome by grouped PTs for SAF-M1 and SAF-M2 as well as to assess details on LLA events for SAF-M2 in patients treated with empagliflozin compared with placebo.		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance®			
Name of active ingredient: empagliflozin			
Protocol date: 12 January 2018	**Study number:** 1245.171	**Version/Revision:** 4.0	**Version/Revision date:** 10 April 2019
Study design:	This is a meta-analysis of 3 studies (1245.25, 1245.110, and 1245.121), which are randomised, placebo-controlled, double-blind, parallel-group, and event-driven studies		
Population:	Study 1245.25 (completed): patients with type 2 diabetes mellitus and increased cardiovascular risk Study 1245.110 (ongoing): patients with chronic heart failure with preserved ejection fraction Study 1245.121 (ongoing): patients with chronic heart failure with reduced ejection fraction		
Variables:	LLA events and adverse events (AEs) related to amputation		
Data sources:	Study databases of 1245.25, 1245.110, and 1245.121		
Study size:	This meta-analysis will be based on treated patients. Study 1245.25 (completed): 7020 patients treated with empagliflozin 10 mg, empagliflozin 25 mg, or placebo in an approx. 1:1:1 ratio Study 1245.110 (ongoing): approx. 4126 patients randomised to empagliflozin 10 mg or placebo in a 1:1 ratio Study 1245.121 (ongoing): approx. 2850 patients randomised to empagliflozin 10 mg or placebo in a 1:1 ratio		
Data analysis:	This meta-analysis will be exploratory, using frequency analyses, incidence rates, Kaplan-Meier estimates, and Cox proportional hazards models to compare empagliflozin with placebo		
Milestones:	This meta-analysis will be event driven by the ongoing studies 1245.110 and 1245.121, and the final report is expected in Q3 2022		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
Version 1.0	12 Jan 2018	Not applicable	Not applicable	Initial version
Version 2.0	15 Jun 2018	Title page, Sections 2, 4 to 9, and 13, Annex 1	Update	Comments from EMA's PRAC and update
Version 3.0	07 Dec 2018	Title page, Sections 2, 4, 5, 7 to 9, and 13, Annex 1	Update	Comments from EMA's PRAC and update
Version 4.0	10 Apr 2019	Title page, Sections 4 to 7, 9.3.3, 9.7.2.1, and 9.9	Update	Comments from EMA's PRAC and update

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	Not applicable for the meta-analysis
Start of data collection	Study 1245.25: 26 August 2010 Study 1245.110: 04 April 2017 Study 1245.121: 21 June 2017
End of data collection	Study 1245.25: 21 April 2015 Study 1245.110: ongoing and event driven, database lock expected in Q3 2021 Study 1245.121: ongoing and event driven, database lock expected in Q3 2020
Final report of study results:	Event driven, final report of the meta-analysis expected in Q3 2022

7. RATIONALE AND BACKGROUND

In the canagliflozin cardiovascular outcome studies CANVAS and CANVAS-R, the SGLT2 inhibitor canagliflozin was associated with an increased risk for lower-limb amputation (LLA; including minor and major amputations) versus placebo (HR 1.97, 95% CI 1.41, 2.75) in patients with type 2 diabetes and high cardiovascular risk [R17-3389].

In Europe, the review of canagliflozin was initiated at the request of the European Commission on 15 April 2016, under Article 20 of Regulation (EC) No 726/2004. The review was extended to include the other medicines in the same class, dapagliflozin and empagliflozin, on 7 July 2016. A thorough review of the clinical trial data of empagliflozin took place during that procedure. Since in completed empagliflozin trials (including 1245.25), LLA or related events were not specifically captured on eCRF pages, they were identified via a systematic search of SAE narratives, from events reported as AEs, from those reported as a “medical procedure” under “concomitant therapy”, and from investigator comments describing the AEs. Overall, the clinical trial data did not show an increased risk of LLA or events potentially associated with LLA in patients treated with empagliflozin.

The PRAC concluded that LLA should be added as a new important identified risk for canagliflozin and as an important potential risk for empagliflozin and dapagliflozin. However, the data for empagliflozin (see above) and dapagliflozin have certain limitations. In addition, the PRAC was of the view that it was not possible to identify an underlying cause for the observed imbalances in amputation risk that would be specifically attributable to canagliflozin-containing medicines and not to the other products of the class.

A warning was added to the EU SmPC of the SGLT2 inhibitors reflecting the important identified risk of LLA for canagliflozin and the important potential risk for empagliflozin and dapagliflozin.

To further investigate the risk for LLA in patients treated with empagliflozin, events leading to LLA are defined as AESIs in all ongoing and future clinical trials with treatment duration of >12 weeks (including 1245.110 and 1245.121), and specific information related to an LLA event is to be recorded on dedicated eCRF pages.

As an additional pharmacovigilance activity, BI was requested to conduct a meta-analysis of the 2 chronic heart failure studies (1245.110 and 1245.121) together with the EMPA-REG OUTCOME trial (1245.25).

At the time of writing of this protocol, 4 other clinical studies with empagliflozin are ongoing (1245.148, 1245.167, and 1245.168) or in preparation (1245.137; see Table 7: 1). The detailed data on LLA and related events will be included in the respective clinical trial reports (CTRs).

Table 7: 1 Other clinical studies with empagliflozin

Study	Brief description	Planned randomised patients	Duration of treatment	LLA and related events specifically captured?	Expected database lock
1245.148	Mechanistic cardiac physiology and metabolism in patients with heart failure; phase III	86 (43 to empa 10 mg and 43 to placebo)	12 weeks	No (treatment duration of ≤12 weeks)	Dec 2019
1245.167	Exercise ability in patients with chronic heart failure (preserved ejection fraction); phase III	300 (150 to empa 10 mg and 150 to placebo)	12 weeks	No (treatment duration of ≤12 weeks)	Jan 2020
1245.168	Exercise ability in patients with chronic heart failure (reduced ejection fraction); phase III	300 (150 to empa 10 mg and 150 to placebo)	12 weeks	No (treatment duration of ≤12 weeks)	Jan 2020
1245.137	Renal outcomes in patients with chronic kidney disease; phase III	5000 (2500 to empa 10 mg and 2500 to placebo)	Event driven; up to 4 years	Yes	Jul 2022

Planned as of Feb 2019

8. RESEARCH QUESTION AND OBJECTIVES

The primary objective of this exploratory meta-analysis is to evaluate the frequencies, incidence rates, and hazard ratios of lower-limb amputation (LLA) events (primary outcome) and of AEs related to amputation (secondary outcome) in patients treated with empagliflozin compared with placebo in the pooled population of the long-term studies 1245.25, 1245.110, and 1245.121 (SAF-M1), in the pooled population of studies 1245.110 and 1245.121 (SAF-M2), and in each of the 3 studies separately.

The exploratory objectives are to evaluate the frequencies of recurrent LLA events and of AEs related to recurrent LLA events and to assess the frequencies and incidence rates of patients with AEs related to amputation preceding the amputation for empagliflozin compared with placebo in SAF-M1, SAF-M2, and in each of the 3 studies separately. Further exploratory objectives are to evaluate the frequencies, incidence rates, and hazard ratios of the primary and secondary outcomes by subgroup and of the secondary outcome by grouped PTs for SAF-M1 and SAF-M2 as well as to assess details on LLA events for SAF-M2 in patients treated with empagliflozin compared with placebo.

9. RESEARCH METHODS

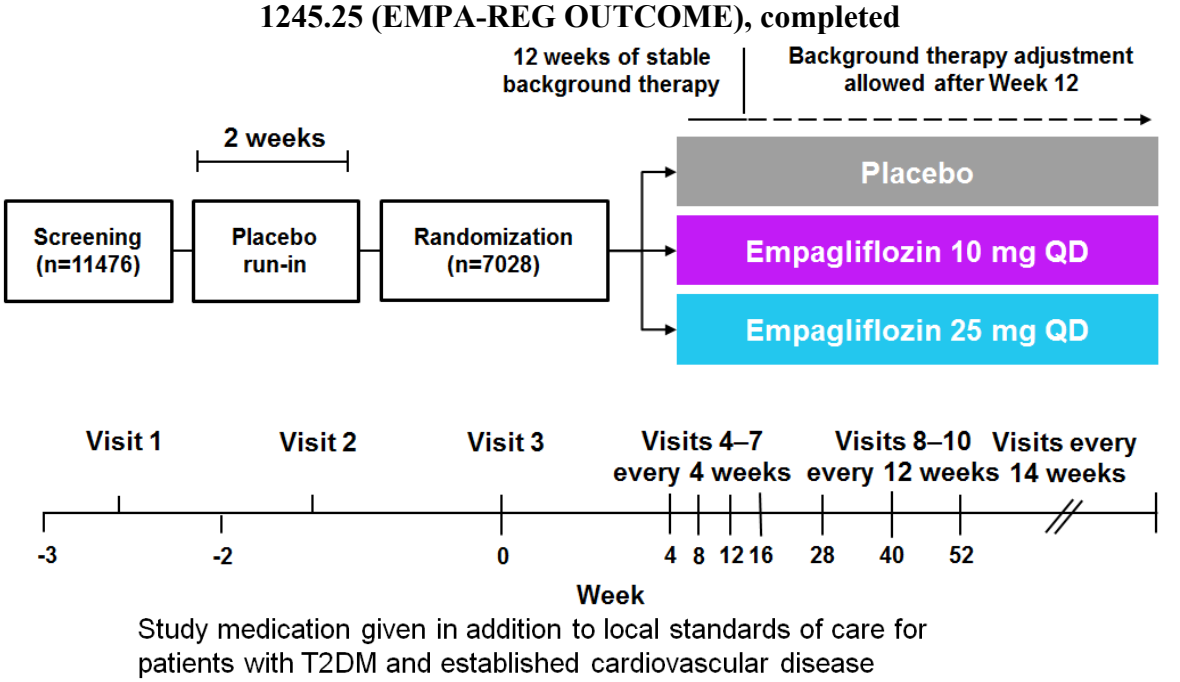
9.1 STUDY DESIGN

This is a meta-analysis of 3 studies (1245.25, 1245.110, and 1245.121), which are randomised, placebo-controlled, double-blind, parallel-group, and event-driven studies. A meta-analysis of the 3 studies is considered appropriate to explore the risk for LLA events due to the large study size (approx. 14 000 patients in total in the 3 studies) and long-term exposure (median treatment exposure was 2.6 years in 1245.25; treatment exposure of up to 3 years are expected in ongoing studies 1245.110 and 1245.121). Data from individual patients from the 3 studies, not the result estimates of the 3 studies, will be pooled in the meta-analysis.

Study 1245.25 has been completed and the CTR is available [c02695839]. The study title is "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".

Study 1245.110 and 1245.121 are ongoing and the CTPs are available [c03946327, c09098452]. The study title of 1245.110 is "A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction". The study title of 1245.121 is "A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with reduced ejection fraction".

The overall designs of the studies are shown in Figure 9.1: 1.



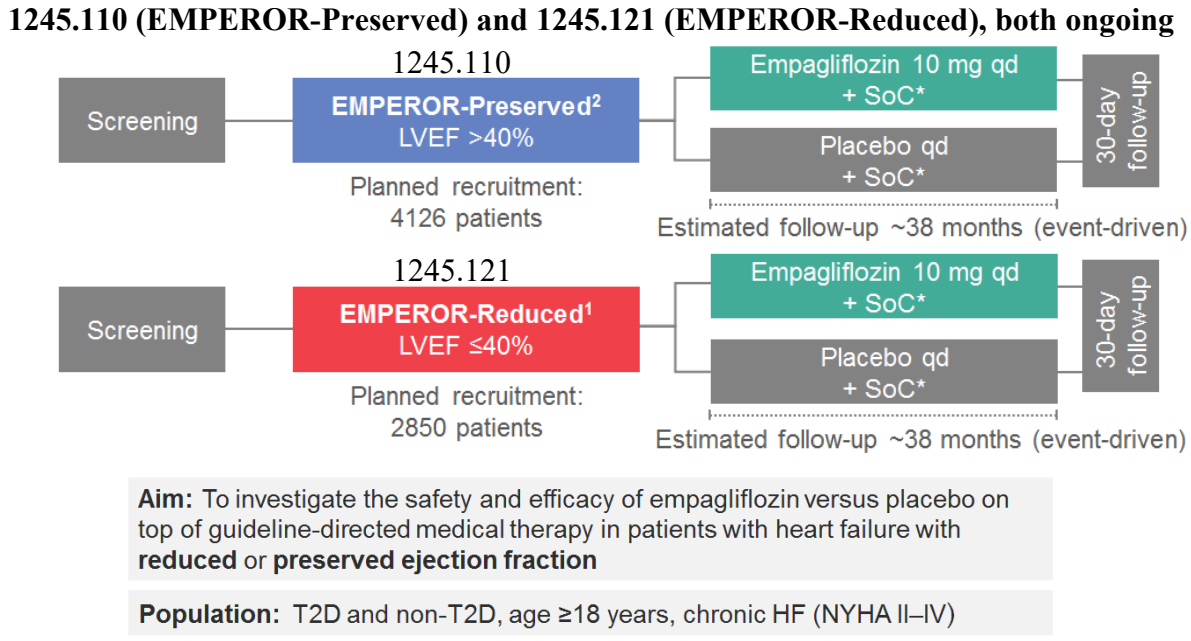


Figure 9.1: 1 Design of studies 1245.25, 1245.110, and 1245.121

QD/qd, once daily; T2DM, type 2 diabetes mellitus; LVEF, left ventricular ejection fraction; SoC, standard of care
* Guideline-directed therapies

This meta-analysis will be exploratory. All analyses will be based on the treated set, which includes all patients treated with at least 1 dose of study medication (as randomised). Due to the different patient eligibility criteria (see Section 9.2.2) and methods in capturing LLA and related events (see Section 9.3.2.1), two analysis groupings will be used in the meta-analysis. SAF-M1 includes all 3 studies while SAF-M2 includes studies 1245.110 and 1245.121. All

analyses will be carried out separately for each SAF and for each study, unless otherwise indicated in Section 9.7.1 and 9.7.2.

The primary outcomes are LLA events (see Section 9.3.2.1).

LLA events will be analysed using frequency analyses, incidence rates, Kaplan-Meier estimates, and Cox proportional hazards models to compare empagliflozin with placebo. For SAF-M2, where additional information on LLA events are collected on the eCRF, the reasons leading to LLA, the number of LLA episodes, level of LLA, etc., will be summarised.

As the primary analysis, the "on-treatment" approach will include events with an onset date within the treatment period (from first to last dose of study medication plus 7 days to account for the residual drug effect). An ITT approach will be used as a secondary analysis, which includes all events during the observation period after starting randomised treatment, regardless if the patient was taking study medication or not when the event occurred.

Since deaths are competing events to amputations, a competing risk analysis considering all-cause death and a cumulative incidence analysis will be carried out.

Subgroups by demographics, baseline medical conditions, and baseline therapies will be analysed for LLA events for SAF-M1 and SAF-M2 (see Section 9.3.3 for subgroup variables).

The secondary outcomes are AEs related to amputation (see Section 9.3.2.2).

AEs related to amputation will be summarised using frequency analyses, incidence rates, and time to onset analyses for all patients. Additionally, AEs related to amputation preceding the amputation will be summarised for patients with amputation; AEs with onset after the amputation will not be considered in the analysis of this sub-population. Subgroup analyses for SAF-M1 and SAF-M2 will be carried out.

Patient disposition, demographics, baseline conditions, exposure, and concomitant diagnoses and therapies will also be summarised.

9.2 SETTING

9.2.1 Study sites

Study 1245.25 was conducted in 607 centres in 42 countries worldwide (Argentina, Australia, Austria, Belgium, Brazil, Canada, Columbia, Croatia, Czech Republic, Denmark, Estonia, France, Georgia, Greece, Hong Kong, Hungary, India, Indonesia, Israel, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, New Zealand, Norway, Peru, Philippines, Poland, Portugal, Romania, Russia, Singapore, South Africa, Spain, Sri Lanka, Taiwan, Thailand, Ukraine, United Kingdom, and United States). Patient disposition by country and centre is detailed in CTR 1245.25 [c02695839, Appendix 16.1.9.2, Tables 1.1 and 1.2].

It is planned to randomise approx. 4126 patients in 500 centres from 22 countries in study 1245.110 [c03946327, Section 3.3], and approx. 2850 patients in 350 centres from

15 countries in study 1245.121 [c09098452, Section 3.3]. Recruitments of these 2 studies are ongoing at the time of writing of this protocol.

9.2.2 Study population

9.2.2.1 Study 1245.25

Study 1245.25 included patients with type 2 diabetes mellitus and increased cardiovascular risk. Detailed eligibility criteria can be found in CTR 1245.25 [c02695839, Section 9.3] and the key criteria are summarised below.

The key inclusion criteria were:

- Age ≥18 years, diagnosis of T2DM
- Drug-naïve or pretreated with any background therapy
- HbA_{1c} criteria
  - Patients who were drug-naïve: HbA_{1c} of 7 to 10%
  - Patients with background therapy: HbA_{1c} of 7 to 9%
- BMI ≤45 kg/m^2
- With high cardiovascular risk, defined as ≥1 of the following criteria
  - History of myocardial infarction (>2 months prior to enrollment)
  - Multi-vessel coronary artery disease: ≥2 major vessels or left main coronary artery
  - Single-vessel coronary artery disease with no scheduled revascularization/previously unsuccessful revascularization
  - Hospital discharge due to unstable angina pectoris (>2 months prior to enrollment)
  - History of stroke (>2 months prior to enrollment)
  - Peripheral occlusive arterial disease

The key exclusion criteria were:

- Uncontrolled hyperglycemia: fasting plasma glucose >240 mg/dl
- Severe renal impairment defined as eGFR <30 ml/min by MDRD formula
- Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial, or participating in another trial (involving an investigational drug and/or follow-up)

9.2.2.2 Studies 1245.110 and 1245.121

Study 1245.110 will include patients with chronic heart failure with preserved ejection fraction. Study 1245.121 will include patients with chronic heart failure with reduced ejection fraction. Detailed eligibility criteria can be found in CTPs [c03946327, c09098452, Section 3.3] and the key criteria are summarised below.

The key inclusion criteria are:

- Age ≥18 years (Japan, age ≥20 years)
- Chronic HF NYHA class II to IV
- Ejection fraction (EF) and NT-proBNP criteria

  - 1245.110: preserved EF (LVEF >40%) and elevated NT-proBNP (>300 pg/ml; >900 pg/ml for patients with atrial fibrillation)
  - 1245.121: reduced EF (LVEF ≤40%) and elevated NT-proBNP (≥2500 pg/ml if EF 36 to 40%, ≥1000 pg/ml if EF 31 to 35%, ≥600 pg/ml if EF ≤30% or if EF ≤40% with documented hospitalisation for HF within 12 months prior to screening; for patients with atrial fibrillation, double the level of NT-proBNP is applied for each EF category)
- 1245.110 only: structural heart disease within 6 months or documented hospitalisation for HF within 12 months prior to screening
- 1245.121 only: stable dose of medical therapy for HF consistent with local and international cardiology guidelines

The key exclusion criteria are:

- Myocardial infarction, coronary artery bypass graft surgery or other major cardiovascular surgery, stroke or transient ischaemic attack ≤90 days before screening
- Heart transplant recipient, or listed for heart transplant
- Acute decompensated HF
- SBP ≥180 mmHg at randomisation
- Symptomatic hypotension and/or SBP <100 mmHg at screening or randomisation
- Impaired renal function defined as eGFR $(CKD\text{-}EPI)_{cr}$ <20 ml/min/1.73 m^2 or requiring dialysis at screening

9.2.3 Study visits

9.2.3.1 Study 1245.25

There was a 2-week placebo run-in period between screening and randomisation visits. During the randomised treatment period, visits were to occur every 4 weeks in the first 4 months, every 12 weeks thereafter until the first year, every 14 months after the first year (see Figure 9.1: 1). There was to be a follow-up visit 30 days after treatment stop. Details can be found in CTR 1245.25 [c02695839, Table 9.5.1: 1].

9.2.3.2 Studies 1245.110 and 1245.121

Randomisation (Visit 2) follows screening (Visit 1) with no placebo run-in. During the randomised treatment period, visits are planned at Week 4, 12, 32, 52, and every 24 weeks thereafter. Starting at Week 22, phone calls are planned between the on-site visits to monitor safety. There will be a follow-up visit 30 days after treatment stop. Details can be found in the flow charts in CTPs [c03946327, c09098452].

9.2.4 Study discontinuation

Study discontinuation is not applicable for this meta-analysis. Study 1245.25 has been completed. See CTPs 1245.110 and 1245.121 for rules on study discontinuation [c03946327, c09098452, Section 3.3.4].

9.3 VARIABLES

There are no confirmatory endpoints in this study. All variables in this meta-analysis will be analysed in an exploratory manner.

9.3.1 Exposures

Exposure is defined as the time exposed to study medication (on-treatment approach; calculated as the difference between the date of last intake of study medication and the date of the first administration of the study medication plus 1 day) or the time under observation after starting randomised treatment (ITT approach; calculated as the difference between the date of last follow up and the date of the first administration of the study medication plus 1 day; also see SAP [c16853237, Section 4.3.2.1]).

For incidence rate, the derivation of time at risk is as follows:

Patients with event:
time at risk in days = date of start of first event – treatment start date + 1

Patients without event:
time at risk in days = last date on treatment + 7 days* (or last date in study for secondary analysis based on ITT approach) – treatment start date + 1

* This is according to the definition of the residual effect period of 7 days as defined in the trial protocols for safety analyses for treatment-emergent events (also see SAP [c16853237, Section 4.3].

9.3.2 Outcomes

The objective of the meta-analysis is to evaluate the risk for LLA in an exploratory manner.

All outcome data, including recurrent events, are collected over the full trial period even after the first amputation event.

9.3.2.1 Primary outcomes

The primary outcomes are LLA events.

In studies 1245.110 and 1245.121, events leading to LLA are defined as AESIs in the protocols (see below). Specific information related to an LLA event (as a therapy) is to be recorded on dedicated eCRF pages. The specific information include: medical history of LLA, the date of each LLA event, the level (location) of the LLA event, and the medical reason leading to the LLA event.

A major LLA represents amputation above the ankle (below knee, knee, above knee). A minor LLA represents amputation at the ankle and below (ankle, tarsometatarsal, transmetatarsal and toes).

In study 1245.25, LLAs were not pre-specified in the protocol or specifically captured on eCRF pages, they were identified via a systematic search of SAE narratives, from events

reported as AEs, from those reported as a "medical procedure" under "concomitant therapy", and from investigator comments describing the AEs. For details see SAP [c16853237, Appendix 6.2].

Refer to Sections 9.7.1 and 9.7.2 for the planned analyses.

Definition and reporting of LLA events in the trial protocols (also see Section 11.1):

In the protocols of the ongoing studies 1245.110 and 1245.121, events leading to LLA are defined as AESIs and include any event leading to a lower-limb procedure of amputation, auto-amputation, or disarticulation. Amputation is defined as a resection of a limb through a bone. Auto-amputation is a spontaneous separation of non-viable portion of the lower limb. Disarticulation is a resection of a limb through a joint. The following procedures are not included in the definition of events leading to LLA: debridement (removal of callus or dead tissue), procedures on a stump (such as stump revision, drainage of an abscess, wound revision, etc.), and other procedures (such as nail resection or removal) without a concomitant resection of a limb (amputation or disarticulation). The definitions are consistent with the 2015 guidance from the [redacted] (website: [redacted]).

Each lower-limb amputation, disarticulation, or auto-amputation should be reported separately. The SAE report for this type of AESI is to include the date of the procedure, the level of amputation or disarticulation, the medical condition(s) leading to the procedure, and if the patient had any of the known risk factor(s) for lower-limb amputation.

In the completed study 1245.25, events related to LLA were not defined as AESIs in the protocol, but were identified via a systematic search of the study database (see above).

9.3.2.2 Secondary outcomes

The secondary outcomes are AEs related to amputation.

A search with a pre-defined list of MedDRA PTs will be performed to identify all AEs related to amputation. These AEs include vascular disorders, diabetic-foot-related events, wound/infections, nervous system disorders, and volume depletion events. For the list of preferred terms for preceding/related events see SAP [c16853237, Appendix 6.1]. The occurrences of these AEs do not necessarily lead to amputation procedures.

Refer to Sections 9.7.1 and 9.7.2 for the planned analyses.

[redacted]

9.3.3 Covariates

Covariates such as demographics (sex, race, geographical region, age), baseline medical conditions (renal function, hypertension, diabetes, peripheral arterial occlusive disease, diabetic foot, coronary artery disease, diabetic neuropathy, diabetic retinopathy, history of lower-limb amputation, osteomyelitis, gangrene, nephropathy, HF at baseline, smoking

status; for patients with diabetes: HbA_{1c}), and baseline therapies (diuretics, loop diuretics, anticoagulants, anti-platelets; for patients with diabetes: insulin, metformin, sulphonyl urea) will be investigated in subgroup analyses of the LLA events and AEs related to amputation.

In addition, further demographic and baseline variables will be descriptively summarised (i.e. ethnicity, BMI, weight, time since diagnosis of diabetes, blood pressure).

All demographic and baseline variables with categories are shown in Table 9.3.3: 1 (also see the SAP [c16853237, Table 4.3: 2]).

Table 9.3.3: 1 Demographic and baseline variables with categories

Variable	**Demographics/Baseline characteristics Categories**
Sex	Male Female
Race	White Black/African Asian Hawaiian/Pacific Islander Amer. Ind./ Alaska Nat.
Ethnicity	Hispanic/Latino Not Hispanic/Latino
Geographical region[&]	Europe Africa/Middle East North America Latin America Asia Other (if any)
Age (years) categories	Version 1 <65 65 to <75 75 to <85 ≥85 Version 2 <65 65 to <75 ≥75 (Decision will be taken on which version to use based on the size of the elderly population group ≥85 years of age)
BMI (kg/m^2)	<25 25 to <30 30 to <35 ≥35
Weight (kg)	≤70 >70 to ≤80 >80 to ≤90 >90

To be continued

Table 9.3.3: 1 Demographic and baseline variables with categories (continued)

Variable	**Demographics/Baseline characteristics** **Categories**
Smoking status	Never smoked Ex-smoker Currently smokes
Time since diagnosis of diabetes	Version 1 for SAF-M1 pool: ≤1 year >1 year to 5 years >5 years to 10 years >10 years Not applicable (as no diabetes diagnosed) Version 2 for SAF-M2 pool: ≤1 year >1 year to 5 years >5 years to 10 years >10 years to 20 years >20 years Not applicable (as no diabetes diagnosed)
Baseline HbA_{1c} (%)	Version 1 Version 2 <8.5 <8 ≥8.5 8 to <9 (for diabetic patients only)
Blood pressure (mmHg)	≥130/80 <130/80 (controlled)*
Renal function (eGFR) (CKD-Epi) ($mL/min/1.73m^2$)	<30 30 to <45 45 to <60 60 to <90 ≥90
Insulin use	Yes/No
Metformin use	Yes/No
Sulphonyl urea use	Yes/No
Loop diuretics	Yes/No
Diuretics	Yes/No
Anticoagulant use	Yes/No
Anti-platelet use	Yes/No
Hypertension	Yes/No
Diabetes	T1DM T2DM No Diabetes
Peripheral arterial occlusive disease	Yes/No
Diabetic foot at baseline	Yes/No
Coronary artery disease	Yes/No

To be continued

Table 9.3.3: 1 Demographic and baseline variables with categories (continued)

Variable	**Demographics/Baseline characteristics Categories**
Diabetic neuropathy	Yes/No
Diabetic retinopathy	Yes/No
History of lower limb amputation	Yes/No
Osteomyelitis	Yes/No
Gangrene	Yes/No
Nephropathy	Yes/No
Heart failure at baseline	Yes/No

* Patients must have both SBP below 130 and DBP below 80 to be considered controlled.
& Australia included in North America and South Africa included in Africa/Middle East.

All subgroup variables with categories are shown in Table 9.3.3: 2 (also see the SAP [c16853237, Table 4.3: 3].

Table 9.3.3: 2 Subgroup variables and categories

Variable	**Subgroup Analysis Categories**
Sex	Male Female
Race	White Black/African Asian Other
Geographical region	Europe Africa/Middle East North America Latin America Asia Other (if any)
Age (years) categories	Version 1 <65 65 to <75 75 to <85 ≥85 or Version 2 <65 65 to <75 ≥75 In case of low number of events for patients ≥85
Renal function (eGFR) (CKD-Epi) ($mL/min/1.73m^2$)	<30 30 to < 45 45 to <60 60 to <90 ≥90
Insulin use	Yes/No (Diabetic patients only)
Metformin use	Yes/No (Diabetic patients only)
Sulphonyl ureas use	Yes/No (Diabetic patients only)
Loop diuretics	Yes/No
Baseline HbA_{1c} (%)	<8.0, ≥8.0
Baseline HbA_{1c} (%)	<8.5, ≥8.5
Anticoagulant use	Yes/No
Anti-platelets use	Yes/No
Diuretics	Yes/No
Hypertension	Yes/No
Diabetes	T1DM T2DM No Diabetes (Diabetes yes/no if number of events too low)

To be continued

Table 9.3.3: 2 Subgroup variables and categories (continued)

Variable	Subgroup Analysis Categories
Peripheral arterial occlusive disease	Yes/No
Diabetic foot at baseline	Yes/No (Diabetic patients only)
Coronary artery disease	Yes/No
Diabetic neuropathy	Yes/No
Diabetic retinopathy	Yes/No (Diabetic patients only)
History of lower limb amputation	Yes/No
Osteomyelitis	Yes/No
Gangrene	Yes/No
Nephropathy	Yes/No
HF at baseline	Yes/No
Smoking status	current smoker ex-smoker never smoked

9.4 DATA SOURCES

The data source for this meta-analysis is the study databases for 1245.25, 1245.110, and 1245.121. All 3 studies are large, long-term, randomised, placebo-controlled, double-blind, parallel-group, and event-driven. Data from individual patients from the 3 studies, not the result estimates of the studies, will be pooled in the meta-analysis. See Section 9.1 for more details.

9.5 STUDY SIZE

This meta-analysis will be based on patients treated with at least 1 dose of study medication ("treated set") in the 3 studies. Patients are assigned to treatment groups according to randomisation.

Study 1245.25 included 7020 patients treated with empagliflozin 10 mg (N = 2345), empagliflozin 25 mg (N = 2342), or placebo (N = 2333).

Study 1245.110 will randomise approx. 4126 patients to empagliflozin 10 mg or placebo in a 1:1 ratio. Study 1245.121 will randomise approx. 2850 patients to empagliflozin 10 mg or placebo in a 1:1 ratio. Almost all randomised patients are expected to be treated.

9.6 DATA MANAGEMENT

The study databases for 1245.25, 1245.110, and 1245.121 will be used. The data is collected and managed according to the respective clinical trial protocols. SAS data sets from

individual trials will be combined for the meta-analysis based on individual patient data. All statistical analyses will be implemented using the statistical software SAS® 9.4 or higher.

9.7 DATA ANALYSIS

This meta-analysis will be exploratory. For the primary outcome of LLA events and for the secondary outcome of AEs related to amputation, a Cox proportional hazards regression model for modelling the time to first event will be used, including the factors study, diabetes mellitus status (T1DM, T2DM, no diabetes), and treatment (all empa vs. placebo). Study is assumed as fixed effect in this meta-analysis. For treatment comparison, hazard ratios with corresponding 95% CIs as well as corresponding p-values will be presented (see the SAP [c16853237, Section 4.3]).

All analyses will be based on the treated set, which includes all patients treated with at least 1 dose of study medication (as randomised). Due to the different patient eligibility criteria (see Section 9.2.2) and methods in capturing LLA and related events (see Section 9.3.2.1), two analysis groupings will be used in the meta-analysis. SAF-M1 includes all 3 studies while SAF-M2 includes studies 1245.110 and 1245.121 (Table 9.7: 1; also see the SAP [c16853237, Table 3.1.2: 1]). All analyses will be carried out separately for each SAF and for each study, unless otherwise indicated in Table 9.7: 2.

Table 9.7: 1 Overview of analysis groupings and individual studies

Grouping	Description	Studies	Purpose
SAF-M1	All studies	1245.25 1245.110 1245.121	Frequencies, incidence rates and time to onset of amputation events Frequencies, incidence rates and time to onset for related events based on selected adverse events
SAF-M2	Chronic heart failure studies	1245.110 1245.121	Frequencies, incidence rates and time to onset of amputation events Frequencies, incidence rates and time to onset for related events based on selected adverse events Details on lower limb amputations

The results of the meta-analysis will be presented mainly in tabular form, and when appropriate, in graphical form.

Tabulations of frequencies for categorical data will include all different categories and display the number of observations and the percentage (%) in a category relative to the respective treatment group (placebo, empa 10 mg, 25 mg, all empa). The category "missing" will be displayed if there are actually missing values. Percentages will be based on all patients in the respective patient set whether they have non-missing values or not.

For continuous variables the set of summary statistics in tables is: N (number of patients with non-missing values) / Mean / SD / Min / Q1 (lower quartile) / Median / Q3 (upper quartile) / Max.

For frequency analyses based on pooled data the estimates for the relative frequency is defined as follows:

$$\hat{p}_j = \frac{\sum_{i=1}^{k} w_{ji} \cdot \hat{p}_{ji}}{\sum_{i=1}^{k} w_{ji}}, \text{ where}$$

p_{ji} relative frequency in treatment group j and study (i=1,.., k)

$w_{ji} = \frac{n_{ji}}{\sum_i n_{ji}}$ denotes the weight of study *i, i*=1,...,*k* in treatment group j

n_{ji} number of patients in treatment group j and study i (i=1, ..k)

The frequency (%) of AEs does not take into account the duration of treatment. This is particularly important when studies with different treatment durations are pooled for analysis. In this case incidence rates may provide more accurate comparisons among groups.

Incidence rate is the number of new cases of an event occurring in a specified time period divided by the cumulative time at risk (see Section 9.3.1 for the derivation).

The incidence rate per 100 patient-years is calculated as follows:

Incidence rate [1/100 pt-yrs] = 100 * number of patients with event / sum of time at risk over all patients [years].

The estimate for a pooled incidence rate in treatment group j is defined as follows:

$$\hat{IR}_j = \frac{\sum_{i=1}^{k} w_{ji} \cdot \hat{IR}_{ji}}{\sum_{i=1}^{k} w_{ji}}, \text{ where}$$

IR_{ji} Incidence rate in treatment group j and study (i=1,.., k)

$w_{ji} = \frac{t_{ji}}{\sum_i t_{ji}}$ denotes the weight of study *i, i*=1,...,*k* in treatment group j

$w_{ji} = \frac{t_{ji}}{\sum_i t_{ji}}$ denotes the weight of study *i, i*=1,...,*k* in treatment group j

t_{ji} sum of time at risk in treatment group j and study i (i=1, ..k)

Due to the different study designs, not all analyses will be performed for each of the 2 pools. Table 9.7: 2 indicates which safety analyses will be performed for which pool and the individual studies (also see the SAP [c16853237, Table 4.3: 1]).

Table 9.7: 2 Overview of analyses that will be performed for the different study poolings and for the individual study

	Poolings and individual study				
Endpoint	**SAF-M1**	**SAF-M2**	**Study 1245.25**	**Study 1245.110**	**Study 1245.121**
Disposition, demographics, exposure	Yes	Yes	Yes	Yes	Yes
Concomitant diagnoses and therapies	Yes	Yes	Yes	Yes	Yes
Lower limb amputation					
Frequencies	Yes	Yes	Yes	Yes	Yes
Incidence rates	Yes	Yes	Yes	Yes	Yes
Time to onset analyses	Yes	Yes	Yes	Yes	Yes
Time to onset analyses with competing risk	Yes	-	-	-	-
Sensitivity analyses (heterogeneity analyses, forest plot)	Yes	Yes	-	-	-
Adverse events related to amputations (definition based on list of PTs)					
All patients					
Frequencies	Yes	Yes	Yes	Yes	Yes
Incidence rates	Yes	Yes	Yes	Yes	Yes
Time to onset analyses	Yes	Yes	Yes	Yes	Yes
Patients with amputations only, i.e. preceding events					
Frequencies	Yes	Yes	Yes	Yes	Yes
Incidence rates	Yes	Yes	Yes	Yes	Yes
Time to onset analyses (KM only)	Yes	Yes	Yes	Yes	Yes
Lower limb amputation events occurring after the first LLA event					
Descriptive Statistics (Frequency tables with absolute and relative frequencies)	Yes	Yes	Yes	Yes	Yes
Adverse Events related to amputations occurring after the first LLA event					
Descriptive Statistics (Frequency tables with absolute and relative frequencies)	Yes	Yes	Yes	Yes	Yes

9.7.1 Main analysis

LLA events (primary outcome) and AEs related to amputation (secondary outcome) will be analysed using frequency analyses, incidence rates, Kaplan-Meier estimates, and Cox proportional hazards models to compare empagliflozin with placebo in the pooled populations of SAF-M1, SAF-M2, and for each of the 3 studies (1245.25, 1245.110, and 1245.121) separately. Kaplan-Meier analyses (cumulative incidence functions) for time to first event will be provided by treatment and stratified by study.

Cox proportional hazards models will include the factors study, diabetes mellitus status (T1DM, T2DM, no diabetes), and treatment (all empa vs placebo).

As the primary analysis, the "on-treatment" approach will include events with an onset date within the treatment period (from first to last dose of study medication plus 7 days to account for the residual drug effect).

9.7.2 Further analysis

9.7.2.1 Further analyses of LLA events, AEs related to amputation, and details on LLA events

LLA events
Subgroups by demographics, baseline medical conditions, and baseline therapies will be analysed for LLA events for SAF-M1 and SAF-M2 (see Section 9.3.3 for subgroup variables and categorisation and Section 9.7.2.3).

An ITT approach will be used as a secondary analysis, which includes all events during the observation period after starting randomised treatment, regardless if the patient was taking study medication or not when the event occurred.

Since deaths are competing events to amputations, a competing risk analysis considering all-cause mortality and a cumulative incidence analysis will be carried out. The regression model will include the following co-variables: study, diabetes mellitus status (T1DM, T2DM, no diabetes), and treatment (all empa vs. placebo). Cumulative incidence for amputations and the competing events of deaths will also be displayed graphically.

The number of LLA episodes per patient will be summarised in a frequency table.

A listing of patients with recurrent events will be provided. Descriptive statistics (frequency tables with absolute and relative frequencies) will be provided to summarise all amputation events occurring after the first LLA event.

AEs related to amputation
Subgroup analyses for SAF-M1 and SAF-M2 will be carried out.

For AEs related to amputation, analyses for different grouped events will be performed (see the SAP [c16853237, Appendix 6.1]). Cumulative proportions of patients and the number of patients at risk will be provided. In addition, Cox regression analyses will be performed for vascular AEs, diabetic-foot-related AEs, wound/infection, nervous system disorders, and

volume depletion events if the sample size is statistically sufficient, i.e. at least 14 patients with events in total over the 2 treatment groups have been reported.

An ITT approach will be used as a secondary analysis, which includes all events during the observation period after starting randomised treatment, regardless if the patient was taking study medication or not when the event occurred.

A listing of AEs with onset during any treatment other than the randomised treatment will be provided.

Additionally, AEs related to amputation preceding the amputation will be summarised for patients with amputation; AEs with onset after the amputation will not be considered in the analysis of this sub-population.

AEs related to amputations occurring after the first amputation event will be summarised using descriptive statistics (frequency tables with absolute and relative frequencies).

Details on LLA events
For SAF-M2, where additional information on LLA events are collected on the eCRF, the following analyses will be performed:

- Frequencies of reasons leading to the LLA
- Number of LLA episodes per patient
- Number of LLA episodes per patient excluding those due to trauma and tumor
- Level of amputation for the first LLA, excluding amputation due to trauma and tumor (highest)
- Number of patients having a major LLA as first LLA
- Number of patients with any major LLA
- Number of patients having a knee or above knee LLA as first LLA
- Number of patients with any knee or above knee LLA

9.7.2.2 Analysis of AEs

AEs will be coded using the most recent version of the MedDRA coding dictionary. All analyses of AEs will be based on the number of patients with AEs (not the number of AEs). For this purpose, AE data will be combined in a 2-step procedure into AE records. In a first step, AE occurrences, i.e. AE entries on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence
- Treatment did not change between the onset of the occurrences or treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

In a second step, AE episodes will be condensed into AE records provided that the episodes were reported with the same term on the respective MedDRA level and that the episodes are assigned to the same treatment. Internal BI guidelines will be followed for the handling of AE data. Frequency tables of patients with AEs by system organ class and preferred terms will be provided and sorted by frequency (within system organ class).

The primary analysis for AEs, the "on-treatment" approach, will be based on the concept of treatment-emergent AEs. That means all AEs with an onset date between first drug intake (post run-in) until 7 days after last drug intake (or time to last follow-up for analyses up to last follow-up) will be assigned to the randomised study drug (1245.25) or first study drug taken (1245.110, 1245.121).

An ITT approach will be used as a secondary analysis. All AEs with an onset date between first drug intake (post run-in) until time to last follow-up will be assigned to the randomised study drug (1245.25) or first study drug taken (1245.110, 1245.121).

9.7.2.3 Subgroup analysis

All subgroup variables with categories are shown in Table 9.3.3: 2. Subgroup analyses for SAF-M1 and SAF-M2 will be provided for frequency and incidence rate tables, KM analyses, and for Cox models. Subgroup analyses will be performed for LLA events and AEs related to amputation.

For Cox models for time to first event analysis, the following factors will be included in the model: study, treatment, <subgroup>, treatment-by-<subgroup> interaction.

For time-to-event endpoints, at a minimum, a count of events will be provided, and if sample size is statistically sufficient, i.e. 14 patients with events in total over the 2 treatment groups for each subgroup category, a statistical analysis using the Cox regression model will be performed. If the affected category is too small (<14 patients with events), the category may be only described descriptively and no inferential analysis is performed, or the category may be pooled with another category if this is justifiable from a scientific perspective.

9.7.2.4 Other analysis

Patient disposition, demographics, baseline conditions, exposure, and concomitant diagnoses and therapies will also be summarised based on the treated set. The disposition will show patients randomised and completed, patients who withdrew after randomisation and categorised reason for withdrawal. In addition, a table summarising patients with diabetes and the type of diabetes will be shown. Demographic and baseline variables with categories are shown in Table 9.3.3: 1. Concomitant diagnoses will be summarised by system organ class and preferred term. Relevant diabetic medical history by treatment group will also be presented. Concomitant medications will be summarised by ATC3 and preferred name, for medications taken at baseline and those initiated on randomised treatment. Antidiabetic, antihypertensive, ASA, and lipid-lowering medications will also be summarised.

9.7.3 Handling of missing data

9.7.3.1 Missing amputation date

In studies 1245.110 and 1245.121, the date and other details on LLA events are to be captured on eCRF pages; therefore, no missing dates are expected. However, LLA events were not specifically captured via eCRF in study 1245.25.

For any missing date of the LLA event, the date is imputed as the date of admission to the hospital or the date of the diagnosis of the event triggering the amputation, whichever is later. In case the date information is incomplete (e.g. only year and month are reported), the mid-point of the possible interval will be used according to BI standard imputation rules for concomitant therapies.

For LLA event, a sensitivity analysis will be conducted for incidence rate calculation in SAF-M1 and SAF-M2 excluding all patients with amputations with missing onset dates. This analysis will only be performed if >10% of onset dates are missing.

9.7.3.2 Missing AE onset date

Adverse events with missing or incomplete onset dates will be imputed according to a BI standard algorithm, which is based on a conservative approach. In short, this approach ensures that all AEs with missing dates will be counted as “on-treatment” unless there is well-documented data showing otherwise. For the calculation of time to event, the earliest possible date on-treatment (i.e. date of start of treatment) will be used to impute missing onset dates. Partially missing onset dates will also be imputed with the corresponding earliest possible date (e.g. if only the year and month are available, use the first day of the month or the date of start of treatment, whichever is later).

9.8 QUALITY CONTROL

Standard operating procedures are used to guide the conduct of the studies. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing statistical analysis plans, and requirements for senior scientific review.

9.9 LIMITATIONS OF THE RESEARCH METHODS

This will be a meta-analysis of 3 studies with heterogeneous patient populations. Patients with type 2 diabetes mellitus and increased cardiovascular risk (1245.25) will be pooled together with patients with chronic heart failure with preserved (1245.110) or reduced (1245.121) ejection fraction (see Section 9.2.2 for more detailed eligibility criteria) in SAF-M1. In general, some heterogeneity between the studies can be expected due to the different populations involved in the trials to be pooled. The degree of heterogeneity of the treatment effect between studies will be assessed statistically and clinically/visually. For time-to-event outcomes, visual inspection of heterogeneity includes a forest plot of the individual study hazard ratios, alongside the corresponding estimate from the individual patient data meta-analysis in SAF-M1 and SAF-M2. For statistical assessment of heterogeneity, a Cox model will be provided including in addition the treatment-by-study interaction term. The p-value of

the interaction term from the Cox model in SAF-M1 and SAF-M2 will be used as a statistical measure for heterogeneity. For binary outcomes (frequencies and incidence rates of LLAs and AEs related to amputation), visual inspection of heterogeneity will be performed using forest plots. These will display the frequencies/incidence rates per treatment arm within each study, alongside the corresponding estimate from the pooled analysis in SAF-M1 and SAF-M2. For statistical assessment of heterogeneity, I^2 will be calculated for the relative risk of an LLA or AEs related to amputation. If heterogeneity between studies is present, potential sources of variability will be assessed clinically and conclusions outlined in the final report.

The Cox model is based on the proportional hazards assumption. The proportional hazards assumption will be explored by plotting log(-log(survival function)) against the log of time by treatment group and checked for parallelism. The interaction of treatment with log of time will be included in the model described above for an exploratory analysis. Further, Schoenfeld residuals for each covariate and treatment will be plotted against time and log(time). If the proportional hazards assumption cannot be verified, potential sources will be assessed clinically and conclusions outlined in the final report.

Considering the potential differences in patient populations, subgroup analyses by demographic and baseline conditions will be carried out to assess any potential impact of these differences on the results (see Section 9.3.3).

For study 1245.25, LLA-related events were not pre-specified in the protocol or specifically captured on eCRF pages (see Section 9.3.2.1). Therefore, the extent of reporting may be different from studies 1245.110 and 1245.121. As details on LLA events collected in studies 1245.110 and 1245.121 (the reasons leading to LLA, the number of LLA episodes, level of LLA, etc.) are not available in 1245.25, SAF-M2 is created for the purpose of analysing these specific details.

Although approx. 14 000 patients are expected to be included in this meta-analysis (see Section 9.5), the number of studies involved is low (N=3). The 3 studies were designed to investigate empagliflozin's effect on cardiovascular events, and not specifically designed or powered to investigate LLA events. As all 3 studies are event-driven, duration of treatment and observation will be different for each patient, which will be taken into account using "time at risk" to adjust the incidence of outcomes (see Section 9.3.1). As all 3 studies investigate patients who meet the specific study entry criteria, the patients in this meta-analysis may not exactly reflect the circumstances in which empagliflozin is used in the routine clinical practice, thereby limiting the generalisability of the results.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

Data-quality assurance measures according to BI standards have been implemented in study 1245.25 (see details in CTR [c02695839, Section 9.6]) and will be implemented in studies 1245.110 and 1245.121 (see CTPs [c03946327, c09098452, Section 8.2]).

The collection of LLA events is detailed in Section 9.3.2.1.

9.10.2 Study records

Electronic CRFs via remote data capture were used for all patients in study 1245.25 [c02695839, Section 9.6] and will be used in studies 1245.110 and 1245.121 [c03946327, c09098452, Section 8.3] according to BI standards.

9.10.2.1 Source documents

Source documents have been documented in study 1245.25 [c02695839, Section 9.6] and will be documented in studies 1245.110 and 1245.121 [c03946327, c09098452, Section 8.3.1] according to BI standards.

9.10.2.2 Direct access to source data and documents

Direct access to source data and documents is described for study 1245.25 [c02695839, Section 9.6] and for studies 1245.110 and 1245.121 [c03946327, c09098452, Section 8.3.2].

9.10.3 Completion of study

The EC/competent authority in each participating EU member state has been notified about the end of the study 1245.25, and will be notified about the end of the studies or early termination of the studies 1245.110 and 1245.121.

10. PROTECTION OF HUMAN SUBJECTS

Study 1245.25 was carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and in accordance with applicable regulatory requirements. Contract research organisations (CROs) involved in trial conduct could follow their own standard operating procedures (SOPs) as long as the SOP content was consistent with BI standards, GCP requirements, and requirements of local law [c02695839, Section 5].

Studies 1245.110 and 1245.121 will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for GCP and in accordance with applicable regulatory requirements [c03946327, c09098452, Section 8].

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

Standard procedures for study approval, patient information, and informed consent have been or will be applied. See details in CTR 1245.25 [c02695839, Section 5] and CTPs 1245.110 and 1245.121 [c03946327, c09098452, Section 8.1].

10.2 STATEMENT OF CONFIDENTIALITY

Standard procedures to ensure confidentiality have been or will be applied. See details in CTR 1245.25 [c02695839, Section 5.3] and CTPs 1245.110 and 1245.121 [c03946327, c09098452, Section 8.5].

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

The definitions of AEs follow ICH E6 (Good Clinical Practice) and BI standards and can be found in CTR 1245.25 [c02695839, Section 9.5.3.2.1] and CTPs 1245.110 and 1245.121 [c03946327, c09098452, Section 5.3.7.1].

In the protocols of the ongoing studies 1245.110 and 1245.121, events leading to LLA are defined as AESIs and include any event leading to a lower-limb procedure of amputation, auto-amputation, or disarticulation. Amputation is defined as a resection of a limb through a bone. Auto-amputation is a spontaneous separation of non-viable portion of the lower limb. Disarticulation is a resection of a limb through a joint. The following procedures are not included in the definition of events leading to LLA: debridement (removal of callus or dead tissue), procedures on a stump (such as stump revision, drainage of an abscess, wound revision, etc.), and other procedures (such as nail resection or removal) without a concomitant resection of a limb (amputation or disarticulation). The definitions are consistent with the 2015 guidance from the [redacted] (website: [redacted]).

Each lower-limb amputation, disarticulation, or auto-amputation should be reported separately. The SAE report for this type of AESI is to include the date of the procedure, the level of amputation or disarticulation, the medical condition(s) leading to the procedure, and if the patient had any of the known risk factor(s) for lower-limb amputation.

In the completed study 1245.25, events related to LLA were not defined as AESIs in the protocol, but were identified via a systematic search of the study database (see Section 9.3.2.1).

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

All data including (S)AEs have been (1245.25) or are collected (1245.110 and 1245.121) in the context of the 3 trials and no additional AE collection is required for this meta-analysis.

The collection and reporting of (S)AEs follow BI standards and can be found in CTR 1245.25 [c02695839, Section 9.5.3.2.2] and CTPs 1245.110 and 1245.121 [c03946327, c09098452, Section 5.3.7.2]. All (S)AEs collected in the trials included in this meta-analysis have been reported in the CTR 1245.25 and will be reported in the CTRs for 1245.110 and 1245.121.

In studies 1245.110 and 1245.121, events leading to LLA are defined as AESIs. The collection and reporting of AESIs follow the rules for SAEs, which require expedited reporting on the BI SAE form (within 24 hours) and the collection of post-study events.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements. Reporting of (S)AEs to health authorities has been

(1245.25) or is carried out (1245.110 and 1245.121) in the context of the 3 trials and no additional reporting is required for this meta-analysis.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The meta-analysis report will be submitted to the EMA in line with the agreed milestone.

13. REFERENCES

13.1 PUBLISHED REFERENCES

R17-3389 Neal B, Perkovic V, Mahaffey KW, Zeeuw D de, Fulcher G, Erondu N, et al, CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377(7):644-657.

13.2 UNPUBLISHED REFERENCES

c16853237-05 1245.171: A Meta-Analysis of Amputation Risk in empagliflozin studies (1245.25, 1245.110, 1245.121). Statistical Analysis Plan for trial 1245.171. Version 5.0, 10 Apr 2019.

c02695839-01 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. CTR 1245.25. 12 Oct 2015.

c03946327-03 A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic Heart Failure with preserved Ejection Fraction (HFpEF). EMPEROR-Preserved, CTP 1245.110. Version 3.0, 19 Jul 2018.

c09098452-03 A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic Heart Failure with reduced Ejection Fraction (HFrEF). EMPEROR-Reduced, CTP 1245.121. Version 3.0, 18 Jul 2018.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	c16853237-05	10 Apr 2019	1245.171: A Meta-Analysis of Amputation Risk in empagliflozin studies (1245.25, 1245.110, 1245.121). Statistical Analysis Plan for trial 1245.171
2	c03946327-03	19 Jul 2018	A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic Heart Failure with preserved Ejection Fraction (HFpEF). EMPEROR-Preserved, CTP 1245.110
3	c09098452-03	18 Jul 2018	A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic Heart Failure with reduced Ejection Fraction (HFrEF). EMPEROR-Reduced, CTP 1245.121
4	c02695839-01	12 Oct 2015	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. CTR 1245.25.