Boehringer Ingelheim

Statistical Analysis Plan

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BI Trial No.:	1245.171
Title:	1245.171: A Meta-Analysis of Amputation Risk in empagliflozin studies (1245.25, 1245.110, 1245.121) Meta-Analysis
Investigational Product:	empagliflozin
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2 LIST OF ABBREVIATIONS

AE	Adverse events
ASA	Acetylsalicylic Acid
BI	Boehringer Ingelheim
ATC	Anatomical-Therapeutic-Chemical classification
CHF	Chronic heart failure
DM	Diabetes mellitus
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
Empa	Empagliflozin
EU	European Union
IR	Incidence rate
KM	Kaplan Meier
ITT	Intention to treat
LLA	Lower limb amputation
Max	Maximum
MedDRA	Medical dictionary for regulatory activities
Min	Minimum
PT	Preferred term
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
SOC	System organ class
TSAP	Study statistical analysis plan
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TS	Treated set

3 INTRODUCTION

Following the finalisation of the Art 20 procedure in the EU [EMEA/H/A-20/1442], the potential amputation risk after treatment with empagliflozin should be evaluated as an additional pharmacovigilance activity with a meta-analysis of the two chronic heart failure (CHF) studies 1245.110, 1245.121 together with the EMPA-REG OUTCOME® study 1245.25.

The objective of this SAP is to define the meta-analysis outlined in the PASS protocol 1245.171 and to provide details on individual patient data from studies 1245.25, 1245.110 and 1245.121. All pooled analyses for this meta-analysis will be performed on patient level data. Details on treatment regimens, study intervals, analysis populations and safety analysis on study level are provided in the corresponding TSAPs.

3.1 CLINICAL STUDIES AND STUDY GROUPINGS

3.1.1 Clinical Studies

Individual patient data from the completed EMPA-REG OUTCOME® study 1245.25 and the ongoing/planned studies 1245.110 and 1245.121 see Table 3.1.1:1 below are the basis for the meta-analysis in which the individual patient level data of these three trials are first analysed individually and then pooled together; for study pool definitions see Table 3.1.2:1.

Table 3.1.1:1 Studies included in meta-analysis

No	Study	Title
1	1245.25	A Phase III, multicentre, international, randomized, 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
2	1245.110	A phase III randomized, double-blind study to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction
3	1245.121	A phase III randomized, double-blind study to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with reduced ejection fraction

3.1.2 Overview of Study Groupings

Since the 3 studies differ concerning their treatment groups and the way amputation risk data were and are captured, two analysis groupings, SAF-M1 and SAF-M2, are arranged to define the most appropriate data sets for the different objectives.

Table 3.1.2: 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	CHF 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

3.2 STATISTICAL SOFTWARE

SAS® System [redacted], version 9.4 (or later) will be used for all statistical analyses.

4 STATISTICAL ANALYSES

The results of the meta-analysis are presented mainly in tabular form. When appropriate, data are presented in graphical form.

Tabulations of frequencies for categorical data will include all different categories and will 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.

4.1 OUTCOMES

In the following sub-sections all endpoints which are relevant for the meta-analysis are described.

AEs will be coded using the most recent version of the MedDRA coding dictionary. The following types of events will be distinguished.

All outcome data is collected over the full trial period even after the first amputation event. We collect all events including recurrent events during the trial period.

4.1.1 Primary Outcomes: Lower Limb Amputation Events

Definition of Lower Limb Amputations Events

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).

For studies 1245.110 and 1245.121 events leading to lower limb amputations (LLA) are considered as AEs of special interest. LLA events are captured on a specific eCRF page.

For study 1245.25 LLA events were not captured systematically. Therefore LLA events were derived based on a medical review of adverse events, concomitant therapy and adverse event narratives. For details see Appendix 6.2.

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

See Section 4.3.2.2.1 for details about the planned analysis.

4.1.2 Secondary Outcomes: Adverse Events Related to Amputation

The term "adverse events related to amputation" is used for events generally known to be related and often preceding amputations. The occurrence of these types of events not necessarily leads to amputation procedures.

Appendix 6.1 contains a list of preferred terms for selecting AEs related to amputation. This list will be reviewed before the conduct of the analysis to ensure that all the PTs are still current in the latest MedDRA version used for the analysis.

This endpoint will be analysed for all patients and for the subset of patients with amputations.

See Section 4.3.2.2.2 for details about the planned analysis.

4.2 ANALYSIS SETS AND HANDLING OF MISSING DATA

All analyses will be based on the treated set (TS).

For study 1245.25 the TS consists of all randomized patients who received at least one dose of study medication. Patients will be assigned to treatment groups according to their randomization.

For studies 1245.110 and 1245.121 the TS will include all patients who were dispensed study medication and were documented to have taken at least one dose of study medication. Patients will be assigned to treatment groups according to their randomization.

Missing amputation dates

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 midpoint of the possible interval is used according to BI standard imputation rules for concomitant therapies.

All missing amputation dates that were imputed will be displayed individually by study, including a narrative justification.

Missing AE onset dates (not applicable for LLA events)

For imputation of missing dates and times BI standards will be used. These are 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).

4.3 PLANNED ANALYSES

The following sections describe in detail the statistical analyses planned for disposition, demographic, and baseline characteristics considerations as well as the analyses planned for the safety endpoints described in Section 4.1.

Meta-analysis methods

The meta-analysis will be performed in an exploratory manner. For the main outcomes (time to first LLA and time to first AE related to amputation), a Cox proportional hazards regression model for modelling the time to first event will be used, including the factors study, DM status (T1DM, T2DM, no diabetes) and treatment (all empa vs placebo). Study is assumed as a fixed effect in this meta-analysis.

Frequency analyses

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)

Incidence rates

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. The derivation of time at risk and incidence rates 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.

The incidence rate per 100 patient years can then be 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:

$\widehat{IR}_j = \frac{\sum_{i=1}^{k} w_{ji} \cdot \widehat{IR}_{ji}}{\sum_{i=1}^{k} w_{ji}}$, 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*, $i=1,\ldots,k$ in treatment group j

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

The incidence rates will be calculated with two types of time at risk calculations.

The main analysis is the on-treatment approach where patients are censored at the date of treatment stop + 7 days and the secondary analysis is the ITT analysis where patients are censored at the last day of follow-up if no event occurred.

Time to event analyses

Kaplan Meier (KM) methods of cumulative incidence functions will be performed for time to event data (time to first event).

For pooled data across studies the cumulative incidence functions will be shown overall and stratified by study. The main analysis will be performed with censoring at the date of last study medication intake + 7 days for patients without event. An additional analysis will be performed whereby patients with no events will be censored at the date of last follow-up.

Cox proportional hazards models for modelling time to first event will be applied using factors study, DM status (T1DM, T2DM, no diabetes) and treatment (all empa vs placebo). For treatment comparison, hazard ratios with corresponding 95% confidence intervals as well as corresponding p-values will be presented.

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).

Competing risk analyses for time to event endpoints

Death is a competing risk for lower limb amputations. A competing risk analysis using a regression model by Fine and Gray (1999) [1] for amputations considering death as a competing event will therefore be performed. The regression model will include the following co-variables: study, diabetes mellitus (T1DM, T2DM, no diabetes), and treatment (empa vs. placebo).

In addition as graphical display a cumulative incidence analysis for amputations and competing event of death will be performed.

The competing risk analysis will be performed according to the standard time to event analysis with censoring at the date of last study medication + 7 days and as additional secondary analysis censored at the date of last follow up.

Trial heterogeneity

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.

Sensitivity analysis for missing dates

For LLA 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.

Overview of performed analyses

Due to the different study designs not all analyses will be performed for each of the 2 pools. The following table indicates which safety analyses will be performed for which pool and the individually studies.

Table 4.3: 1 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	Yes	Yes	Yes	Yes	Yes
Frequencies	Yes	Yes	Yes	Yes	Yes
Incidence rates	Yes	Yes	Yes	Yes	Yes
Time to onset analyses					
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

4.3.1 Disposition, demographic data and baseline characteristics

Patient disposition, demographic data and baseline characteristics will be analysed by means of descriptive statistical measures for each study grouping. The demographic and baseline

efficacy variables along with their categories for demographic and baseline characteristics are defined in the following table.

Table 4.3: 2 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)

Variable	Demographics/Baseline characteristics Categories
BMI (kg/m^2)	<25 25 to <30 30 to <35 ≥35
Weight (kg)	≤70 >70 to ≤80 >80 to ≤ 90 >90
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
SU use	Yes/No

Variable	Demographics/Baseline characteristics Categories
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
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.

4.3.1.1 Disposition

The disposition tables will be based on the treated set. Percentages of patients who prematurely discontinued study medication will be based on the number of treated patients. In addition, a table summarising the number of patients with diabetes and by type of diabetes (T1DM/T2DM) will be produced by treatment group, overall and by study.

The disposition will show the randomized and completed subjects, subjects who withdraw after randomisation and categorised reason for withdrawal. The disposition tables will include these numbers in the pooled sets as well as by individual study.

4.3.1.2 Demographics

The demographic tables will be based on the TS.

4.3.1.3 Baseline characteristics

The baseline characteristics tables will be based on the TS.

4.3.1.4 Concomitant and anti-diabetic therapy

Only descriptive statistics are planned using the TS. Concomitant medication use will be summarised by Anatomical-Therapeutic-Chemical classification 3 (ATC3) and preferred name. Summaries will be presented for concomitant therapies taken at baseline and those initiated on randomised treatment. Separate summaries of drugs used in diabetes at enrolment, use of antihypertensive, ASA or lipid lowering drugs at enrolment by preferred name will be presented. Tables will be provided for each defined SAF grouping.

4.3.1.5 Concomitant diagnoses and diabetic history

Concomitant diseases will be summarised by system organ class and preferred term. Relevant diabetic medical history by treatment group will also be presented. Both summaries will be presented using the TS. Tables will be provided for each defined SAF grouping.

4.3.2 Safety Analyses

All safety analyses will be performed on the TS.

4.3.2.1 Extent of exposure

Extent of exposure will be calculated as the difference between the date of last intake of study drug and the date of the first administration of the study drug plus one day. A descriptive statistics table with mean, SD, median and range of the number of days a patient was on treatment will be provided.

For the secondary ITT approach time in study will be calculated as the difference between the date of last follow up and the date of the first administration of the study drug plus one day. A descriptive statistics table with mean, SD, median and range of the number of days a patient was in the study will be provided. The calculations will be based on the TS, so treatment switches within a study or periods off treatment will not influence the extent of exposure calculation.

The extent of exposure table as well as the table of time in study will also provide a frequency analysis of number and percent of patients belonging to the following categories of exposure/ time in study ranges:

0 to 12 weeks, >12 to 26 weeks, >26 to 52 weeks, >52 to 78 weeks, >78 to 104 weeks, >104 to 156 weeks, >156 weeks.

The number of patient years of exposure/ time in study, calculated as the sum of days over all patients per treatment group divided by 365.25, will also be given per treatment.

4.3.2.2 Adverse Events

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.

Processing of individual AE information

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 (SOC) and preferred terms will be provided and sorted by frequency (within system organ class).

Assignment of AEs to treatment

The primary analysis, the "on-treatment" approach for the analysis of AEs, will be based on the concept of treatment emergent AEs. That means that 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 randomized study drug (1245.25)/first study drug taken (1245.110, 1245.121)).

An ITT approach will be used as 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 randomized study drug (1245.25)/first study drug taken (1245.110, 1245.121)).

4.3.2.2.1 Lower limb amputation

Frequency tables of patients with LLA (see Section 4.1.1.1) by treatment, SOC and PT will be provided. In addition incidence rates will be displayed.

Kaplan Meier analyses (cumulative incidence functions) for time to first LLA will be provided by treatment and stratified by study if feasible. Cumulative proportion of patients and the number of patients "at risk" will be provided.

The number of LLA episodes per patients will be summarized in a frequency table. Additionally a listing of patients with recurrent events will be provided.

For SAF-M2 the following analyses will be performed additionally:

- 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

Descriptive statistics will be provided to summarize all amputation events occurring after the first LLA event.

4.3.2.2.2 Adverse events related to amputation

The types of analyses to be performed on these events are outlined in Table 4.3:1. The analyses will be performed for these events based on all treated patients and in the subgroup of patients with a subsequent amputation, but for events before the actual amputation only. Events occurring after the first amputation will not be included.

Frequency tables of patients with events preceding amputations (see Section 4.1.1.2) by treatment, group of PT as specified in Appendix 6.1, SOC and PT will be provided. In addition incidence rates will be displayed.

Kaplan Meier analyses (cumulative incidence functions) for time to first event will be provided by treatment and stratified by study; hereby the analysis will not be provided on individual PT level but events being grouped into vascular AEs, diabetic foot related AEs, wound/infections or nervous system disorders and volume depletion (see Appendix 6.1). Cumulative proportion of patients and the number of patients "at risk" will be provided. In addition, Cox regression analyses will be performed for the above defined AE groups if sample size is statistically sufficient, i.e. if at least 14 patients with events in total over the 2 treatment groups have been reported.

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

AEs related to amputations occurring after the first amputation event will be analysed using descriptive statistics and will be provided in the final report.

4.3.2.3 Subgroup analyses

Subgroup analyses will be performed for the subgroups displayed in Table 4.3: 3. 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 amputation events as well as for the adverse events related to amputations analysis.

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 otherwise the affected category is too small (<14 patients with events) a category may be only described descriptively and no inferential analysis is performed, or the category might be pooled with another category if this is justifiable from a scientific perspective.

Table 4.3: 3 Subgroup analyses

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

	< 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)
SU 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-platelet use	Yes/No
Diuretics	Yes/No
Hypertension	Yes/No
Diabetes	T1DM T2DM No Diabetes (Diabetes yes/no if number of events to low)
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

5 REFERENCES

[R18-0018] Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999; 94(446):496–509.

6 APPENDIX

6.1 LIST OF PREFERRED TERMS FOR PRECEDING/RELATED EVENTS

Vascular AEs

Angiopathy

Arterial bypass operation

Arterial disorder

Arterial graft

Arterial occlusive disease

Arterial stenosis

Arterial stent insertion

Arteriosclerosis

Arterial thrombosis

Arterial therapeutic procedure

Diabetic microangiopathy

Diabetic vascular disorder

Femoral artery occlusion

Iliac artery occlusion

Intermittent claudication

Ischaemic limb pain

Microangiopathy

PAOD Peripheral arterial occlusive disease

Peripheral ischaemia

Peripheral coldness

Peripheral artery stenosis

Peripheral artery restenosis

Peripheral artery occlusion

Peripheral artery thrombosis

Peripheral vascular disorder

Peripheral ischaemia

Peripheral arterial re-occlusion

Peripheral vascular disorder

Poor peripheral circulation

Peripheral artery angioplasty

Peripheral endarterectomy

Peripheral artery bypass

Peripheral artery stent insertion

Spontaneous amputation

Thrombosis

Diabetic foot related AEs

Atherosclerotic gangrene

Bone abscess

Diabetic foot

Diabetic foot infection

Diabetic gangrene

Diabetic neuropathic ulcer

Diabetic ulcer

Dry gangrene

Cellulitis enterococcal

Cellulitis staphylococcal

Cellulitis streptococcal

Cellulitis gangrenous

Extremity necrosis

Gangrene

Infections Cellulitis

Infected skin ulcer

Infected skin ulcer

Ischaemic ulcer

Localised infection

Necrosis ischaemic

Neuropathic ulcer

Osteitis

Osteomyelitis

Osteomyelitis acute

Osteomyelitis bacterial

Osteomyelitis chronic

Osteomyelitis fungal

Osteomyelitis salmonella

Osteonecrosis

Penetrating atherosclerotic ulcer

Post-operative wound infection

Skin erosion

Skin ulcer

Staphylococcal osteomyelitis

Soft tissue infection

Subperiosteal abscess

Wound/Infection

Abscess limb

Burn infection

Impaired healing

Wound

Skin wound

Skin infection

Subcutaneous abscess

Vasculitic ulcer

Wound abscess

Wound complication

Wound dehiscence

Wound infection

Wound infection bacterial

Wound infection fungal

Wound infection staphylococcal

Wound infection pseudomonas

Wound necrosis

Wound sepsis

Wound treatment

Nervous System Disorders

Areflexia

Autonomic neuropathy

Burning sensation

Diabetic neuropathy

Hypoaesthesia

Neuropathy peripheral

Paraesthesia

Peripheral sensory neuropathy

Peripheral sensorimotor neuropathy

Sensory disturbance

Volume depletion

Hypovolaemia

Dehydration

6.2 DATA RETRIEVAL FOR LOWER LIMB AMPUTATIONS IN STUDY 1245.25

Data from study 1245.25 were reviewed for cases of amputation of the (part of) lower limb. Only the treated set was considered. The entire period of the patient's participation in the trial, including after a potential study drug permanent interruption, was included for the case retrieval.

Amputations are not considered adverse events (AE) per se (a stand-alone untoward medical occurrence), but a therapeutic procedure for an AE. Therefore they were not expected to be reported as separate AE with diagnosis "Amputation of …" and MedDRA coded.

Nevertheless, the investigators often reported it in the free-text comment field of the AE leading to the amputation. Being a therapeutic procedure, it was often reported as concomitant therapy as well.

Taking into consideration how amputations were reported, the following search strategy was established:

The adverse events were reviewed for any PT of amputation.

The concomitant treatment was searched for any amputation based on the coded entries. The output included an aggregated table per type of amputation and a line listing.

The treated sets were searched for any mentioning of "amput" (to account for "amputation", "amputed", "amputing" etc.) and "disarticul" (to account for "disarticulation", "disarticulating", "disarticulated" etc.) in the concomitant therapy, adverse event comments, investigators comments or change of antidiabetic background therapy. The output included line-listings.

The narratives (in case of serious adverse event) or line-listings of the adverse events and concomitant therapies of the patients included in these outputs were medically reviewed to confirm / reject the occurrence of LLA (e.g. in case of rectum amputation).

To account for potential cases of amputation not reported as a comment of an event or as concomitant therapy, a medical review of all the narratives (all the narratives were considered, including for the patients who permanently stopped the study drug but remained in the trial) was done, which had a hit in a syntax search. The search included any mentioning of "amput" or "disarticul".

To increase the sensitivity, a search for "resect" (to account for "resection", "resected", "resecting" etc.) or "remov" (to account for "removed", "removal", "removed", "removing" etc.) was also done.

The identification of the confirmed cases of LLA was based on the medical review. Cases included were any amputation/disarticulation of the lower limb, independent of the cause.

The following cases were excluded:

- Amputation/resection/removal of other part of the body than limb (e.g. rectum amputation).
- Amputation of the (part of) upper limb. This is in line with the common medical knowledge that the diabetes mellitus is a risk factor of LLA, not for upper limb.
- Debridement without mentioning of concomitant amputation. It does not include loss of the lower limb segment.
- Necrosectomy without mentioning of concomitant amputation. It does not include loss of the lower limb segment.
- Amputation stump revision without mentioning of an extension of the amputation, and were amputation a preexisting condition at study start.
- Nail removal or resection without mentioning of concomitant amputation. It does not include loss of the lower limb segment.

If the date of the amputation was not properly documented, it was derived by BI based on the available information, i.e. if the date of the procedure was not reported, the date of the admission in the hospital, or the date of the diagnosis for which the amputation was done – whatever occurred later – was used. In one case the day of admission (which was after the date of the diagnosis) was not reported, but only the month and year. It was imputed to 15th in accordance to the imputation done for the CTR.

7 HISTORY TABLE

This is a revised SAP including the following modifications to the final SAP

Table 7: 1 History table

Version	Date	Author	Sections changed	Brief description of change
Final	**10 May 2017**	[redacted]	None	This is the final SAP without any modification
Revised	**08 Jan 2018**		Section 3 & Section 4	This is the revised SAP after receiving comments from EMA PRAC.
2nd Revision	**12 Jun 2018**		Section 3 & Section 4	This is the second revised SAP after receiving comments from EMA PRAC in April 2018.
3rd Revision	**30 NOV 2018**		Section 4	This is the third revised SAP after receiving comments from EMA PRAC in October 2018.
4th Revision	**10 APR 2019**		Section 4	This is the fourth revised SAP after receiving comments from EMA PRAC in February 2019.