AstraZeneca

Statistical Analysis Plan Amendment
Study Code D1683C00005
Edition Number 4.0
Date 09th Aug 2017

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A Multi-Center, Randomised, Double-Blind, Active-Controlled, Parallel Group, Phase III Trial to Evaluate the Safety and Efficacy of Saxagliptin 5mg Co-administered with Dapagliflozin 5mg compared to Saxagliptin 5mg or Dapagliflozin 5mg all given as Add-on therapy to Metformin in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on Metformin Alone

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AZ Study Statistician PPD

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	American Diabetes Association
AE	Adverse event
AESI	Adverse events of special interest
ANCOVA	Analysis of covariance
B&I	Biometrics & Information Sciences
BMI	Body mass index
BP	Blood pressure
cm	centimetre
CRF	Case report form
eGFR	estimated Glomerular Filtration Rate
EPS	Enrolled Patients Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
HbA1c	Haemoglobin A1c
HR	Heart rate
kg	kilogram
MCMC	Markov Chain Monte Carlo methodology
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MTD	Maximum Tolerated Dose
NMAR	Not missing at random
PDs	Protocol deviations
PMM	Pattern mixture model
PPG	Post-prandial glucose
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious adverse event
SAF	Safety Analysis Set

Abbreviation or special term	Explanation
SAS	Statistical Analysis Software
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
T2DM	Type 2 diabetes mellitus

AMENDMENT HISTORY

Date	Brief description of change
02 August 2017	The following updates were made: - Marked abnormality criteria has been updated with the gender specific abnormality range removed in Appendix 1
30 July 2017	The following updates were made: - The SAP was updated to incorporate a contingency analysis plan of excluding one site having serious potential GCP violations. Additionally, inserted definition of on-treatment for safety labs.
14 July 2017	The following updates were made: - Per protocol population definition updated using relevant protocol deviations detailed in section 2.2 Violations and deviations
4 July 2017	The following updates were made: - protocol deviations have been updated - additional efficacy sensitivity analysis has been added as per request from FDA - tipping point analysis updated to remove pre-defined points - imputation rules of partial dates for concomitant medications and AEs were updated to be more explicit - US and Non-US subgroup categories have been updated to be North American and Other Regions as per request at BDR1 - New table defined for the presentation of metformin exposure which will present number and percentage of subjects that ever took metformin therapy at a dose of <1500mg per day during the treatment period - lab tables will present both SI and Conventional units for the following parameters, as requested at time of BDR1, by Safety Physician - wording for the presentation of abnormal laboratory values - AE overview will present updated categories to be in line with previous Saxa-Dapa studies.

Date	Brief description of change
10 January 2017	The following updates were made: - removal of <9/≥ 9% baseline HbA1c, as this is not required per protocol, update of categories from to :<8%,> 8 to ≤8%,> 8, as per protocol. - update to Markedly Abnormal values (Appendix 2) - Rewording of text surrounding the specific delta values used - Include the following criteria for excluding patient from per protocol population 'Patient was given rescue medication in error.' - Study day definition updated to be based on first treatment date for both safety and efficacy outputs. - Visit Window table updated. - Included following text for Urinalysis: In addition to the above assessments, hematuria to be defined basing on dipstick urinalysis results (for algorithm please refer to appendix E of protocol) and summarized separately in yes/no table. - Removal of following text in how to identify 'Documented symptomatic hypoglycaemia:', as this is not needed 'This is identified by ticking 'Yes' in the CRF for 'Any symptoms?' but having a measure BPG of <=70mg/dL'
6 October 2016	The following updates were made: - include 6 weeks in the exploratory analysis of change from baseline in HbA1c - include 6 weeks in the exploratory analysis of change from baseline in FPG - include 6 weeks in the exploratory analysis of change from baseline in Body Weight - include 6 weeks in the exploratory analysis of change from baseline in systolic BP - include change from baseline in diastolic BP at 6, 12 and 24 weeks in the exploratory analysis - update to the method used to analyse secondary endpoint proportion of subjects achieving a therapeutic glycemic response at Week 24 - update to Body mass index (kg/m^2) categories to be presented as per AZ standard: now grouped as Normal (<25 kg/m^2), Overweight (≥25 kg/m^2- - ≤30 kg/m^2), Obese (>30 kg/m^2)) - Extent of Exposure updated wording to include 'each' as will be presenting the exposure of each treatment separately. - Removed 'excluding interruptions' from exposure analysis as these will no longer be presented. - Compliance updated to include 'Overall Compliance' and its derivation - Updated subgroup '≤ 65 years, >65 years' to be '<65 years, ≥65 years' in order to be consistent with demography tables.

Date	Brief description of change
27 June 2016	- N/A

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

Primary Objective:	Outcome Measure:
To demonstrate the superiority of the change from baseline Haemoglobin A1c (HbA1c) achieved with the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually after 24 weeks	Change from baseline HbA1c to week 24

1.1.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To demonstrate the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on proportion of patients achieving therapeutic glycaemic response with after 24 weeks	Proportion of patients achieving HbA1c <7.0% at 24 weeks
To demonstrate the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on fasting plasma glucose (FPG) after 24 weeks	Change in fasting plasma glucose (FPG) at 24 weeks
To demonstrate the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to saxagliptin 5mg on total body weight after 24 weeks	Change in total body weight at 24 weeks

1.1.3 Safety objectives

Primary Objective:	Outcome Measure:
To evaluate the safety and tolerability of the co-administered saxagliptin 5mg and	Adverse Events (AEs)/Serious Adverse Events (SAEs) Vital signs

dapagliflozin 5mg to either agent individually after 24 weeks	Collection of clinical chemistry/hematology parameters

1.1.4 Exploratory objectives

Exploratory Objective:	**Outcome Measure:**
To explore the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on the change from baseline HbA1c after 6 and 12 weeks	Change from baseline HbA1c to week 6 and 12
To explore the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on proportion of patients achieving therapeutic glycaemic response with after 12 weeks	Proportion of patients achieving HbA1c <7.0%, after 12 weeks
To explore the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on percent of patients who require glycaemic rescue or discontinue study treatment for lack of efficacy after 12 and 24 weeks	Percent of patients who require glycaemic rescue or discontinue study treatment for lack of efficacy at 12 and 24 weeks
To explore the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on FPG after 6 and 12 weeks	Change in FPG at 6 and 12 weeks
To explore the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to saxagliptin 5mg on total body weight after 6 and 12 weeks	Change in total body weight at 6 and 12 weeks
To explore the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on systolic blood pressure (BP) after 6, 12 and 24 weeks	Change from baseline in systolic BP (6, 12 and 24 weeks)
To explore the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to	Change from baseline in diastolic BP (6, 12 and 24 weeks)

either agent individually on diastolic blood pressure (BP) after 6, 12 and 24 weeks	
To explore the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on change of HbA1c after 12 weeks in patients whose baseline HbA1c was >8%	Change from baseline HbA1c after 12 weeks in patients whose baseline HbA1c was >8%
To explore the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on change of HbA1c after 12 weeks in patients whose baseline HbA1c was ≤8%	Change from baseline HbA1c after 12 weeks in patients whose baseline HbA1c was ≤8%
To explore the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on change of HbA1c after 24 weeks in patients whose baseline HbA1c was >8%	Change in HbA1c from baseline in patients with baseline >8% at 24 weeks
To explore the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on change of HbA1c after 24 weeks in patients whose baseline HbA1c was ≤8%	Change in HbA1c from baseline in patients with baseline ≤8% at 24 weeks
To compare the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on proportion of patients achieving therapeutic glycaemic response and a weight loss after 24 weeks	Proportion of patients achieving HbA1c <7.0% and a weight loss of 2 kg after 24 week
Collect and analyse blood samples for changes from baseline after 24 weeks for exploratory research into biomarkers, such as, but not limited, to ketones.	Change from baseline of blood biomarker values at 24 weeks

1.2 Study design

Figure 1 below presents the overall design of the study.

Study D1683C00005 is a 24-week, multi-center, randomised, parallel-group, double-blind, active-controlled Phase III study to evaluate safety and efficacy of therapy with saxagliptin 5mg co-administered with dapagliflozin 5mg added to metformin, compared to therapy with

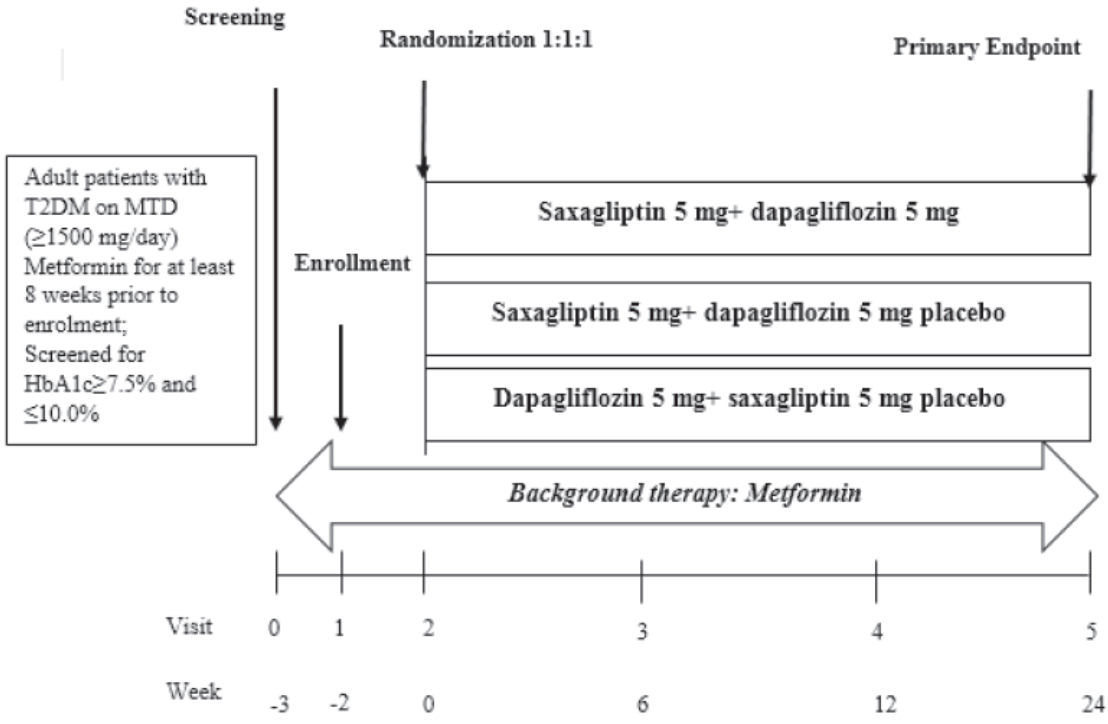
saxagliptin 5mg or dapagliflozin 5mg added to metformin in adult patients with Type 2 Diabetes Mellitus (T2DM) who have inadequate glycaemic control (HbA1c ≥7.5% to ≤10.0%) on maximum tolerated dose (MTD) of ≥1500mg/day of metformin monotherapy.

In this study, sites will be allowed to perform a pre-study screening assessment (at Week -3) prior to enrolment visit to screen for HbA1c criteria. All potentially eligible patients will be enrolled, provide informed consent, undergo screening for all applicable inclusion/exclusion criteria, and submit laboratory samples at Enrolment (Visit 1, 2 weeks prior to randomisation). Patients should be treated with a stable, MTD of metformin monotherapy (≥1500mg/day) for at least 8 weeks prior to enrolment, and remain on the same type and dose of metformin therapy for the duration of the study as the background therapy for all treatment arms as indicated below:

1. Dapagliflozin 5mg + saxagliptin 5mg + metformin
2. Dapagliflozin 5mg + saxagliptin placebo + metformin
3. Saxagliptin 5mg + dapagliflozin placebo + metformin

Study duration will be at least 27 weeks, including a 1-week pre-study Screening period, a 2-week enrolment period, and a 24-week double-blind treatment period.

Figure 1 - Study Design



1.3 Number of patients

Approximately 900 patients with T2DM with inadequate glycaemic control receiving metformin at a MTD of ≥1500mg/day for at least 8 weeks prior to enrolment will be randomised to 1 of 3 treatment groups.

A sample size of 300 patients per group will provide at least 90% power to simultaneously detect a difference in mean change from baseline to week 24 in HbA1c of -0.30 (%) for both primary endpoint comparisons of saxagliptin plus dapagliflozin vs its components at the 2-sided -alpha = 0.05 level. This assumes a common standard deviation of 1.0% and a 3% non-evaluability rate.

2. ANALYSIS SETS

2.1 Definition of analysis sets

There are four analysis (population) sets defined below for this study. Analysis sets will be finalized prior to unblinding of the study.

2.1.1 Enrolled patients set

The enrolled patients set (EPS) will consist of all patients who sign informed consent. This data set will be used to summarize the patient disposition data.

2.1.2 Full analysis set

The full analysis set (FAS) is defined as all randomised patients who take at least one dose of the study medication and have a baseline value for HbA1c. Analysis of the FAS will be based on the randomised treatment.

Note, that subjects from one site with potential serious GCP violations will be excluded from all tables and figures. A selection of key tables and figures will be rerun with the site data included to assess the impact of the exclusion. See section 2.2.

FAS will be used to summarize important PDs, patient demography and baseline data; and conduct efficacy analyses.

2.1.3 Per protocol set

The per protocol set (PPS) will be defined as all FAS patients without a relevant protocol deviation (PD) that might affect the primary analyses. The criteria for relevant protocol deviations are detailed in Section 2.2 below.

PPS will be used mainly to assess the sensitivity of the primary and secondary efficacy analyses conducted on FAS by excluding relevant PDs. Specifically, PPS will be used to summarize change of primary and secondary efficacy endpoints from baseline to week24, and repeat primary and secondary efficacy analyses done on FAS.

2.1.4 Safety analysis set

The safety analysis set (SAF) will be defined as all randomised patients who received at least one dose of study medication. This data set will be used to summarize safety data (AE, vital signs and laboratory parameters), and patient demography and their baseline data as well.

Note, that subjects from one site with potential serious GCP violations will be excluded from all tables and figures. A selection of key tables and figures will be rerun with the site data included to assess the impact of the exclusion. See section 2.2.If there is a difference between the SAF and FAS, baseline and demography data will also be presented for the FAS.

Data in this data set will be analysed based on randomised treatment, except in cases where a patient received a different treatment for the entire course of his/her participation in the double-blind treatment period. In this case, safety data for such a patient will be analysed based on the first treatment the patient actually received.

2.2 Violations and deviations

Important PDs are defined as those deviations from the protocol likely to have an impact on the efficacy and/or safety of study treatments. Protocol deviations that the study team considers to be important will be tabulated or listed in CSR. Relevant PDs are defined as those deviations likely to have an impact on the primary efficacy analysis and are the basis for exclusion of data for the per protocol analysis of the primary endpoint. The criteria for relevant protocol deviations and any action to be taken regarding the exclusion of patients or affected data from the per protocol primary efficacy analysis are defined in

Table 1 **– List of Important Protocol Deviations** below**.**

Important and Relevant PDs will be identified from two sources:

1. IMPACT monitoring – deviations will be reported as a protocol deviation in the IMPACT system by the Site Monitor. A report will be generated in IMPACT and will be sent from a study team representative to Biometrics & Information Sciences (B&I).
2. Statistical programming - deviations will be identified by execution of programs run on the clinical database.

The reports or information collected from the IMPACT monitoring report will be reviewed and assessed periodically during study conduct by AZ/vendor study team and documented in an EXCEL spreadsheet (or other appropriate format).

The final derivation of the per protocol criteria will be done using both approaches above. A meeting of the study team will be held prior to unblinding to make the final determination (or rules for the final determination in the case of criteria which require unblinding) of all subject and data exclusions for the per protocol analysis based on consideration of the results of the 2 approaches above and resolving any inconsistencies between the two approaches. In the case of a discrepancy (e.g. statistical programming shows patient is 100% compliant with study drug but IMPACT monitoring report shows patient is non-compliant), the statistical

programming from the clinical database will generally be considered as the more definitive source, but decisions will be made by the study team.

Note that the content of **Table 1** is not an exhaustive list of important PDs but rather applies only to relevant PDs for the per protocol analysis. A complete list of protocol deviations (including important protocol deviations) will be compiled separately and finalised prior to DBL.

Table 1 – List of Important Protocol Deviations

No.	Deviation	Action
1	Randomized subjects without Type II diabetes or with central laboratory HbA1c at screening outside of specified limits (i.e. violation of inclusion criterion # 2a or screening HbA1c value out of range specified in 2a)	Completely Exclude from PPS
2	Randomized subjects who did not receive stable doses of metformin for at least 8 weeks prior to enrolment (visit 1) (i.e. violation of inclusion criterion 2c)	Completely Exclude from PPS
3	Randomized subjects with abnormal free T4 values at enrolment (i.e. violation of exclusion criterion #9c)	Completely Exclude from PPS
4	Randomized subjects with a history of haemoglobinopathy with the exception of sickle cell trait (SA) or thalassemia; or chronic recurrent hemolysis. (i.e. violation of exclusion criterion #7a)	Completely Exclude from PPS
5	Randomized subjects with current or frequent use of therapeutic doses of systemic glucocorticoids (i.e. violation of exclusion criterion #8e) at enrolment	Completely Exclude from PPS
6	Patient's overall compliance is < 80% or > 120%.	Completely Exclude from PPS
7	Patient incorrectly received rescue medication	Exclusion from the day the rescue medication was given onwards.
8	Randomized subjects newly initiating or changing treatment with systemic glucocorticoids for >= 5 days after enrolment	Exclude data from PPS from the 5th day onwards. If this day is prior to randomization then this becomes a complete exclusion.
9	Randomized subjects who used anti-hyperglycaemic medication other than IP, metformin or rescue therapy for more than 14 days during the 8 weeks prior to enrolment (i.e. violation of exclusion criterion #8a) or afterwards (i.e. use of prohibited concomitant diabetes medication).	Exclude data from PPS from the 15th day onwards. If this day is prior to randomization then this becomes a complete exclusion.
10	Randomized subjects who took no metformin or < 1500 mg metformin per day for more than 2 consecutive weeks after enrolment.	Exclude data from PPS from the 15th day onwards. If this day is prior to randomization then this becomes a complete exclusion.
11	Randomized subjects who did not take the required study medication (either saxagliptin, dapagliflozin or both) for more than 2 consecutive weeks after randomization.	Exclude data from PPS from the 15th day onwards.

12	Randomized subjects given incorrect study treatment for more than 2 consecutive weeks after randomization.	Exclude data from PPS from the 15th day onwards.

The Per protocol analysis will not be conducted if <10% of patients have relevant protocol deviations.

Note, during the conduct of the study, serious potential GCP violations were found in one site. These issues cast doubt on the validity of the data from this site. Consequently, all key tables and figures will include a version which excludes data from this site. Specifically, a selected set of key tables (which will include the primary and key secondary endpoints and key safety tables) will be run twice (both with and without the site) to assess the impact of this exclusion. Listings will include all sites.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General principles taken for analysis variables

3.1.1 Study Day Definition

For the purposes of the data summaries, Study Day 1 is defined as the first date of study treatment. For visits (or events) that occur on or after first date of study treatment, study day is defined as:

(date of visit [event] - first date of study treatment + 1).

For visits (or events) that occur prior to first date of study treatment, study day is defined as:

(date of visit [event] - first date of study treatment).

There is no Study Day 0.

For listings (such as for AEs/SAEs that include the derivation of "days since last dose", this is defined as:

(event date - date of last dose).

Events that occur on the same day as the last dose of study treatment will therefore be described as occurring zero days from the last dose of study treatment.

3.1.2 Duration of Type 2 Diabetes

Duration of T2DM is calculated as the number of years from T2DM diagnosis date to informed consent date:

(consent date - diagnosis date +1) / 365.25.

The duration of diabetes will be included in the baseline diabetes characteristics listing.

If the date T2DM was diagnosed is partially missing, the following rules will take effect:

- Missing day, but month and year are present: the day will be imputed as the 15th day of the month.
- Missing day and month, but year is present: the day and month will be imputed as 30 June of the year (provided that the imputed date is less than the consent date).
- Missing year, but day and month are present: No imputations will occur, and the patient will be excluded from all summaries related to duration of T2DM.
- Missing day, month and year: No imputations will occur, and the patient will be excluded from all summaries related to duration of T2DM.
- If any such imputed date falls after the consent date, then the diagnosis date will be taken as equal to the consent date.

These durations, even if partially imputed, will be listed. However, only the portion of the date of diagnosis actually observed, rather than imputed dates, will be displayed in listings.

3.1.3 Definition of Baseline Measurements

Unless otherwise stated, for each patient, baseline value of a parameter (e.g., efficacy laboratory parameter, safety laboratory test) is defined as the last assessment on or prior to the date of the first dose of the study medication.

3.1.4 Change from Baseline

Change from baseline to any Week t is defined as follows:

$$C_{Week\ t} = M_{Week\ t} - M_{baseline},$$

where:

- $C_{Week\ t}$ is the change from baseline at Week t,
- $M_{Week\ t}$ is the measurement at Week t,
- $M_{baseline}$ is the measurement at baseline.#

The "Week t" to which a measurement belongs is determined using the conventions described in Table 2 below.

3.1.5 Visit Windows

For summaries of vital signs and laboratory data, assessments will be assigned to calculated visit windows (using study day) as described in Table 2 below.

Inclusion within the visit window should be based on the actual date and not the intended date of the visit. The window for the visits following baseline (including unscheduled visits) will be constructed in such a way that the upper limit of the interval falls half way between the two visits.

For laboratory and non-laboratory parameters, unless otherwise specified, if a patient has more than one measurement included within a window, the assessment closest to the target

day will be used. In case of ties between observations located on different sides of the target day, the earlier assessment will be used. In case of ties located on the same side of the target day (i.e. more than one value for the same day but different time), the value with the earlier entry date/time will be used.

Table 2 - Visit Windows

Assessment	Visit	Week	Target Day	Day Range
Screening/Baseline	0			
Post Baseline	1.5			2-22* (1-22)
Week 6	2	6	43	23-64
Week 12	3	12	85	65-126
Week 24/ End of Treatment	4	24	169	127-190
Post Treatment	999	PT		>190

* for vital signs and laboratory assessments only. These will only be displayed in the listings.

3.1.6 Handling missing data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing, with some exceptions specified for certain efficacy variables.

The main analysis for change from baseline specified for primary and secondary endpoints in following sections will use the repeated measures model. There will be no imputations used for missing values for the primary analysis data. There will be four sensitivity analyses, as described below, which will look at the effect of missingness.

1) For patients who started rescue medication or terminated the study medication, a sensitivity analysis will be performed using the same MMRM model as the primary analysis where only measurements taken prior to the date of the first dose of rescue medication or up to 8 days post the last dose date of the study medication will be used. This model assumes that the time course of the endpoint values for patients who discontinue treatment or are rescued at a specified time point is consistent with the time course for patients who are ongoing at that time point.

2) A tipping point sensitivity analysis using ANCOVA for the primary endpoint at week 24 that will use the delta-adjustment method to impute missing data via the multiple imputation method within the pattern-mixture model [1].

A sensitivity analysis will be done which utilizes ANCOVA for the primary endpoint at week 24 with a multiple imputation that makes a not missing at random (NMAR) assumption for missing data from subjects who discontinued treatment. Multiple imputation models will be built separately for each arm which utilize only the data from subjects who discontinued treatment but still obtained the week 24 endpoint assessment (called MI-RD). The delta adjustment method uses the assumption that patients from the main treatment arm of interest (saxagliptin 5mg co-administered with dapagliflozin 5mg added to metformin) who discontinue treatment would have, on average, their unobserved HbA1c at week 24 worse by some amount compared with the observed HbA1c at week 24 of similar patients that continue treatment. Patients who discontinue from the control arms (saxagliptin 5mg or dapagliflozin 5mg added to metformin) would exhibit the same evolution of the disease as similar control patients that stay on study.

Using these assumptions we can define 4 groups of patients with regards to observed data and patterns of missingness. The control patients refer to saxagliptin 5mg or dapagliflozin 5mg added to metformin patients, and the experimental arm patients refer to saxagliptin 5mg + dapagliflozin 5mg + metformin patients.

At each time-point t, consider four groups of patients:

- (P1) control patients with assessment observed at time-point t
- (P2) pattern of control patients with missing assessment at time-point t
- (P3) experimental arm patients with assessment observed at time-point t
- (P4) pattern of experimental arm patients with missing assessment at time-point t

Observed data (P1) serves as a model for the pattern (P2) such that the imputation model estimated within (P1) is used without any changes to draw imputations for patients in pattern (P2). Observed data (P3) would serve as a basis for a model for the pattern (P4). However, predictions from the model estimated within (P3) would be altered before being imputed for patients in (P4). Specifically, the predicted values would be worsened by a pre-fixed value, δ, (δ adjustment strategy) using a regression based multiple imputation method, at week 24. This would reflect an assumption that patients who drop out from the experimental arm would do worse after dropout than otherwise predicted by their observed outcomes and covariates.

The tipping point analysis will be performed as follows if the primary analysis is statistically significant:

1. The missing data should first be imputed assuming MAR with the delta being added the week 24 endpoint.
2. Run the delta-adjustment method using a binary search (or other appropriate algorithm) to select the value of delta which yields a p-value exactly equal to 0.05.
3. Also report the analysis results for delta values with p-values equal to 0.01 and 0.025.

The multiple imputation sensitivity analysis will build three separate multiple imputation models using the regression method for monotone missing data. Nonmonotone missing data

should be imputed using the Markov Chain Monte Carlo (MCMC) method prior to using the regression method. The data used in the imputation model will be restricted to only those subjects who have discontinued treatment but have the primary endpoint available at week 24.

The secondary efficacy variable of proportion of patients achieving a therapeutic glycaemic response is defined as having HbA1c <7.0% at Week 24. Patients who did not have A1c measurement at week 24 will be treated as those who did not to achieve a therapeutic glycaemic response.

3.1.6.1 Imputation of partial dates

Concomitant Medication Dates

Imputation of start dates allows medications for subjects to be classified into the categories of prior, concomitant (or both) for tables. An assessment should be made as to the possibility that the subject's medication could fall into each category given the information available for the dates. If it is possible given the date information that a subject's medication could fall into a given category, then the subjects' medication should be included for tables for that category. If a particular category can be ruled out based on partial or full dates available, then the subject's medication should be excluded from that category. The following date imputation should accomplish this:

Start Dates

- If year is missing (or the date is completely missing), set start date equal to the consent date.
- If (year is present and month and/or day are missing then impute start date as the earliest possible date given the partially entered date, i.e. first day of month, or first day of first month.
- If the resulting imputed start date is after a non-missing (i.e. not imputed) end date then set the start date equal to the end date.

End Dates

- If year is missing (or the date is completely missing) set end date equal to the latest database extraction date.
- If the year is known but month and/or day is missing, then set end date equal to the latest known date for this patient unless it is after the concomitant med start date (actual or imputed). If it is before the concomitant med start date then set it equal to the concomitant med start date.

Adverse Events Dates

In case of missing dates, prior to assigning the treatment that the subject received at the onset of an AE or at the time of a laboratory assessment, imputation rules will be applied as follows:

If the onset date for an AE is missing or incomplete, an imputed date will be derived. This derived date will not be reported in summary tables or listings. Every effort will be made to determine the actual onset date for the event or to obtain a reliable estimate for the onset date from the investigator.

If an onset date is completely **missing** (or the year is missing), the **derived onset date** will be calculated as the first non-missing valid (actual) date from the following list (in order of precedence):

- First active study medication date
- Consent date
- If a valid non-missing date is not available for any of these dates, the derived onset date will be set to missing.

If an onset date is incomplete, the derived onset date will be calculated using the following algorithm:

Calculate a surrogate date as the first non-missing valid date from the following list (in order of precedence):

- First active study medication date
- Consent date
- If a valid non-missing date is not available for any of these dates, the surrogate date will be set to missing.

Based on the information provided, set the initial derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month.
If the surrogate date is non-missing then:

- If the derived date is on or after the surrogate date use the derived date as calculated
- If the derived date is prior to the surrogate date and the surrogate date is consistent with the partial data provided for the onset date, use the surrogate date as the derived date
- If the derived date is prior to the surrogate date and the surrogate date is not consistent with the partial data provided for the onset date then set the derived onset date to be the latest possible date based on the partial onset date information provided. If only a year is provided, set the derived date to December 31st of that year. If a year and month is provided, set the derived date to the last day of that month.

If all dates used to determine the surrogate date are missing, then based on the information provided, set the derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month.

<u>End Dates</u>

A missing or incomplete end date of an AE will be imputed according to the following conventions:

- If an end date is missing, the derived end date will be set to missing
- If an end date is incomplete, set the derived end date to be the latest possible date based on the partial onset date information provided. If only a year is provided, set the derived date to December 31st of that year. If a year and month is provided, set the derived date to the last day of that month.

3.2 Primary efficacy variable

The primary efficacy variable is the mean change from baseline in HbA1c at Week 24.

3.3 Secondary efficacy variable

The following secondary efficacy variables will be analysed:

- Percent of patients achieving a therapeutic glycaemic response, defined as a HbA1c <7.0% at Week 24
- Mean change in Fasting plasma glucose (FPG) at 24 weeks
- Mean change in total body weight at 24 weeks

3.4 Exploratory efficacy variable

The following exploratory endpoints will be analysed:

- Mean change from baseline in HbA1c at week 6 and 12
- Proportion of patients achieving therapeutic glycaemic response, defined as HbA1c <7.0%, after 12 weeks
- Percent of patients who require glycaemic rescue or discontinue study treatment for lack of efficacy (12 and 24 weeks)
- Mean change in FPG at 6 and 12 weeks
- Mean change in total body weight at 6 and 12 weeks
- Mean change from baseline in systolic BP (6, 12 and 24 weeks)
- Mean change from baseline in diastolic BP (6, 12 and 24 weeks)
- Mean change from baseline HbA1c after 12 weeks in patients whose baseline HbA1c was >8%
- Mean change from baseline HbA1c after 12 weeks in patients whose baseline HbA1c was ≤8%
- Mean change in HbA1c from baseline in patients with baseline >8% at 24 weeks
- Mean change in HbA1c from baseline in patients with baseline ≤8% at 24 weeks
- Proportion of patients achieving HbA1c <7.0% and a weight loss of 2 kg after 24 weeks
- Mean change from baseline of blood biomarker values at 24 weeks

3.5 Safety variables

The following safety data will be collected and analysed: AEs/SAEs, clinical chemistry/hematology parameters and vital sign measurements.

3.5.1 Adverse Events

All AEs and SAEs occurring during the study will be recorded. Details such a start and stop date of AE, action take and outcome will be recorded.

3.5.2 Vital sign

Vital sign measurements in this study will include sitting systolic and diastolic BP and heart rate (HR). Vital signs should be measured from Visit 1 after the patient rests for approximately 5 minutes and with the patient in a sitting position, and again as per the schedule of event defined in protocol.

3.5.3 Laboratory Safety Variables

Safety laboratory variables will be analysed including values regardless of rescue but on treatment. On treatment is defined as first dose to last dose + 4 days for all variables except liver function tests (alanine aminotransferase, aspartate aminotransferase, bilirubin and alkaline phosphatase) which will use first dose to last dose + 30 days.

The following laboratory variables will be summarised:

Table 3 - Chemistry and haematology assessments

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Red blood cell count Red Blood Count indices: _Mean Cell Haemoglobin (MCH) _Mean Cell Volume (MCV) _Mean Cell Haemoglobin Concentration (MCHC) **_White blood cell Count and Differential** _Platelet count	S/P-Creatinine. Glomerular Filtration Rate will be calculated by the Central Laboratory using the re-expressed abbreviated (four-variable) Modification in Diet and Renal Disease (MDRD) formula and results will be reported to the sites and the Sponsor. *(Levey AS, Coresh J,Greene T, et al. Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. Clinical Chemistry 2007; 53:766-72).* S/P-Bilirubin, total (TB)
B-Haemoglobin (Hb)	S/P-Alkaline phosphatase (ALP)
B-Haematocrit	S/P-Aspartate transaminase (AST) S/P-Alanine transaminase (ALT) S/P-Uric acid S/P-Potassium S/P-Calcium, total S/P-Sodium S/P-Chloride S/P-Bicarbonate S/P-Magnesium S/P-Phosphorus S/P- Total Protein S/P Creatinine Kinase (CK). *Reflex Testing: Troponin I will be ordered if CK >400IU/L).*

Abbreviations: AST aspartate transaminase, ALP alkaline phosphatase, ALT alanine transaminase, B blood, Hb haemoglobin, P plasma, S serum, TB total bilirubin.

Urinalysis

Urinalysis assessments will be performed according to Study Plan (Table 1) of protocol and will include the following: blood, protein, albumin, glucose, urine ketones, creatinine and calculated urinary albumin: creatinine ratio.

In addition to the above assessments, hematuria to be defined basing on dipstick urinalysis results (for algorithm please refer to appendix E of protocol) and summarized separately in yes/no table.

4. ANALYSIS METHODS

4.1 General principles

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), standard error (SE), upper quartile, median, lower quartile, minimum and maximum unless otherwise stated. In addition, 95% confidence interval for the mean (percent) change from baseline will be calculated for continuous efficacy variables. They will be presented by treatment group and time point where applicable. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database and the SE will be reported to three more decimal places than the raw data recorded in the database . In general, the maximum number of decimal places reported shall be four for any summary statistic.

Descriptive summaries of categorical variables will consist of frequencies and percentages for each treatment group and overall, where applicable.

Descriptive summaries of change from baseline in categorical variables will be provided using shift tables. Frequencies and percentages of patients within each treatment group will be generated for levels of cross-classifications of baseline and the on-treatment value of the parameter. The on-treatment value can either be the value at a certain time point, or e.g. for laboratory tests, the minimum/maximum value in the direction of toxicity, which has been observed during the treatment period. Treatment group differences will not be assessed in summaries of shifts.

Note, that subjects from one site with potential serious GCP violations will be excluded from all tables and figures. A selection of key tables and figures will be rerun with the site data included to assess the impact of the exclusion. See section 2.2.

4.2 Analysis methods

4.2.1 Patient disposition

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion. Summaries of patient disposition will be presented by treatment and overall (column), while summaries in the EPS (when applicable) will be presented only by overall (column). The following patient disposition summaries will be provided:

- Number and percentage of patients in the EPS, FAS, PP and SAF populations will be presented on their own as well as by country, study centre and overall (row) (Analysis Population: EPS).

- Number and percentage of screen-failure patients (i.e., patients enrolled but not randomized), further classified by reasons for screen failure (Analysis Population: EPS).

- Number and percentage of patients who complete the study and who withdraw from the study, further classified by reasons for withdrawal from the study (as recorded on Disposition (DS) page of Case Report Form [CRF]).(Analysis Population: FAS)

4.2.2 Demographics and other baseline characteristics

Demographic and baseline patient characteristics will be listed and summarised for the SAF. If the FAS differs significantly from the SAF, the analysis will be repeated for the FAS. All summaries of continuous characteristics will be based on non-missing observations. For categorical characteristics, percentages will be calculated out of the total number of patients in the data set, overall and by treatment group, where applicable (i.e., each denominator includes the number of patients with missing/unknown values for the characteristic).

4.2.2.1 Demography data

Standard descriptive statistics will be presented for the continuous variables of:

- Age (years).
- Weight (kg).
- Height (cm).
- Body mass index (BMI) (kg/m^2), calculated as: $weight/(height)^2$

The total frequency counts and percentages of patients will be presented for the categorical variables of:

- Sex (grouped as male, female)
- Age group (years) (grouped as <65, ≥ 65 and ≥ 75)
- Race (grouped as White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, or Other)
- Ethnic group (grouped as Hispanic/Latino, Non Hispanic/Latino)
- Body mass index (kg/m^2) (grouped as Normal (<25 kg/m^2), Overweight (≥ 25 kg/m^2- - ≤ 30 kg/m^2), Obese (>30 kg/m^2))
- Geographic Region (grouped as North American/ Other Regions)

4.2.2.2 Other baseline characteristics

Standard descriptive statistics will be presented for the continuous variables of:

- Duration of Type 2 Diabetes (years).
- HbA1c
- FPG
- Post-prandial glucose (PPG)

The total frequency counts and percentages of patients will be presented for the categorical variables of:

- Duration of Type 2 Diabetes (years) (grouped as < 3, ≥ 3 and ≤ 10 yrs, > 10 yrs)
- Diabetes Complications (grouped as Any, Retinopathy, Neuropathy Autonomic, Neuropathy Peripheral, Nephropathy Angiopathy, Other)
- HbA1c (grouped as: ≤8%,> 8)

4.2.2.3 Medical History

Diabetes related medical history and general medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA). All disease related medical history will be listed and the number and percentage of patients with any disease related medical history will be summarised for the FAS by system organ class (SOC) and preferred term (PT).

All general medical history will be listed and summarised similarly.

4.2.2.4 Prior Medications

Previous medications, including any medication (other than study medications) with a start date prior to Day 1 of treatment period, will be summarized.

Missing and partial date handling of start and stop dates of previous medications is described in Section 3.1.6.1 above. The AZ Drug Dictionary v16.1is used to code the non-study medication.

4.2.3 Extent of Exposure and Treatment Compliance

4.2.3.1 Extent of Exposure – Study and Rescue Medications

The extent of exposure to each study medication during the treatment period is defined as:

treatment end date – treatment start date +1

The extent of exposure to study medication will be summarized using the SAF for the treatment period and the treatment period prior to rescue, where the number and percent of patients with an extent of exposure within specified day ranges (1-7, 8-30, 31-60, 61-90, 91-120, 121-180, > 180 days) will be presented by treatment group.

The mean, standard deviation (SD), median and range of the number of days of exposure to study medication will also be presented. Summaries will be presented including periods of interruptions (defined by record of 0 tablets of study medications on the CRF).

All rescue medication use during the treatment period will be summarized and listed by treatment group.

A listing of patients by batch number of study medication will also be generated.

4.2.3.2 Extent of Exposure – Concomitant Medications

Concomitant medications include any medication taken from start of the treatment period up to the end of the treatment period.

Concomitant medications will be summarized using the SAF dataset by drug class and (generic) drug name. A summary table by drug class and generic drug name will be generated for each of the following:

- all concomitant medication
- all concomitant diuretic medication
- all concomitant anti-hypertensive medication

To identify each type of diuretic medication and anti-hypertensive medication a list of terms will be selected before database lock and unblinding of the database. Missing and partial date handling of start and stop dates of concomitant medications is described in Section 3.1.6.1 above.

4.2.3.3 Measurement of Treatment Compliance

Percent treatment compliance is calculated during treatment period for study medication (i.e. saxagliptin or matching placebo and dapagliflozin or matching placebo) and overall.

(Number of tablets taken / Planned number of tablets)*100%

Where the planned number of tablets is calculated as:

(End date – Start date +1) * prescribed daily number of tablets

The number of tablets taken is calculated as:

total number of tablets dispensed - total number of tablets returned

based on the CRF accountability pages.

Overall compliance is defined as :

(Total number of tablets taken / Total planned number of tablets)*100; where

the planned number of tablets is calculated as:

(latest end date – earliest start date +1) * prescribed daily number of tablets

and the number of tablets taken is calculated as:

total number of tablets dispensed - total number of tablets returned.

A patient is considered compliant if percent compliance is ≥ 80% and ≤ 120%. For each type of medication and overall, the number and percent of patients compliant during the treatment period will be displayed for the SAF.

For metformin, a summary for the SAF, including number and percentage of subjects that ever took metformin therapy at a dose of <1500mg per day during the treatment period, will be provided separately in addition to the compliance summary of the study medications.

4.2.4 Efficacy analyses

This section addresses separately the analyses to be conducted on the primary efficacy endpoint, on the secondary and other efficacy endpoints.

Summary statistics will be presented for each primary, secondary and exploratory variable as described in Section 4.1, as well as the statistical analyses as described below.

This study is designed to demonstrate the superiority of the co-administered saxagliptin 5mg and dapagliflozin 5mg vs its components in mean change from baseline to week 24 in HbA1c at the 2-sided alpha = 0.05 level.

4.2.4.1 Primary efficacy outcome variable

A longitudinal repeated measures analysis using 'direct likelihood' will be performed. The SAS procedure PROC MIXED will be used. The preferred model will include the fixed categorical effects of treatment, week and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.

The following model will be used:

$$C_{ijk} = \text{intercept} + ß_1\,[M_{baseline,ij}] + \tau_i + \alpha_k + (\alpha\,\tau)_{ik} + (\alpha\,M_{baseline})_{ijk} + \text{error}_{ijk}$$

where

- C_{ijk} is the change from baseline for patient j in treatment group i at time k,
- $ß_1$ is the slope coefficient for the baseline measurement,
- $M_{baseline,ij}$ is the baseline measurement of patient j in treatment group i,
- τ_i is the mean effect of treatment group i,
- α_k is the mean effect at time k
- $(\alpha\,\tau)_{ik}$ is the interaction term between treatment group i and time k.
- $(\alpha\,M_{baseline})_{ijk}$ is baseline measurement-by-week interaction term for patient j in treatment group i at time k, and
- error_{ijk} is the error term for patient j in treatment group i at time k.

An unstructured matrix for the within-patient error variance-covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method.

In case of non-convergence of the preferred model or memory space issues, the following back-up models are defined:

- The first backup model is the same as the preferred model but the Kenward-Roger method will be replaced by Satterthwaite approximation.
- The second backup model is the same as the preferred model but without the term for baseline measurement-by-week interaction.

The second back-up model will only be provided if the first back-up model does not converge or has memory issues.

The model will provide least-squares mean estimates, SE and 2-sided 95% confidence intervals for mean change at all time points within and between treatments.

Sensitivity analysis

A sensitivity analysis will be conducted for the primary efficacy using data up to date of rescue medication or prior to the study medication termination + 8 days and will be completed using the same model as described above.

Additional sensitivity analyses of HbA1c changes from baseline at Week 24 (having used SAS procedures PROC MI and MIANALYZE to impute any missing data and analyze the data after imputation, see Section 3.1.6) will be performed using an ANCOVA model at week 24. If the missing data pattern is non-monotone, then the Markov Chain Monte Carlo methodology (MCMC) is first employed to generate a monotone missing pattern (the number of simulation is 1000 and a simulation seed is 725). When the missing data pattern is monotone, then a linear regression will be used to impute the missing HbA1c, i.e. missing values of HbA1c are predicted in turn, given the observed values of HbA1c (a simulation seed is 229).

The per protocol analysis of the primary endpoint, if it is done, will exclude data after rescue or more than 8 days after treatment discontinuation.

For each sensitivity analysis least squares mean estimates and 2-sided 95% confidence intervals for mean changes from baseline within and (when warranted) differences in mean change from baseline between treatments will be provided.

A value of the delta in the tipping point analysis will be reported if it exists.

4.2.4.2 Secondary efficacy variable

The primary endpoint will be tested for saxagliptin plus dapagliflozin versus saxagliptin and dapagliflozin arms simultaneously at the alpha = 0.05 level (two sided). In order to protect the overall type I error rate, the interpretation of the statistical significance of treatment comparisons for each secondary efficacy endpoint will be done using a stepwise procedure. The secondary endpoints then will be tested sequentially as follows:

1- saxagliptin plus dapagliflozin versus saxagliptin on percent of patients achieving a therapeutic glycaemic response, defined as a HbA1< 7.0% at Week 24
2- saxagliptin plus dapagliflozin versus dapagliflozin on percent of patients achieving a therapeutic glycaemic response, defined as a HbA1< 7.0% at Week 24
3- saxagliptin plus dapagliflozin versus saxagliptin on mean change from baseline in FPG at Week 24
4- saxagliptin plus dapagliflozin versus dapagliflozin on mean change from baseline in FPG at Week 24
5- saxagliptin plus dapagliflozin versus saxagliptin on mean change from baseline in total body weight at Week 24

Each comparison will be tested at the alpha = 0.05 (two-sided) level.

The analysis of the change from baseline for FPG and total body weight at week 24 will be performed using the same longitudinal repeated measures model as for the primary efficacy endpoint.

The proportion of subjects achieving a therapeutic glycemic response (defined as HbA1c <7.0%) at Week 24 will be summarized by treatment group and compared between treatment groups using the methodology of Zhang, Tsiatis, and Davidian [3], and Tsiatis, Davidian, Zhang, and Lu [4]. 95% confidence intervals for the response rate within each treatment group as well as for the difference in response rates between treatment groups will be calculated with adjustment for baseline HbA1c. As defined in Section 3.1.6 patients who did not have A1c measurement at week 24 will be treated as those who did not achieve a therapeutic glycaemic response.

4.2.4.3 Exploratory efficacy variables

The following exploratory endpoints will be analysed using a repeated measure mixed model as was used for the primary efficacy variable:

- The mean change from baseline in HbA1c at week 6 and week 12
- Mean change in FPG at 6 and 12 weeks
- Mean change in total body weight at 6 and 12 weeks
- Mean change from baseline in systolic BP (6, 12 and 24 weeks)
- Mean change from baseline in diastolic BP (6, 12 and 24 weeks)
- Mean change from baseline HbA1c after 12 weeks in patients whose baseline HbA1c was >8%
- Mean change from baseline HbA1c after 12 weeks in patients whose baseline HbA1c was ≤8%
- Mean change in HbA1c from baseline in patients with baseline >8% at 24 weeks
- Mean change in HbA1c from baseline in patients with baseline ≤8% at 24 weeks
- Mean change from baseline of blood biomarker values at 24 weeks

Whilst the following exploratory efficacy endpoints will be summarized by treatment group and compared between treatment groups using the methodology described for analysis of proportion of patients achieving a therapeutic response at week 24, above. 95% confidence intervals for the response rate within each treatment group as well as for the difference in response rates between treatment groups will be calculated with adjustment for baseline HbA1c.

- Proportion of patients achieving therapeutic glycaemic response, defined as HbA1c <7.0%, after 12 weeks
- Percent of patients who require glycaemic rescue or discontinue study treatment for lack of efficacy (12 and 24 weeks)
    - if > 10% require glycaemic rescue or discontinue study treatment for lack of efficacy (12 and 24 weeks) a KM curve will present time to this event.
- Proportion of patients achieving HbA1c <7.0% and a weight loss of 2 kg after 24 weeks

4.2.5 Safety analyses

4.2.5.1 Adverse Events

Adverse Events (AEs) will be classified by Primary SOC and PT according to the MedDRA.

In summaries by SOC and PT, AEs will be sorted by overall decreasing frequency within each SOC and PT. In summaries by PT, AEs will be sorted by decreasing frequency within PT according to the highest of either of the combinational dose group across the study.

Separate pages to capture events of hypoglycemia are contained within the CRF. Hypoglycemia or discontinuation due to hypoglycemia would not be reported on an AE CRF page unless the event fulfilled criteria for an SAE in which case an SAE form would be completed. Hypoglycemia events that are reported as SAEs will be included in all summaries of AEs or SAEs. Separate summaries will be provided including hypoglycemia events reported on the special CRF pages.

All Adverse Events

An overall summary of adverse events at patient level, including patients who experienced at least one: AE, hypoglycaemic event, treatment-related AE, death, SAE, treatment-related SAE, SAE leading to the discontinuation of study medication, hypoglycaemic event leading to the discontinuation of study medication, and AESI. All AEs (serious and non-serious, excluding hypoglycemic events that are not reported as SAEs) will be summarized by SOC and PT. In addition, a patient listing of all reported AEs will be produced, displaying all events that occurred prior to the start date of treatment period, if any. All AEs (serious and non-serious) including all hypoglycemic events will also be summarized by treatment group, where applicable.

Adverse events and SAEs with an onset from Day 1 of treatment up to and including 4 days and 30 days respectively, after the last dose date in the treatment period will be considered as occurring during the treatment period.

In addition, the following summaries will be provided for the treatment period (excluding hypoglycemic events that are not reported as SAEs):

- Most common adverse events by preferred term and treatment group (i.e., reported by ≥ 2 % of patients in any treatment group),
- Adverse events by system organ class, preferred term, intensity and treatment group,
- Adverse events related to study medication by system organ class, preferred term and treatment group.
- Proportion of patients with adverse events by SOC and PT in subgroups of patients defined by age category (< 65 and ≥ 65 years), gender and race.

No formal comparisons will be made between treatments. No formal statistical testing will be performed, only summary statistics will be provided.

Adverse Events of Special Interest

Event categories of adverse events special interest (AESI) for this study may include, but are not limited to, hypoglycaemia, hypersensitivity reactions, severe cutaneous adverse reactions, all infections, decreased lymphocyte count, pancreatitis, all malignancies, cardiac failure (including confirmed adjudicated cardiac failure events), renal impairment/renal failure, volume depletion (hypotension, dehydration, and hypovolemia), and liver injury(including confirmed adjudicated hepatic events).

To identify each type of adverse event of special interest, a list of PTs will be selected before database lock and unblinding of the database. AEs and SAEs of special interest with an onset from Day 1 of treatment up to and including 4 days and 30 days respectively, after the last dose date will be considered as occurring during the treatment period.

Separate summaries similar to those produced for AEs/SAEs will be provided for AESI.

Hypoglycemic Events

Separate pages to capture events of hypoglycemia are contained within the CRF. Hypoglycemic events with an onset from Day 1 of treatment to and including 4 days after the last dose date of treatment will be considered as occurring during the treatment period, or up to rescue. The proportion of patients with hypoglycemic events will be tabulated by treatment group.

Hypoglycemia episodes will be categorised according to the American Association of Diabetes (ADA) Criteria [5] which classifies hypoglycemia as follows:

Severe hypoglycaemia:	An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

	A severe hypoglycemic event is identified by those ticking 'Yes' on the CRF for 'Was third party intervention required for this episode of hypoglycaemia?'
Documented symptomatic hypoglycaemia:	An event during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration less than or equal to 70mg/dL (3.9mmol/L).
Asymptomatic hypoglycaemia:	An event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration less than or equal to 70mg/dL (3.9mmol/L).
Probable symptomatic hypoglycaemia:	An event during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L).
Relative hypoglycaemia	An event during which the person with diabetes reports any of the typical symptoms of hypoglycaemia, and interprets the symptoms as indicative of hypoglycaemia, but with a measured plasma glucose concentration greater than 70mg/dL (3.9mmol/L).

Number and percentage of patients who had any hypoglycaemic event and total number of events by treatment group will be presented for the SAF.

A summary of proportion of patients having severe hypoglycemia, documented symptomatic hypoglycemia or asymptomatic hypoglycemia as categorised by the ADA criteria above will also be presented for the SAF. All incidences of hypoglycaemic events and their ADA categorisation will be listed.

Hypoglycemic events will be categorized using the following classes in addition to overall reported hypoglycemic events:

- Major episodes of hypoglycemia - defined as symptomatic episodes requiring external (3rd party) assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value < 3 mmol/L (< 54 mg/dL) and prompt recovery after glucose or glucagon administration,
- Minor episodes of hypoglycemia - defined as either a symptomatic episode with a capillary or plasma glucose measurement below 3.5 mmol/L (63 mg/dL) regardless of need for third-party assistance or an asymptomatic capillary or plasma glucose measurement below 3.5 mmol/L (63 mg/dL), that does not qualify as a major episode,

- Other episodes of hypoglycemia - defined as episodes reported by the investigator that are suggestive of hypoglycemia but do not meet the above criteria.

A summary of proportion of patients having major, minor and other episodes of hypoglycemia will be presented for the SAF.

4.2.5.2 Deaths

All deaths recorded on the disposition page, the AE page, or SAE page (with a death date, cause of death, outcome or SAE categorization present) of the CRF will be considered a death in the analyses. Any deaths that occur during the study will be described in depth as narrative in the CSR. A listing of all deaths that occur during the study will be produced.

4.2.5.3 Clinical laboratory variables

Summary statistics for observed values and change from baseline at each visit will be presented for each laboratory parameters in SI units. The following parameters will also be presented for conventional units: alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, bicarbonate, bilirubin, calcium, chloride, creatine kinase, creatinine, glucose, magnesium, phosphate, potassium, total protein, sodium, urate, hemoglobin, urinary albumin to creatinine ratio. Shift tables will present the change from baseline value categorised as low/normal/high based on the laboratory reference range, to post baseline value category.

The number and percent of patients with laboratory values meeting marked abnormality criteria, as per criteria defined in Appendix 1 – MARKED ABNORMALITY CRITERIA, will be summarized for each treatment group. Shift tables will present the change from baseline value (categorized as low/normal/high based on the laboratory reference range), to post baseline value category.

Other safety assessments including serum creatinine, and eGFR by Modification of Diet in Renal Disease (MDRD) will be summarized by treatment group using descriptive statistics of values and changes from baseline at each scheduled time point.

Additional analyses for laboratory marked abnormalities will be performed excluding data after rescue in the double-blind treatment period.

4.2.5.4 Vital signs

Values and changes from baseline at each scheduled time point for vital signs, including weight, blood pressure and heart rate, will be summarized by treatment group using descriptive statistics.

4.2.6 Subgroup analyses

The subgroup analysis will be performed on the primary efficacy endpoint (mean change from baseline in HbA1C) in subgroups defined by the following variables:

- Baseline HbA1c (≤8%, >8%)
- Gender (male, female)
- Age (<65 years, ≥65 years)
- Region (North American, Other Regions)

Subgroup analyses will be carried out as for the primary analysis model with subgroup by treatment interaction term. Within each subgroup, point estimates and 95% confidence intervals will be calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups. A nominal interaction p-value will be provided for the purpose of the completeness of the data analysis.

Additionally, the following data will be presented for the North American Region subgroup, as requested by the FDA

- patient disposition
- demographics and baseline characteristics
- medical history
- adverse events/ serious adverse events

5. INTERIM ANALYSES (NOT APPLICABLE)

6. CHANGES OF ANALYSIS FROM PROTOCOL

The following updates were made 6th Oct 2016:

- include 6 weeks in the exploratory analysis of change from baseline in HbA1c
- include 6 weeks in the exploratory analysis of change from baseline in FPG
- include 6 weeks in the exploratory analysis of change from baseline in Body Weight
- include 6 weeks in the exploratory analysis of change from baseline in systolic BP
- include change from baseline in diastolic BP at 6, 12 and 24 weeks in the exploratory analysis

The following updates were made 30th of July 2017:

- Subjects from one site with potential serious GCP violations will be excluded from all tables and figures. A selection of key tables and figures will be rerun with the site data included to assess the impact of the exclusion.

7. REFERENCES

1 Pharmaceutical Statistics, 2013: Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models† Bohdana Ratitch,a*Michael O'Kelly,b and Robert Tosielloc

2 CV181169: A Multicenter, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of add-on therapy with Saxagliptin and Dapagliflozin added to Metformin compared to add-on therapy with Saxagliptin in combination with Metformin or Dapagliflozin in Combination with Metformin in subjects with Type 2 Diabetes who have inadequate glycemic control on Metformin alone

3 Zhang M., Tsiatis A., Davidian M. Improving efficiency of inference in randomized clinical trials using auxiliary covariates. Biometrics. 2008; DOI: 10.1111/j.1541-0420.2007.00976.x.

4 Tsiatis A., Davidian M., Zhang M., Lu X. Covariate adjustment for two-sample treatment comparisons in randomized clinical trials: a principled yet flexible approach. Statistics in Medicine. 2007; DOI: 10.1002/sim.3113.

5 Diabetes Care, 2005, 28: 1245 American Diabetes Association Workgroup on Hypoglycemia; Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005;28:1245–1249.

8. APPENDIX 1 – MARKED ABNORMALITY CRITERIA

Clinical Laboratory variables	Units	Marked Abnormality Criteria	
		Low	High
HAEMATOLOGY			
HCT (haemoatocrit)	%	< 20%	> 55%
HCT	%		> 60%
Haemoglobin	g/dL	< 6 g/dL	> 18 g/dL
Haemoglobin	g/dL		> 20 g/dL
BLOOD CHEMISTRY			
Albumin	g/dL	≤ 2 g/dL	> 6 g/dL
Total protein	g/dL		> 10 g/dL
ALP	U/L		> 3X ULN
ALT	U/L		> 3X ULN
AST	U/L		> 3X ULN
ALT	U/L		> 5X ULN
AST	U/L		> 5X ULN
ALT	U/L		> 10X ULN
AST	U/L		> 10X ULN
ALT	U/L		> 20X ULN
AST	U/L		> 20X ULN
Total Bilirubin	mg/dL		> 2X ULN if PreRx ≤ ULN; > 3X ULN if PreRx > ULN
Glucose, Plasma Unspecified	mg/dL	< 54 mg/dL	> 350 mg/dL
Na (Sodium)	mEq/L	< 130 mEq/L	> 150 mEq/L
Na (Sodium)	mEq/L	< 120 mEq/L	
K (Potassium)	mEq/L	≤ 2.5 mEq/L	≥ 6.0 mEq/L
HCO3 (Bicarbonate)	mEq/L	≤ 13 mEq/L	

The criteria for marked abnormality for each variable are listed in the following table. Note

Clinical Laboratory variables	Units	Marked Abnormality Criteria	
		Low	High
Creatinine	mg/dL		≥ 1.5X PreRx CREAT
Creatinine	mg/dL		≥ 2.5 mg/dL
CK (Creatine Kinase)[1]	U/L		> 5X ULN
CK (Creatine Kinase)[1]	U/L		> 10X ULN
Total Calcium	mg/dL	< 7.5 mg/dL	≥ 1 mg/dL from ULN and ≥ 0.5 mg/dL from PreRx CA
Phosphorus, inorganic	mg/dL	≤ 1.8 mg/dL if age 17-65 or ≤ 2.1 mg/dL if age ≥ 66	≥ 5.6 mg/dL if age 17-65 or ≥ 5.1 mg/dL if age ≥ 66
Magnesium, serum	mEq/L	<1 MEQ/L	>4 mEq/L
QUANT. URINE CHEMISTRY (TIMED SPECIMEN)			
Albumin/Creatinine Ratio	mg/g		>1800 mg/g

[1]Forcreatine kinase, ULN: Males (<65 years=250 U/L; ≥65 years=203 U/L), Females (<65 years=170 U/L; ≥65 years=160 U/L)

Elevated AT (ALT and/or AST) and Total Bilirubin

The following three criteria will be summarized in examination of elevated AT (ALT and/or AST) and total bilirubin:

- (AST or ALT > 3XULN) and (Bilirubin > 1.5XULN within 14 days on or after AT elevation)
- (AST or ALT > 3XULN) and (Bilirubin > 2XULN within 14 days on or after AT elevation)
  (AST or ALT > 3XULN) and {(Bilirubin > 2XULN and no ALP >= 2XULN) within 14 days on or after AT elevation)}