AstraZeneca

Statistical Analysis Plan

Study Code	D1690C00017
Edition Number	2.0
Date	11 March 2020

A 24 Week, Multicenter, Randomized, Double-Blind, Parallel Group, Phase 3 Trial With a 28 Week Long Term Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 10 mg in T2DM Patients Aged 10-24 Years

STATISTICAL ANALYSIS PLAN
FOR SHORT-TERM AND SHORT-TERM PLUS LONG-TERM ANALYSES

A 24 WEEK, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, PHASE 3 TRIAL WITH A 28 WEEK LONG TERM SAFETY EXTENSION PERIOD EVALUATING THE SAFETY AND EFFICACY OF DAPAGLIFLOZIN 10 MG IN T2DM PATIENTS AGED 10-24 YEARS

PROTOCOL(S) MB102-138

VERSION # 2.0

A 24 Week, Multicenter, Randomized, Double-Blind, Parallel Group, Phase 3 Trial with a 28 Week Long Term Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 10 mg in T2DM Patients aged 10-24 years

Study Statistician [redacted]

A 24 Week, Multicenter, Randomized, Double-Blind, Parallel Group, Phase 3 Trial with a 28 Week Long Term Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 10 mg in T2DM Patients aged 10-24 years

[redacted]

Global Product Statistician

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	American Diabetes Association
AE	Adverse event
ALT	Aalanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AT	Aminotransferases
AZ	AstraZeneca
BMI	Body mass index
BOCF	Baseline last observation carried forward
BUN	Blood urea nitrogen
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CK	Creatine kinase / Creatine phosphokinase
CRF	Case report form
CSR	Clinical Study Report
DILI	Drug-induced liver injury
DKA	Diabetic ketoacidosis
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FAS	Full Analysis Data Set
FPG	Fasting plasma glucose
FSH	Follicle stimulating hormone
FU	Follow-up
HbA1c	Glycated hemoglobin
IGF-1	Insulin-like growth factor-1
IGFBP3	Insulin-like growth factor binding protein-3
IP	Investigational product
ISPAD	International Society of Pediatric and Adolescent Diabetes
ITT	Intent to Treat
IXRS	Interactive Web/Voice Recognition system
LH	Luteinizing hormone
LLN	Lower limit of normal

Abbreviation or special term	Explanation
LLOQ	Lower limit of quantification
Ln	Natural logarithm
LOCF	Last observation carried forward
LT	Long-term
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MDRD	Modified Diet in Renal Disease, study equation
MedDRA	Medical Dictionary for Regulation activities
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
MI	Multiple imputation
MI-WO	Multiple imputation wash-out
NLME	Non-linear mixed effects
OR	Odds ratio
PK	Pharmacokinetics
PRA	Pharmaceutical Research Associate
PT	Preferred Term
PTH	Parathyroid hormone
RPD	Relevant protocol deviation
Q1	1st Quartile
Q3	3rd Quartile
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
SGLT-2 inhibitor	sodium glucose cotransporter-2
SMBG	Self-monitoring blood glucose
SMBK	Self-monitoring blood ketone
SOC	System Organ Class
SMQ	Standard MedDRA Query
ST	Short-term
T2DM	Type 2 diabetes mellitus
TSH	Thyroid-stimulating hormone
UKPDS	United Kingdom Prospective Diabetes Study
ULN	Upper limit of normal

Abbreviation or special term	Explanation
WHO	World Health Organization

AMENDMENT HISTORY

Date	Brief description of change
4 May 2016	Initial SAP approved
4 March 2019	Update number of subjects to be randomized as per protocol amendment#3
	Addition of sensitivity analyses to change from baseline to Week 24 in HbA1c endpoints based on multiple imputations assuming strategy for missing data are missing not at random
	To assess the incidence of diabetic ketoacidosis
14 November 2019	To redefine the randomized subject data set as any patient randomized and to consider this population as the Full Analysis Set
	To update ANCOVA analysis to impute missing Week 24 assessment using either a LOCF approach or a BOCF approach for subjects without any evaluable post-baseline assessment

1 BACKGROUND AND RATIONALE

1.1 Background

Type 2 diabetes mellitus (T2DM) is a complex and multifactorial metabolic disorder with contributions from genetic, behavioral, and environmental risk factors. Despite a wealth of information concerning T2DM in adults, data unique to the pediatric age group regarding the pathophysiology and therapy for T2DM are limited.[1]

As in adults, T2DM in children is characterized by hyperglycemia associated with initial relative insufficiency of insulin secretion and increased insulin resistance, and is ultimately often followed by pancreatic β-cell failure.[2, 3, 4] A potentially important difference between adults and pediatric patients with T2DM is that in the natural course of T2DM in pediatric patients, the glucose dysregulation may develop over a much more rapid time frame than is seen in adults.[5] This may be a contributing factor to the tendency for poorer prognosis for microvascular and macrovascular diabetic complications for pediatric patients with T2DM, as they become adults.[6] An additional factor unique to the development of T2DM in the pediatric age range is the potential additive contribution and impact of the insulin resistance of puberty, which, although a natural phenomenon during pubertal development, may have a negative influence on and potentially exacerbate glycemic dysregulation in susceptible children.[5]

As with adults, it is expected that children and adolescents with T2DM are at risk for eventually developing diabetes-related micro- and macrovascular complications with higher glycemic levels.[1] Data from a number of small studies conducted in limited ethnic groups have confirmed an increased risk of microvascular complications[1, 7] in pediatric patients with T2DM compared with children and adolescents without diabetes. For example, microalbuminuria, macroalbuminuria, and hypercholesterolemia have all shown an increased tendency to develop in Pima Indian children with T2DM. Among Japanese pediatric patients, retinopathy has been observed at a similar rate in those with type 1 and type 2 diabetes, although it appears to be less common in pediatric patients compared with adults with T2DM. A study in Australia found that pediatric patients with T2DM have significantly higher rates of microalbuminuria and hypertension than those with type 1 diabetes, despite shorter duration of disease and lower glycated hemoglobin (HbA1c).[8] Additional small studies have shown an increased occurrence of renal disease (Japanese), non-alcoholic fatty liver disease (the Manitoba Cree), and cardiovascular mortality associated with hypertension and dyslipidemia in pediatric patients with T2DM.[9]

There is evidence in adults from the United Kingdom Prospective Diabetes Study (UKPDS) that normalization of blood glucose substantially decreases the frequency of microvascular complications of T2DM (UKPDS Group 1998), consistent with what has been noted with type 1 diabetes.[10] It is assumed that a management regimen based on adequate glycemic control, via lifestyle changes with modification of diet and physical activity and, as appropriate, medical treatment, should help to reduce the risk of complications in younger persons as well as adults with the disease.

Current therapeutic agents have limited efficacy and are associated with side effects including hypoglycemia, weight gain, edema and gastrointestinal effects. While there are several oral glucose lowering medications approved for adults with T2DM, the only oral glucose lowering medication approved for use in pediatric patients age 10 and older is metformin. Agents with new mechanisms of action for the treatment of T2DM are being studied.

Given the need for additional oral glucose lowering therapy options for pediatric patients with T2DM, it is appropriate to test the hypothesis that dapagliflozin, an orally active SGLT-2 inhibitor, will confer the therapeutic benefits of glucose-lowering and some weight loss, without adding the risk of hypoglycemia, in this population. This program will investigate the efficacy, safety, and tolerability of dapagliflozin versus placebo for the treatment of patients with pediatric or early age onset T2DM.

1.2 Study Rationale

This protocol will be performed to meet the requirements of the European Union Pediatric Investigations Plan for Type 2 Diabetes, and aims to allow for the extended use of dapagliflozin in appropriate pediatric patients.

Dapagliflozin has been shown to be effective in lowering HbA1c in adult patients with T2DM, when studied as monotherapy and in combination with insulin or oral antidiabetic medications. Overall, through its development program, dapagliflozin has been shown to improve HbA1c with a low risk of hypoglycemia, while also demonstrating positive trends for common comorbidities (weight gain and systolic hypertension) associated with increased cardiovascular risk in T2DM adult patients.

A number of studies have demonstrated that the rising prevalence of T2DM in pediatric patients parallels the growing obesity problem in this population as it does in adults.[9,11,12] However, studies from Germany, the United Kingdom, and Sweden indicate that T2DM remains a rarity among children in Europe. [13,14,15] Also, the recruitment of pediatric patients with T2DM into clinical trials has proven very difficult for a number of reasons. Innovative methods are therefore required to ensure that new novel treatments, such as dapagliflozin, are studied and made available to this population.

Given the anticipated challenges to recruitment with this population, a partial extrapolation approach was used to better inform the sample size determination. Full extrapolation was not pursued because the criteria for full extrapolation were deemed not to have been met for this disease. This partial extrapolation approach entails that the pediatric outcome and design is informed by extrapolation from adult data, and the actual data from the trial proposed will be used to validate the extrapolation.

A probability estimate was determined using clinical trial simulation from a non-linear mixed effects (NLME) model for the relationship between dapagliflozin pharmacokinetic (PK) and HbA1c response in adult T2DM subjects. Adjustments were made to the model for expected differences in the covariate effects on PK and pharmacodynamic parameters due to the differences in baseline characteristics between adult and pediatric T2DM subjects. The simulation allowed for the sample size to be reduced, while maintaining 85% probability of demonstrating superiority to placebo for dapagliflozin 10 mg.

Research Hypothesis:

Dapagliflozin results in a greater mean reduction from baseline in HbA1c compared to placebo after 24 weeks of double-blind add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycemic control on diet and exercise with metformin or insulin ± metformin.

Schedule of Analyses:

This analysis plan presents both the short-term (ST) and ST plus long-term (LT) analyses.

The ST analysis will be conducted once assessments and procedures have been completed for the first 24 weeks of the study. In addition, all relevant queries must be resolved before the blind is broken for analyses.

A similar process will be followed for the ST+LT period analysis, which will be conducted once all subjects have either completed or been discontinued from the study. In addition, all relevant queries are resolved and the database is locked.

2 STUDY DESCRIPTION

2.1 Study Design

The study is a prospective, multi-center, 24-week, placebo controlled, double-blind randomized study with a 28-week open label safety extension. Subjects ≥ 10 years and <25 years of age, with confirmed diagnosis of T2DM who are being treated with diet and exercise and a stable dose of metformin immediate or extended release (at least 1000 mg daily) for a minimum of 8 weeks prior to screening, or a stable dose of insulin for a minimum of 8 weeks prior to screening, or a stable combination of metformin and insulin for a minimum of 8 weeks prior to screening, will be screened against the inclusion and exclusion criteria, as per protocol. Eligible subjects meeting all criteria will enter a 4-week placebo lead-in period. Subjects will be instructed to follow a diet and exercise program (in accordance with the American Diabetes Association [ADA] or similar national guidelines) for the duration of the study. Subjects will maintain their baseline types of antidiabetic therapy throughout the study.

Recruitment (randomization) of subjects ≥18 and <25 years old will be limited to <40% of subjects. Recruitment (randomization) of subjects ≥10 and ≤15 years old will include at least 20% of subjects.

After the lead-in period, at least 66 subjects with HbA1c ≥ 6.5% and ≤ 11% at screening will be randomized 1:1 to receive oral blinded dapagliflozin 10 mg or placebo, stratified by gender, age (≥18 years vs. >15 to <18 years vs. ≤15 years) and baseline medication (metformin alone, insulin ± metformin). After completion of the 24-week ST treatment period, all subjects will enter the 28-week open label safety extension period for safety monitoring. All subjects will receive dapagliflozin 10 mg for the duration of this period. This will be followed by a 4-week post-treatment safety follow-up (FU) period.

Subjects who permanently discontinue study drug before the end of the study treatment period will enter a non-treatment, FU phase, in which subjects will follow their visit schedules with modified assessments until study completion.

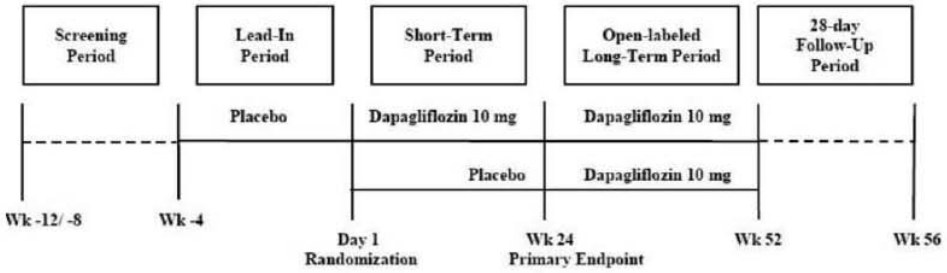
Glycemic rescue is permitted in the study for subjects who meet the criteria for lack of glycemic control in both the 24-week ST treatment period and the 28-week safety extension period.

Investigators will use insulin as rescue. Rescued subjects will continue treatment on study drug. These subjects will be identified by using the rescue insulin information collected in a dedicated case report form (CRF) named "Rescue insulin dosing." Safety measures will be collected throughout the study. This will include regular self-monitored blood glucose (SMBG) levels, self-monitored blood ketone (SMBK) levels, and monitoring of growth and development.

Population PK samples will be collected pre-dose and approximately 2 hours post-dose (± 1 hour) during the week 16 and 24 visits.

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



2.2 Treatment Assignment

At the screening visit each subject will be assigned a unique sequential subject number by the Interactive Web/Voice Response System (IXRS). This number will be used for identification throughout the study and will not be used for any other participant.

Randomized schedules will be generated and kept by the Sponsor or designee. Subjects will be randomly assigned to 1 of 2 blinded treatment groups by the IXRS in a 1:1 ratio. Randomization will be stratified by gender, age (≥18 years vs. >15 to <18 years vs. ≤15 years) and baseline medication (metformin alone, insulin ± metformin).

Subjects entering the 4-week placebo lead-in period

Following completion of the Screening activities, subjects who meet the all the inclusion and none of the exclusion criteria will be registered by the IXRS into the lead-in period, and receive blinded placebo treatment.

Subjects entering the 24-week double-blinded short-term treatment period

Following completion of the placebo Lead-In period, subjects who meet the criteria will be randomly assigned by the IXRS at the Day 1 Randomization visit, to 1 of the following 2 double-blind treatment arms in a 1:1 ratio:

- Blinded dapagliflozin 10 mg,
- Blinded placebo to match dapagliflozin 10 mg.

The 24-week ST period will have been completed for those subjects who continue into the 28-week open label LT period.

Subjects entering the 28-week long-term extension period

In the LT open-label treatment period, all subjects will receive open label dapagliflozin 10 mg, ie, subjects that were assigned to be on the blinded dapagliflozin 10 mg arm will receive open label dapagliflozin 10 mg and subjects that were assigned to be on the blinded placebo arm will receive open label dapagliflozin 10 mg. The 28-week open-term period will have been completed for those subjects who continue into the 4-week FU period.

At all study visits when study drug is dispensed, each subject will be assigned 1 or several Kit ID numbers by the IXRS. Kit ID numbers will be assigned non-sequentially and will correspond to the numbers printed on the bottles containing study drug, and will be recorded on the appropriate electronic case report form (eCRF).

2.3 Blinding and Unblinding

2.3.1 Blinding

The investigator, AstraZeneca (AZ) personnel, and subjects will remain blinded to treatment allocation throughout the ST double-blind treatment period.

For the duration of the ST double-blind treatment period (Day 1 to Week 24), the HbA1c and the urinary glucose values, including the urinary glucose:creatinine ratio, will be masked to the Sponsor and will not be available to the Investigator. During the open label long term extension period (Week 24 to Week 52), treatment and the above measurements will be unmasked and available to the Sponsor and the Investigator.

2.3.2 Unblinding

The database used for the analysis of the ST double-blind data of the study will be unblinded after all subjects have completed the ST double-blind treatment period of the study.

Blinding is critical to the integrity of this clinical trial. However, in the event of a medical emergency or pregnancy, during which knowledge of the identity of the investigational product (IP) is critical to the subject's management, procedures are in place to have the blind broken for an individual subject. A listing of all subjects whose treatment is unblinded during the study will be included in the Clinical Study Report (CSR). A separate procedure is in place for unblinding in case of expedited safety reporting to regulatory authorities.

The exception is for those personnel analyzing the PK data, the AZ Supply Chain Study Management team and the responsible personnel carrying out the packaging and labeling of IPs. The randomization information will be provided to ensure appropriate treatment allocation and that only PK samples from patients who were on the active study treatment are analyzed.

2.4 Protocol Amendments

This amended Statistical Analysis Plan (SAP) is based on Revised Protocol 03 dated 20 September 2017.

Table 1: Protocol History

Document	Date	Brief description of change
Original Protocol	9_Nov-2015	
Revised Protocol 01	15-Jan-2016	The purpose of this amendment was to incorporate new safety information related to diabetic ketoacidosis (DKA) as reflected in Dapagliflozin Investigators Brochure version 12, and correct typographical errors and discrepancies within the protocol.
Revised Protocol 02	13-Feb-2017	The purpose of this protocol amendment was to reflect the end of Bristol-Myers Squibb's role in the study, and to update the details of the Medical Monitor. The duration of the screening period was extended, and details relating to the masking of spot urine glucose, the study weeks relating to lack of glycemic control criteria for initiation of rescue medication, and the use of third-party vendors for Lost to Follow-Up subjects were clarified. The 24-hour emergency telephone numbers and SAE reporting details have been updated to PRA numbers
Revised Protocol 03	20-Sep-2017	The purpose of this protocol amendment was to increase the number of subjects randomized in the study to ensure that at least 50 subjects would complete the 24-week treatment period on IP and the Week 24 assessment

No protocol amendments or administrative letters that may affect the SAP have been processed beyond the version 03 of the protocol on which this SAP is based on.

2.5 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) comprised of Pediatric and Endocrine therapeutic area specialists and statisticians will be formed and will convene on a regular basis to review trial data. The DMC will be responsible for safeguarding the interests of the subjects in the trial by assessing the safety and efficacy of the interventions during the trial, and for reviewing the overall conduct of the clinical trial. The DMC will provide recommendations about stopping or continuing the trial and will be governed by a separate DMC Charter.

2.6 Hepatic Adjudication Committee

An independent Hepatic Adjudication Committee, blinded to the treatment of the subjects, will determine the probability that drug-induced liver injury (DILI) is the cause of liver-related abnormalities, including but not limited to, hepatic disorders leading to death, and liver laboratory abnormalities such as elevated aspartate aminotransferase (AST) and/or alanine

aminotransferase (ALT) with or without total bilirubin elevations (see study protocol for more details).

A separate Adjudication Charter will define and describe the procedure for the handling, reporting and classification of these events.

2.7 Diabetic Ketoacidosis (DKA) Adjudication Committee

An independent DKA Adjudication Committee, blinded to the treatment of the subjects, will adjudicate all potential events of DKA.

A separate Adjudication Charter will define and describe the procedure for the handling, reporting and classification of these events.

3 OBJECTIVES

3.1 Primary Objective

To compare the mean change from baseline in HbA1c achieved with dapagliflozin against the mean achieved with placebo after 24 weeks of double-blind add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycemic control on diet and exercise with metformin or insulin ± metformin.

3.2 Secondary Objectives

- To compare the mean change from baseline in fasting plasma glucose (FPG) achieved with dapagliflozin against the mean achieved with placebo after 24 weeks of double-blind add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycemic control on diet and exercise with metformin or insulin ± metformin.
- To compare the percentage of subjects who require glycemic rescue or who permanently discontinue treatment due to lack of glycemic control with dapagliflozin against the percentage with placebo over the 24 weeks of double-blind add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycemic control on diet and exercise with metformin, or insulin ± metformin.
- To compare the percentage of subjects with baseline HbA1c ≥7% who achieve a HbA1c level <7% with dapagliflozin against the percentage achieved with placebo after 24 weeks of double-blind add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycemic control on diet and exercise with metformin, or insulin ± metformin.

3.3 Safety Objectives

- To assess the safety and tolerability of dapagliflozin as add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycemic control on diet and exercise with metformin or insulin ± metformin when administered for up to 24 weeks of short-term therapy and 52 weeks of total therapy.
- To assess the percentage of subjects who experience hypoglycemia with dapagliflozin against the percentage achieved with placebo as add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycemic control on diet and exercise with metformin, or insulin ± metformin when administered for up to 24 weeks.
- To assess markers of growth and maturation, the incidence of DKA, and changes in markers of bone health with dapagliflozin against those observed with placebo as add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycemic control on diet and exercise with metformin or insulin ± metformin when administered for up to 24 weeks.

3.4 Exploratory Objectives

- To explore the PK and exposure-response relationship of dapagliflozin in patients aged 10 to less than 25 years with T2DM based on the collection of population PK samples.
- To explore the mean change from baseline in HbA1c achieved with dapagliflozin after 52 weeks of add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycemic control on diet and exercise with metformin or insulin ± metformin.
- To explore the mean change from baseline in FPG achieved with dapagliflozin after 52 weeks of add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycemic control on diet and exercise with metformin or insulin ± metformin.
- To explore the percentage of subjects who require glycemic rescue or who permanently discontinue treatment due to lack of glycemic control with dapagliflozin over the 52 weeks of add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycemic control on diet and exercise with metformin or insulin ± metformin.
- To explore the percentage of subjects with baseline HbA1c ≥7% who achieve a HbA1c level <7% with dapagliflozin after 52 weeks of add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycemic control on diet and exercise with metformin or insulin ± metformin.

4 ENDPOINTS

4.1 Primary Endpoint

Change from baseline in HbA1c at Week 24.

4.2 Secondary Endpoints

- The change from baseline in FPG at Week 24.
- The percentage of subjects who require glycemic rescue medication or who permanently discontinue treatment due to lack of glycemic control over the 24-week double-blind treatment period.
- Percentage of subjects with baseline HbA1c ≥7% who achieve HbA1c level <7% at Week 24.

4.3 Exploratory Endpoints

- The PK and exposure-response relationship of dapagliflozin based on the collection of population PK samples.
- The mean change from baseline in HbA1c achieved with dapagliflozin at Week 52.
- The mean change from baseline in FPG achieved with dapagliflozin at Week 52.
- The percentage of subjects who require glycemic rescue medication or who permanently discontinue treatment due to lack of glycemic control during the 52-week treatment period.
- The percentage of subjects with baseline HbA1c ≥7% who achieve a HbA1c level <7% at Week 52.

4.4 Safety Endpoints

Safety endpoints consist of the incidence of adverse events (AEs), serious adverse events (SAEs), hypoglycemic events, DKA events, permanent treatment discontinuations due to AEs, marked abnormalities in clinical laboratory tests, vital signs, Tanner staging, measures of growth and maturation, and safety laboratory tests.

5 SAMPLE SIZE AND POWER

In order to inform the design of this study, a Bayesian approach was employed to predict the potential efficacy of dapagliflozin on HbA1c in pediatric patients from the existing data and knowledge in adult T2DM patients.

Simulation results suggest a difference versus placebo in HbA1c of -0.78% for dapagliflozin 10 mg. Based on this estimated treatment difference of 0.78% and assuming a standard deviation (SD) of 0.9% for change from baseline in HbA1c at Week 24, a sample size of 25 per treatment group has 85% power to demonstrate the superiority of dapagliflozin 10 mg to placebo (where superiority is defined as a placebo-corrected HbA1c at 24 weeks indicating greater improvement that is statistically significant) at a 2-sided alpha level of 5 percent.

To ensure that at least 50 subjects will complete the 24-week double-blind treatment period on IP and the Week 24 assessment, at least 66 subjects will be randomized.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

This study consists of the following study periods:

1. The **screening period**. This period starts with enrollment and ends on the start of the lead-in period.
2. The **4-week lead-in period**. During this period, subjects will receive placebo medication.
3. The **24-week short-term double-blind treatment period**. On the Day 1 visit, subjects who meet all the protocol-specific enrollment and randomization criteria will be randomized. During this period, subjects will receive double-blind treatment.
4. The **28-week long-term open-label safety extension period**. After completing the short-term period, subjects will enter the 28-week open-label safety extension period for safety monitoring. During this period, subjects are planned to receive open-label study drug.
5. The **follow-up period**. In the 4-week (28 days) FU period subjects will not receive study drug, and a phone visit will be performed to assess AEs and medications.

The 52-week treatment period will be referenced as the combined ST+LT treatment period.

6.2 Treatment Groups

The “as randomized” treatment group is defined as the treatment group to which a subject was randomized at the start of the double-blind treatment period (even if the treatment they received was different).

The “as treated” treatment group is the same as the “as randomized” treatment group, except in cases where information was available which indicated that a subject received a different treatment for the entire course of their participation in the study (or period). In this case, the “as treated” treatment group is set to the treatment the subject actually received. In cases where a subject never received the treatment as assigned by randomization, then the “as treated” treatment group is the first treatment received.

6.3 Populations for Analyses

6.3.1 Enrolled Subjects Data Set

The Enrolled Subjects Dataset includes data collected from all subjects who signed informed consent.

6.3.2 Lead-in Subjects Data Set

The Lead-in Subjects Data Set includes data collected from all subjects from the Enrolled Subjects Data Set who received placebo medication during the lead-in period.

6.3.3 Full analysis Subjects Data Set

The Full Analysis Data Set (FAS) will consist of all subjects from the Enrolled Subject Data Set who are randomized and assigned to a treatment group though the IXRS. This is also known as the Intent to Treat (ITT) population or the Randomized Subjects Data Set. This will be the primary efficacy data set. This data set will be used for primary efficacy analysis and sensitivity analyses on the primary efficacy endpoint and secondary endpoint (FPG). Whenever using the FAS, subjects will be presented in the treatment group to which they were randomized at the start of the ST double-blind treatment period (even if the treatment they received was different).

6.3.4 Per Protocol Subjects Data Set

The Per Protocol Subjects Data Set will be a subset of the FAS, with all data points collected after relevant protocol deviations (RPDs) are excluded from the data set. Relevant protocol deviations are defined as deviations, that could potentially affect the interpretability of the study results and will be subject to complete exclusion (see Table 4). This data set will be used for sensitivity analyses of the primary efficacy endpoint if >10% of subjects in either treatment group have RPDs that lead to complete exclusion from efficacy analyses. Whenever using the Per Protocol Subjects Data Set, the subjects will be presented using the randomized treatment group.

6.3.5 Treated subjects Data Set

The Treated Subjects Data Set (also known as Safety Analysis Set) will consist of all subjects who receive at least 1 dose of study medication during the treatment period. This will be the primary safety data set. The Treated Subjects Data Set will include any subject who accidentally received double-blind study medication but was not randomized in the study. These subjects will be included in analyses using the treated subject dataset in the treatment they received. For randomized subjects, all analyses using the treated subject dataset will be presented by randomized treatment group, except in cases where information was available which indicated that a subject received a different treatment for the entire course of their participation in the study (or period). In this case, the safety data for those subjects will be presented by the treatment actually received. In case a subject never received the treatment as assigned by randomization, then the safety data for that subject will be presented by the first treatment received.

6.3.6 Pharmacokinetic Analysis Data Set

The Pharmacokinetic Analysis Data Set will include all subjects who received a dapagliflozin dose and have collected at least 1 PK sample during the 24-week double-blind ST period. The PK data will be presented using the treatment actually received, as described in Section 6.3.5.

7 STATISTICAL ANALYSES

7.1 General Methods

P-values corresponding to treatment group comparisons will be reported for the primary and secondary efficacy endpoints, without adjusting for multiplicity.

For each statistical model described below adjusted on randomization strata, in case of non-convergence (eg, because of sparse data), the following back-up models will be used in the presented order:

1) Collapse randomization strata of background therapy in two modalities to present: metformin only and insulin (with or without metformin),
2) Collapse randomization strata of background therapy and remove randomization strata of gender,
3) Collapse randomization strata of background therapy and remove randomization strata of gender and age,
4) Remove randomization strata of background therapy gender and age.

7.1.1 Definitions

7.1.1.1 Baseline Value

For each subject, the baseline value of a parameter is defined as the last valid assessment value for a parameter on or prior to the date of the first dose of the double-blind study medication.

7.1.1.2 Change from Baseline

Change from baseline to any Week t in any analysis period (ie, ST treatment period and combined ST+LT treatment period) is defined as follows:

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

where:

- $C_{\text{Week t}}$ is the change from baseline at Week *t*,
- $M_{\text{Week t}}$ 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 Section 8.3.

7.1.1.3 Percent Change from Baseline

Percent change from baseline to any Week *t* in any analysis (ie, ST treatment period and combined ST+LT treatment period) is defined as follows:

$$P_{Week\ t} = 100 \times (M_{Week\ t} - M_{baseline}) / M_{baseline}.$$

Where

- $P_{\text{Week t}}$ is the percent change from baseline at Week t,
- $M_{\text{Week t}}$ 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 Section 8.3.

For summaries and analyses of parameters in terms of percent change from baseline to Week t, baseline and Week t values will first be transformed to natural logarithms (Ln) and their difference (Ln(Week t) – Ln(baseline)) will be used in analysis For summaries and analyses of percent change from baseline to Week t, parameter estimates will be used to derive geometric mean percent changes from baseline. Formulae are detailed in Table 2.

Table 2: Formulae Used to Transform Back onto the Original Scale the Estimates of Percent Change from Baseline Analyzed as Geometric Mean

Quantity	Computation method
Geometric mean of the Week *t* to baseline ratio	Exp(mean change from baseline in natural logarithm)
Mean percent change from baseline	100 × [exp(mean change from baseline in natural logarithm*) – 1]
Standard error of mean percent change from baseline	100 × exp(mean change from baseline in natural logarithm) × standard error of mean change from baseline in natural logarithm* – or, equivalently – 100 × Geometric mean of the Week *t* to baseline ratio × standard error of mean change from baseline in natural logarithm*
Lower confidence limit for mean percent change from baseline	100 × [exp(lower confidence limit for mean change from baseline in natural logarithm*) – 1]
Upper confidence limit for mean percent change from baseline	100 × [exp(upper confidence limit for mean change from baseline in natural logarithm*) – 1]
Adjusted geometric mean of the Week *t* to baseline ratio	exp(Adjusted mean change from baseline in natural logarithm*)
Adjusted mean percent change from baseline	100 × [exp(Adjusted mean change from baseline in natural logarithm*) – 1]
Standard error of adjusted mean percent change from baseline	100 × exp(Adjusted mean change from baseline in natural logarithm) × standard error of mean change from baseline in natural logarithm* – or, equivalently – 100 × adjusted geometric mean of the Week *t* to baseline ratio × standard error of mean change from baseline in natural logarithm*
Lower confidence limit for adjusted mean percent change from baseline	100 × [exp(lower confidence limit for adjusted mean change from baseline in natural logarithm*) – 1]
Upper confidence limit for adjusted mean percent change from baseline	100 × [exp(upper confidence limit for adjusted mean change from baseline in natural logarithm*) – 1]
Adjusted geometric mean of the Week *t* to baseline ratio achieved with each dapagliflozin *treatment arm* relative to that achieved with C*ontrol*, expressed as a percent difference. Please note that for the SAS output, a shorter text will be used: Adjusted GM of Week *t*/Baseline for each dapagliflozin *treatment arm* relative to *Control*, in % difference.	100 × (((adjusted mean percent change for dapagliflozin *treatment arm* +100)/(adjusted mean percent change for *Control* +100)) – 1) – or, equivalently – 100 × (exp(difference in adjusted mean change from baseline between dapagliflozin *treatment arm* and *Control* in natural logarithm*) – 1)

*Change in natural logarithm refers to a calculated difference between 2 values after performing a natural logarithmic transformation on each.

7.1.1.4 Last Observation Carried Forward (LOCF including BOCF)

In the analysis of change (or percent change) from baseline, as well as response endpoint at Week *t* LOCF, the Week *t* measurement will be used. If no Week *t* measurement is available (subject has permanently discontinued treatment before Week *t,* or the subject has not discontinued, but the measurement was not taken at Week *t*), the last post-baseline measurement prior to Week *t* will be used. For subjects who started rescue medication or permanently discontinued from study drug due to lack of efficacy prior to Week *t*, their last valid post-baseline measurement taken prior to or on the earliest date between the date of the first dose of rescue medication and the date of discontinuation from study drug due to lack of efficacy will be used. For subjects with no post-baseline readings, the baseline value will be imputed (BOCF) for Week *t*.

7.1.2 Descriptive Summaries of Continuous Variables

Descriptive summaries of continuous variables in terms of absolute values, change or percent change from baseline values will be provided including n, mean, median, SD, minimum, and maximum by treatment group and overall, if applicable. For parameters of interest, for example laboratory values, compliance, duration of exposure, Q1 and Q3 will also be displayed. For dapagliflozin plasma concentration, following back transformation of a log transformed geometric mean will also be provided.

7.1.3 Descriptive Summaries of Categorical Variables

Descriptive summaries of categorical variables will consist of frequencies and percentages for each treatment group (and overall if applicable).

7.1.4 Summaries of Shift in Categorical Variables

Descriptive summaries of change from baseline in selected categorical variables will be provided using shift tables. Frequencies and percentages of subjects within each treatment group will be generated at each level corresponding to cross-classifications of baseline and the on-treatment values of the categorical parameter. The on-treatment value can either be the actual value at a certain post-baseline time point, or the minimum/maximum value in the direction of toxicity (for example, laboratory tests), or values within, outside reference range (laboratory tests) over the analysis period. Treatment group differences will not be assessed in summaries of shifts.

7.1.5 Analysis of Covariance (ANCOVA)

7.1.5.1 ANCOVA Model for Change from Baseline

In summaries of efficacy endpoints examining changes from baseline at Week *t* LOCF (imputing Week *t* BOCF if no evaluable post-baseline Week *t* value), ANCOVA of the differences between post-baseline and baseline measurements will be performed, with treatment group and randomization stratification factors as fixed effects and the baseline measurement as a covariate. The following ANCOVA model will be used:

$$D_{t,ijk} = intercept + \beta\,[Y_{0,ijk}] + \tau_i + s_k + error_{t,\ ijk} \quad (Model\ 7.1.5.1)$$

where

- $D_{t,ijk} = Y_{t,ijk} - Y_{0,ijk}$ = the Week *t* or Week *t* LOCF/BOCF change from baseline of subject *j* in treatment group *i and in stratum k* (as defined in Section 7.1.1.2),

- $Y_{0,ijk}$ is the baseline measurement of subject *j* in treatment group *i and in strata k*,
- $Y_{t,ijk}$ is the Week *t* or Week *t* LOCF/BOCF measurement of subject *j* in treatment group *i and in strata k*,
- β is the slope of $D_{t,ijk}$ regression on the baseline measurement and,
- τ_i is the mean effect of treatment group *i*.
- s_k is the mean effect of randomization stratum *k* (ie, category *k* of the stratification factor).

The model will provide least squares mean estimates and 2-sided 95% confidence intervals (CIs) for mean changes from baseline within and (when warranted) differences in mean change from baseline between treatments. Where applicable, t-statistics corresponding to the Type III sums of squares for the differences in the least squares means will be used to obtain p-values for treatment group comparisons.

7.1.5.2 ANCOVA Model for Percent Change from Baseline

For analyses of parameters in terms of percent change from baseline to Week *t* or Week *t* LOCF, values will first be transformed to logarithms and model estimates will be expressed as geometric mean percent changes from baseline. ANCOVA of the logarithms of the post-baseline to baseline ratios will be performed. Treatment group and randomization stratification factors will be considered as a fixed effect. The natural logarithm (Ln) of the baseline measurement will also be included as a covariate. The following ANCOVA model will be used:

$$Z_{t,ijk} = intercept + \beta\,[Ln(Y_{0,ijk})] + \tau_i + s_k + \text{error}_{t,\,ijk} \qquad \textit{(Model 7.1.5.2)}$$

where

- $Z_{t,ijk} = Ln(Y_{t,ijk}) - Ln(Y_{0,ijk})$ = the Week *t* or Week *t* LOCF change from baseline in the natural logarithm of subject *j* in treatment group *i and in stratum k*,
- $Y_{0,ijk}$ is the baseline measurement of subject *j* in treatment group *i and in stratum k*,
- $Y_{t,ijk}$ is the Week *t* or Week *t* LOCF measurement of subject *j* in treatment group *i and in stratum k*,
- β is the slope of $Z_{t,ijk}$ regression on the natural logarithm of the baseline measurement and,
- τ_i is the mean effect of treatment group *i,*
- s_k is the mean effect of randomization stratum *k* (ie, category *k* of the stratification factor),
- .

The model will provide least squares mean estimates and 2-sided 95% CIs for (geometric, derived) mean percent changes within and (when warranted) between treatments. Where applicable, the t-statistic corresponding to the Type III sums of squares for the differences in the least squares means will be used to obtain p-values for treatment group comparisons.

Table 2 details the formulae that will be used to transform back the results from model 7.1.5.2 to obtain the values reported in the tables.

7.1.6 Longitudinal Repeated Measures Analysis

7.1.6.1 Longitudinal Repeated Measures Analysis

A longitudinal repeated measures analysis using 'direct likelihood' will be performed. The SAS procedure PROC MIXED will be used.

The dependent variable will be the change from baseline to each Week t included in the model for efficacy endpoints examining changes from baseline. For analyses of parameters in terms of percent change from baseline at Week t, values will first be transformed to logarithms. The dependent variable will be the natural logarithms (Ln) of the post-baseline to baseline ratios. The model estimates will be back transformed to original scale using the formulae detailed in Table 2.

The preferred model will include the fixed categorical effects of treatment, week, randomization stratification factors (ie, 1 term for each stratification factor) and treatment-by-week interaction, as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. For parameters analyzed as percent change from baseline, the natural logarithm of the baseline values will be used in the above model specification. An unstructured matrix for the within-subject 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:

1) The first back-up model is the same as the preferred model but the Kenward-Roger method will be replaced by Satterthwaite approximation.
2) 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.
3) The subsequent backup models will be used in case of sparse data: removing randomization strata in sequential order and/or collapsing the randomization strata of background therapy as defined in Section 7.1.
   Similarly, a subsequent back-up model in the order presented Section 7.1 will only be provided if the preceding back-up model does not converge.

The model will provide least-squares mean estimates, standard errors (SEs) and 2-sided 95% CIs for mean change at all time points within and between treatments. Where applicable, for specific weeks, the t-statistic corresponding to the Type III sums of squares for the differences in the least squares means will be used to obtain p-values for treatment group comparisons.

7.1.6.2 Longitudinal Repeated Measures Analysis Model Assumption Assessment

The assumptions underlying the longitudinal repeated measures analysis model will be checked, if specified in Section 7.5. This section also details the steps to follow in case these assumptions would not be satisfied.

Assessment of Treatment-by-Baseline Interaction:

Treatment-by-baseline interaction will be assessed for the Week 24 estimates. In the model defined in Section 7.1.6.1, the interaction will be tested by including the treatment-by-baseline interaction.

The following contrast statements will be used of testing for interaction.

- Contrast coefficients for all weeks but Week 24 will be zero.
- Contrast coefficients at Week 24 are presented in Table 3.

Table 3: Contrast Coefficients for the treatment-by-baseline interaction for Week 24 estimates

Treatment by baseline interaction	Contrast Coefficients
Dapa 10mg by baseline value	1
Placebo by baseline value	-1

The test for interaction will be performed at the 0.10 level of significance. If significant, the interaction will be assessed as qualitative or quantitative. Assessment of the interaction type will be based on regression lines plotted for each treatment group (ie, predicted versus baseline values plotted separately for each treatment in a single overlay plot). The predicted values for these plots will be obtained from the analysis model including the interaction term. The abscissa of the plots will range from the minimum baseline value from all subjects included in the analysis to the maximum baseline value.

If the regression lines do not cross, or the crossing is judged not severe (ie, the crossing occurs near the boundary or beyond the range of baseline values), then the interaction will be considered quantitative and this does not compromise the validity of the treatment comparisons. In this case, the treatment comparisons will be made using the model without the interaction term.

Otherwise, the interaction will be considered qualitative and treatment comparisons will not be presented as a result of the complete model.

Outlier Detection:

Specifically, an outlier is defined as an observation with a residual that is more than 3 times the interquartile range above the 75th percentile or below the 25th percentile. Outliers will be identified based on diagnostics performed for the primary efficacy outcome measure using standardized residuals from the longitudinal repeated measurement model. These diagnostics will be based on the box plot. If outliers are present, then additional sensitivity analyses may be performed with the outliers excluded, in order to assess their impact on the results.

Adjustments for baseline imbalances:

Adjustments for baseline imbalances between treatment groups in the longitudinal repeated measures model may be performed as additional sensitivity analysis: baseline characteristics for which a clinically important imbalance exists between the treatments is identified. If such imbalances exist, an adjustment may be performed by including the corresponding baseline characteristics as additional covariates in the longitudinal repeated measures model. This will allow the assessment of the importance of these imbalances on the treatment group comparisons.

7.1.7 Kaplan-Meier Curve and Estimates for Time-to-Event Analyses

Kaplan-Meier plots[16] of time to event variables will be displayed by treatment group. Unless otherwise specified, the plot will be presented only when there are at least 5 "events" in each treatment group. Additionally, a table will accompany the plot and will display the Kaplan-Meier estimates of the cumulative event probabilities (with 95% CI calculated based on Greenwood's method[17] when applicable) of subjects with event at specific time points by treatment group. If the estimated lower bound of 95% CI is below 0 or the estimated upper bound of 95% CI is over 1, then it will be restricted to 0 or 1 respectively.

7.1.8 Proportion of Subjects with a Pre-defined Characteristic at Week t

The proportion of subjects with a *pre-defined characteristic (responders)* at Week *t* will be analyzed using a logistic regression when there are at least 5 responders by treatment group. For proportion of responders (eg, a responder is defined by HbA1c <7%), estimates, CIs, and tests will be obtained using a logistic regression. Odds ratios (OR) representing the responder odds in the dapagliflozin treatment group versus placebo group will be generated adjusted for baseline variable (eg, adjustment for baseline HbA1c) and randomization stratification factors (ie, 1 term for each stratification factor) using the SAS LOGISTIC procedure.

The frequencies of response/non-response and the associated crude response rates (as percentages) will be presented by treatment groups. In addition, adjusted percentages, SEs, and 95% CIs for each treatment group will also be displayed. Adjusted OR and corresponding 95% Wald CI, and p-values (uncorrected) will also be presented.

In case of non-convergence because of sparse data subsequent backup models will be used in removing randomization strata in sequential order and/or collapsing the randomization strata of background therapy as defined in Section 7.1. A subsequent back-up model in the order presented Section 7.1 will only be provided if the preceding back-up model does not converge.

When there are less than 5 responders by treatment group, the unadjusted (and difference) proportions, exact 95% CI using Chan-Zhang method, and p-values from the Fisher's exact test (when applicable) will be provided.

7.1.9 Multiple Imputation (MI)

Missing quantitative Week 24 data at study endpoint will be imputed from the 2 missing not at random (MNAR) imputation models for missing Week 24 data.

The multiple imputation "wash-out" (MI-WO) method, which is a "copy to reference method," will be implemented using a baseline to predict Week 24 values in the MNAR model. Furthermore, tipping point analyses will also be performed, which will impute missing Week 24 data for each treatment group under a "missing at random" (MAR) assumption (MI-MAR). The MNAR process will then correspond to the tipping point.

The randomization strata will be coded using indicator variables as follow:

- randomization strata of background therapy will be coded as
  - met (1) and ins (0) if metformin only,
  - met (0) and ins (1) if insulin only,
  - met (0) and ins (0) if insulin + metformin;
- randomization of background therapy if randomization strata when insulin only and insulin with metformin are grouped will be coded as
  - metins (1) if metformin only,
  - metins (0) if insulin only or insulin with metformin;
- randomization strata of age group will be coded as
  - age1 (1) and age2 (0) if age ≥10 and ≤15 years old,
  - age1 (0) and age2 (1) if age >15 and <18 years old,
  - age1 (0) and age2 (0) if age ≥18 and < 25 years old;
- randomization of gender will be coded as
  - gender (1) if male,
  - gender (0) if female.
- Treatment arm will be coded using indicator variables as
  - DTRT01P (1) for dapagliflozin treatment group
  - DTRT01P (0) for placebo treatment group

Each imputation model will use a common seed value of 201906.

7.1.9.1 Monotone Data Pattern

Prior to imputation, intermittent missing values (ie, missing values both preceded and followed by at least 1 non-missing value) will be imputed under a MAR model for missing data using a Markov chain Monte Carlo (MCMC) method of imputation.

Since in general the missing pattern will not be monotone, the first step for any of the methods presented below will be to use the MCMC method in conjunction with the MONOTONE statement of the SAS MI procedure to partially impute quantitative parameters, separately for each treatment group, to create imputed datasets with 1,000 values imputed for each missing value each contributing to one of the one thousand (1,000) imputation data sets. Each dataset will have a monotone missing data pattern (for each treatment group created by assuming a MAR missing data pattern. Indicators of randomization strata and treatment group (as described in Section 7.1.9) and visit (ie, baseline HbA1c along with Week 4, Week 8, Week 16 and Week 24 HbA1c) will be the parameters included in MCMC models.

7.1.9.2 Wash-Out Multiple Imputation Method

For each of the 1,000 monotone datasets generated as described in Section 7.1.9.1, the remaining missing data will be imputed separately for each treatment group using a REGRESSION method in conjunction with the MONOTONE statement and either MNAR statement (for dapagliflozin treatment group) or MAR statement (for placebo treatment group) of the SAS MI procedure.

- Step 1, the imputation model used to create monotone data pattern (see Section 7.1.9.1) will include factors and covariate in the following order: indicators representing randomization strata of gender, age group, background therapy and treatment group, baseline HbA1c, as well as Week 4, Week 8, Week 16, and Week 24 HbA1c.
- Step 2:
  For subjects from dapagliflozin treatment group with a non-missing baseline and a missing Week 24 HbA1c value, active treatment baseline value will be used to predict the Week 24 value using non-missing baseline and Week 24 data from the placebo group in modeling the MNAR process. The indicators representing randomization strata will be included in modeling the MNAR processes in the same order as described in Step 1. Therefore, the model used to generate Week 24 values will include, in the following order, indicators representing randomization strata of gender, age group and background therapy, and baseline HbA1c.
  While for subjects from placebo treatment group, missing data will be imputed sequentially at each assessment using a MAR imputation based on all non-missing data from that visit and data from all prior visits (after imputation). The indicators representing randomization strata will be included in modeling the MNAR processes in the same order as described in Step 1. Therefore, the model used to generate Week 24 values will include, in the following order, indicators representing randomization strata

of gender, age group and background therapy as well as, baseline HbA1c, and all HbA1c values (Week 4, Week 8, Week 16).

- Step 3: Each of the 1,000 values generated from the fit of the one thousand (1,000) MI-WO imputation models for each missing value generated Step 2 will correspond to a unique imputation number, and the combination of imputed and non-missing data for each result in 1,000 "complete datasets".

- Step 4: Imputed values from each of the 1,000 imputation datasets selected from Step 3 and the non-missing data will be analyzed by ANCOVA applied at Week 24, with terms for baseline HbA1c, randomization strata and treatment group as described in Section 7.1.5.1. In case of non-convergence, the imputation model will be simplified removing/collapsing the randomization strata indicator variables in a stepwise manner as described in Section 7.1.

- Step 5: Results from each ANCOVA model will be combined as described in Section 7.1.9.3.

7.1.9.3 Combining Multiple Imputation Results

The analysis model will be evaluated in each of the imputed datasets, and the point estimates and SEs will be combined using Rubin's rules to produce valid global estimates with corresponding CIs and p-values. SAS MIANALYZE procedure will be used for this purpose.

7.1.9.4 Tipping point analyses

Using monotone datasets generated as described in Section 7.1.9.1, the remaining missing data will be imputed using a REGRESSION method in conjunction with the MONOTONE statement and the MNAR statement of the SAS MI procedure.

- Step 1, the imputation model used to create monotone data pattern (see Section 7.1.9.1) will include factors and covariate in the following order: indicators representing randomization strata of gender, age group, background therapy and treatment group, baseline HbA1c as well as Week 4, Week 8, Week 16 and Week 24 HbA1c.

- Step2, missing Week 24 values will be imputed from non-missing patient data up to (following imputation) and including that assessment separately for each treatment. MI-MAR will correspond to the first imputation model fit in the tipping-point analysis (ie, at delta=0). In subsequent models, a common (non-zero) delta value (where delta represent HbA1c (in %) will be added following MAR imputation to each imputed value in the active treatment group (eg, the MNAR mechanism), while imputed values for the placebo treatment group remain as MAR (no delta addition). MAR imputations followed by delta additions will be performed at the first scheduled post-treatment assessment through Week 24 and models will include in the following order, indicators representing randomization strata of gender, age group and background therapy, indicator representing treatment group as well as, baseline HbA1c and all HbA1c values (Week 4, Week 8, and Week 16).

For the first imputation model (delta=0), one thousand (1,000) imputation datasets will be generated using the 1000 monotone datasets generated at Step 1. For the subsequent imputation models (delta >0), the same monotone datasets as those used for the first imputation model (delta=0) will be retrieved.

- Step 3, the thousand (1,000) imputation datasets generated for each value of delta will be analyzed by an ANCOVA applied at Week 24, with terms for baseline HbA1c, randomization strata and treatment group as described in section 7.1.5.1.
- Step 4: For each value of delta, results from each ANCOVA model will be combined as described in Section 7.1.9.3.
- The tipping-point corresponds to the first instance where primary inference changes (ie, p>0.05 for the between-group difference in LS Means). Consequently, the testing (Steps 2 to 4) will be repeated over plausible $\delta_{dapagliflozin}$ values using a grid search method. For example, larger changes in delta values initially followed by smaller changes as the tipping-point is reached. Therefore the values of delta will be indexed.
- Step 5: Results corresponding to each delta value will be presented within a summary table following the format of data presentation of results from ANCOVA analyses.

7.2 Study Conduct

Subjects who deviate from protocol conditions (eg, important inclusion/exclusion criteria) will be reported as having Important protocol deviations. A list of Important protocol deviations is provided Table 5. Important protocol deviations that are determined to affect the primary efficacy results are deemed RPDs. A list of RPD criteria, along with the consequent handling of data should those deviations occur, is given in Table 4.

Table 4: List of Relevant Protocol Deviations

Number	RPD criteria	Exclusion Level
1	Randomized subjects without T2DM or central laboratory HbA1c obtained at enrollment not within ± 0.2% of the protocol-specific HbA1c range	Complete exclusion
2	Randomized subjects not satisfying the target population baseline antihyperglycemic therapy requirement.	Complete exclusion
3	Randomized subjects that used antihyperglycemic medication (other than protocol allowed medication, and/or open-label rescue medication) (including situations where subjects randomized to placebo mistakenly received active blinded treatment during the treatment period) for 14 or more consecutive days during short-term double-blind treatment-period.	Partial exclusion (All efficacy data after the 14th day of administration non-protocol required antihyperglycemic medication will be excluded)
4	Randomized subjects that were treated with any systemic corticosteroid therapy for ≥5 consecutive days during short-term double-blind treatment period.	Partial exclusion (All efficacy data after the 5th day of systemic corticosteroid therapy will be excluded)
5	Randomized subjects with treatment compliance <80 % during the 24-week short term double-blind treatment period	Complete exclusion.
6	Abnormal free T4 values at enrollment	Complete exclusion
7	History of hemoglobinopathy, with the exception of sickle cell trait (SA) or thalassemia minor; or chronic or recurrent hemolysis.	Complete exclusion

Table 5: List of Important Protocol Deviations

Number	Important protocol deviation criteria
01	Inclusion Criteria
02	Exclusion Criteria.
03	Study Drug.
04	Assessment Safety.
05	Lab/Endpoint Data
06	Visit Window
07	Informed Consent
08	Prohibited Co-Medication
09	Overdose/Misuse
10	Other (diary completion, site staff qualifications, safety reports etc).

Subjects having RPDs will be summarized by treatment group and overall per level of exclusion (ie, complete/partial) and for all RPDs. They will also be listed. If the proportion of RPDs leading to total data exclusion is 10 percent or more in either treatment, then primary analysis will be repeated with exclusion of all patients with total data exclusions. Subjects with other significant (excluding RPDs) protocol deviations will be listed in a separate report and summarized by treatment group and overall per category as defined in Table 5. Any subject with both relevant and other significant (excluding relevant) protocol deviations will appear in both listings.

Relevant protocol deviations, which are defined during the ST period will be summarized for this study period.

Important protocol deviations will be summarized for the ST period (not including RPDs) and for the combined ST+LT period (including RPDs).

7.3 Study Population

7.3.1 Subject Disposition

The disposition of subjects for the screening period, lead-in, the ST double-blind treatment period and the open-label LT treatment period will be summarized:

1) The summary of status in the screening period will include all subjects enrolled (who signed informed consent). It will summarize the number of subjects enrolled, number of subjects that completed the screening period (ie, entered the lead-in period), number of subjects discontinued from the screening period and a summary of the corresponding reasons for discontinuation.
2) The summary of status in the lead-in period will include all subjects who entered lead-in period. It will summarize the number of subjects who entered in the lead-in period, number of subjects that were randomized, number of subjects who were not randomized and a summary of the corresponding reasons for not being randomized.
3) The summary of status in the combined ST+LT treatment period will include all randomized subjects and will be presented by randomized treatment group (and overall) using the FAS. This summary will include subjects that completed and discontinued treatment/study during the ST period with reasons for discontinuation, entered the LT treatment period, completed the LT treatment period, discontinued the treatment /study during the LT treatment period with reasons for discontinuation. This summary will only be presented at the time of the final database lock.

Listings will also be provided.

Subjects randomized and treated will be summarized by country and study site.

7.3.2 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics, including diabetes-related characteristics and renal function characteristics will be summarized by treatment group and overall, using the FAS (and the Per Protocol Subjects Data Set if deemed necessary). Furthermore, description by estimated glomerular filtration rate (eGFR) category at screening will also be split by age (<18 year old, ≥ 18 year old). In addition, description of the randomization strata will be performed using the FAS. No statistical tests will be performed to compare treatment groups at baseline.

Standardized height, weight and body mass index (BMI) will be derived for subjects ≤20 years old based on their age and for subjects >20 years old based on the age of 20-year-old. The Standardized measures adjusted for age and gender will be derived as z-score using the Centers for Disease Control and Prevention (CDC) growth chart[20]. Standardized values will be summarized as continuous variables, and will be presented by treatment group and overall. In addition, standardized BMI will also be presented using the following category of percentiles: >= 95th (refers to Obese), >= 85th and <95th (refers to Overweight), >= 5th and <85th (refers to Healthy Weight), and <5th (refers to Underweight).

A description of each randomization strata will also be presented per category as defined in the eCRF and overall; split by assigned treatment group and overall.

Demographic and baseline characteristics are listed in Table 6. Diabetes related baseline characteristics are listed in Table 7. Renal function baseline characteristics are listed in Table 8.

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 subjects in the data set, overall and by treatment group (ie, each denominator includes the number of subjects with missing/unknown values for the characteristic).

Table 6: Demographic and Baseline Characteristics

Characteristic	Summarized as	Categories
Gender	Categorical	Male, Female
Age	Categorical and Continuous	≥10 and ≤15 yrs >15 and <18 yrs ≥18 and <25 yrs
Race	Categorical	White, Black or African American, Asian, Other
Body Weight and standardized weight	Continuous	-
Height and standardized height	Continuous	
BMI	Categorical and Continuous	<30 kg/m^2 ≥30 kg/m^2 <25 kg/m^2 ≥25 kg/m^2 ≥27 kg/m^2 ≥30 kg/m^2
Standardized BMI	Categorical and Continuous	*(Percentiles as defined by CDCS)** ≥95th ≥85th and <95th ≥5th and <85th <5th
Geographic Region	Categorical	As defined in APPENDIX 1

** ≥95th refers to Obese; ≥85th and <95th refers to Overweight ; ≥5th and <85th refers to Healthy Weight; <5th refers to Underweight.*

Table 7: Diabetes-Related Baseline Characteristics

Duration of Type 2 Diabetes	Categorical and Continuous	<3 yrs ≥3 and ≤10 yrs >10 yrs
Screening HbA1c	Categorical and Continuous	<6.5% ≥6.5 and <11% ≥11%
Baseline HbA1c	Categorical and Continuous	<6.5% ≥6.5 and <9% ≥9% and <11% ≥11% <8% ≥8%
Baseline/Screening FPG	Categorical and Continuous	≤14.2 mmol/L (255 mg/dL) >14.2 mmol/L (255 mg/dL)
Background anti-diabetic medication	Categorical	Metformin only Insulin only insulin+metformin
Background anti-diabetic medication daily dose	Continuous	Metformin dose (mg) Insulin dose (Insulin dose)
Combinations of randomization stratification factors	Categorical	Male - ≥10 and ≤15 years – Metformin only Male - ≥10 and ≤15 years - insulin only Male - ≥10 and ≤15 years - insulin + metformin Male - >15 years and <18 years – Metformin only Male - >15 years and <18 years - insulin only Male - >15 years and <18 years - insulin + metformin Male - ≥18 and <25 years – Metformin only Male - ≥18 and <25 years - insulin only Male - ≥18 and <25 years - insulin + metformin Female - ≥10 and ≤15 years – Metformin only Female -≥10 and ≤15 years - insulin only Female - ≥10 and ≤15 years - insulin + metformin Female - >15 years and <18 years – Metformin only Female - >15 years and <18 years - insulin only Female - >15 years and <18 years - insulin + metformin Female - ≥18 years – Metformin only Female - ≥ and <25 18 years - insulin only Female - ≥18 and <25 years - insulin + metformin

Table 8: Baseline Renal Function Characteristics

Characteristic	Summarized as	Categories
Screening eGFR	Categorical and Continuous	<60 mL/min/1.73m^2
		≥60 and <80 mL/min/1.73m^2
		≥80 mL/min/1.73m^2
Baseline eGFR	Categorical and Continuous	<60 mL/min/1.73m^2
		≥60 and <90 mL/min/1.73m^2
		≥90 and <120 mL/min/1.73m^2
		≥120 mL/min/1.73m^2

7.3.3 Specific and General Disease Histories

The number (percent) of subjects with T2DM, diabetes-related disease histories will be summarized by treatment group and overall using the FAS.

The number (percent) of subjects with general medical history findings will also be summarized per Medical Dictionary for Regulatory Activities (MedDRA), System Organ Class (SOC) and Preferred Term (PT), by treatment group and overall using the FAS.

7.4 Extent of Exposure

7.4.1 Study Medication

The extent of exposure to study medication for the ST double-blind treatment period is defined as the difference between the last and the first dose of study medication in the ST double-blind treatment period plus 1 day.

The extent of exposure to study medication for the ST+LT treatment period is defined as the difference between the day of the last dose of study medication and the day of the first dose of double-blind treatment period plus 1 day.

The extent of exposure to study medication will be summarized using the Treated Subjects data set for the ST double-blind treatment and for the ST+LT open-label treatment periods. The same summaries will be repeated prior to rescue medication initiation.

The number and percent of subjects with an extent of exposure within pre-specified day ranges will be presented by treatment group. The categorization for the ST double-blind treatment period of 24 weeks is 1-7, 8-14, 15-28, 29-42, 43-56, 57-70, 71-84, 85-98, 99-140, 141-182, and >182 days. The categorization for the ST+LT open-label treatment periods of 52 weeks is 1-90, 91-180, 181-270, 271-365, >365 days. The mean (SD), median, first and third quartiles and range of the number of days of exposure will also be presented. In addition, the exposure in terms of total patient-years will be calculated by treatment group as the sum of the exposure to study medication of all subjects (in years) in a treatment group.

The extent of exposure will be presented for the ST period following unblinding of the ST data, and for the combined ST+LT period at the time of the final database lock.

A listing of subjects by batch number of study medication will also be generated, identifying IP dispensed for the lead-in period, the ST period and the LT period.

7.4.2 Current and Concomitant Medications

Current and concomitant medications will be summarized using the Treated Subjects 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 current medication,
- all concomitant medication,
- All insulin anti-diabetic medication
- All non-insulin anti-diabetic medication

Current medications are defined as medications with a start date prior to the first day of ST double-blind treatment period and without a stop date prior to the consent date, ie, current medication will be any medication with at least 1 dose taken on or after the day of consent date up to the day prior to the first dose of study medication.

Concomitant medication during the ST double-blind treatment period or during the ST+LT treatment period is defined a medication with either

- a recorded medication start date falling within the ST double-blind treatment period or during the ST+LT treatment period, or
- a recorded medication start date prior to the first day of study medication during the ST double-blind treatment period or during the ST+LT treatment period without any recorded medication stop date prior to the start of the ST double-blind treatment period.

Concomitant medications for the ST double-blind treatment period (or for the ST+LT treatment period) will be any medication taken from start of the ST double-blind treatment period up to the end of the ST double-blind treatment period (or of the ST+LT treatment period).

Missing and partial date handling of start and stop dates of current and concomitant medications, is described in Section 8.6. The WHO dictionary will be used to code the non-study medication.

7.4.3 Measurements of Treatment Compliance

Percent treatment compliance is calculated during the ST double-blind treatment period and the ST+LT treatment period for the study medication. Percent compliance is defined as the number of tablets taken divided by the number of tablets that should have been taken multiplied by 100. A subject is considered compliant if percent compliance is ≥80% and ≤120%. The number and percent of subjects compliant during the ST double-blind treatment period and during the ST+LT treatment period will be displayed for the Treated Subjects data set. Treatment compliance will be presented for the ST period following data unblinding and for the combined ST+LT period at the time of the final database lock.

Details in calculating percent compliance are specified in Section 8.9.

7.5 Efficacy

7.5.1 Primary Efficacy Analyses

The primary endpoint is the change in HbA1c from baseline to Week 24. The comparison between dapagliflozin and placebo groups will be performed at a Type I error level of the 0.05 level (two-sided).

The primary analysis of the primary endpoint will be based on a mixed model for repeated measures (MMRM), as described in Section 7.1.6.1, including all scheduled time points following randomization up to and including Week 24. This model will include subjects in the FAS who have a baseline measurement and at least 1 post-baseline measurement. The primary analysis will only include measurements prior to the administration of rescue medication or permanent discontinuation from study drug. MMRM will be performed using a 'direct likelihood' approach, with model terms as outlined in Section 7.1.6.1.

Point estimates and 95% CIs for the mean change in HbA1c for each treatment group as well as the difference in the estimated mean change between the dapagliflozin treatment group and placebo will be calculated. The p-value of the difference in Week 24 estimates between dapagliflozin and placebo will be presented. In addition, a line plot of LSmean ± 95% CI will be displayed for the ST and combined ST+LT periods.

7.5.2 Sensitivity Analyses on primary endpoint

To assess the robustness of the primary efficacy analysis for the change in HbA1c from baseline to Week 24, additional sensitivity analyses will be carried out using the following approaches:

- A longitudinal repeated measures analysis, similar to the primary analysis, but using all available data, ie, regardless of rescue therapy initiation or discontinuation from the study drug will be performed for the FAS.

- If at least 10 percent of patients in either treatment group have RPDs leading to complete data exclusion from the ST period, then a longitudinal repeated measures analysis will be performed using the Per Protocol Subjects Data Set. This will be, similar to the primary analysis, but including subjects in the Per Protocol Subjects Data Set who have a baseline assessment and any post-baseline assessment prior to rescue therapy initiation or permanent discontinuation from study drug (see Section 7.1.6.1).

- Intend-to-treat analysis by MI-WO
  Multiple imputation based the MI-WO (copy to reference) method will be performed (See Section 7.1.9.2). This method will include all subjects from the FAS (as described in Section 7.1.9.2).

- Tipping point analysis
  This method, as described in Section 7.1.9.4, will include all subjects from the FAS. All the observations will be included regardless of rescue therapy initiation or permanent discontinuation from study drug to support the intent-to-treat principle.

- ANCOVA analysis will include all subjects from the FAS who have a baseline assessment. In case of no change from baseline to Week 24 value prior to rescue therapy initiation or

permanent discontinuation from study drug, Week 24 observations will be imputed using LOCF methodology for those patients having at least 1 post-baseline assessment of change and a change of 0 will be imputed using a BOCF approach for those without any post-baseline evaluable assessment (as described in Section 7.1.1.4).

In addition to these analyses, descriptions of missing HbA1c as well as HbA1c data collected following rescue therapy initiation or permanent treatment withdrawal will include:

- A description per visit by treatment group during the ST period of:
  - the cumulative number of subjects who permanently discontinued study medication,
  - the cumulative number of subjects who permanently discontinued study medication but still on study,
  - the cumulative number of subjects rescued,
  - the cumulative number of subjects rescued but still on study,
  - the cumulative number of subjects rescued or who permanently discontinued study medication,
  - the cumulative number of subjects rescued or who permanently discontinued study medication but still on study,
  - the cumulative number of subjects withdrawn from study,
  - the cumulative number of subjects rescued or who permanently discontinued study medication but having a HbA1c value,
  - the number of subjects still on treatment, still on study, not rescued but who missed a given visit,
- A graphical summary presenting the monotone missing data pattern from baseline to Week 24 presenting HbA1c values for completers as well as presenting HbA1c values collected before and after rescue therapy initiation or premature end of study medication by treatment group, along with corresponding summary table.

7.5.2.1 Summaries of Change in HbA1c from baseline at Week 24 within Subgroups

The primary efficacy endpoint of HbA1c will be summarized for the subgroups defined on the basis of the categorized variables listed in Table 9, and for stratification factors (also listed in Table 9).

Table 9: Subgroup Analyses of Primary Efficacy Endpoint for HbA1c

Group variable	Subgroups
Race	White Non-White
Gender	Female Male
Baseline HbA1c	<8% ≥8%
Subject age	≥10 and ≤15 yrs, >15 and <18 yrs, ≥18 and <25 yrs
Geographic region	EU* Non-EU
Background medication	Metformin, only Insulin only Insulin+metformin
Baseline Body Mass Index	<30 kg/m^2 ≥30 kg/m^2

*EU means Europe

If the value of the group variable cannot be determined, the subject will be excluded from the corresponding subgroup analysis.

The subgroup-by-treatment interaction will be assessed for the primary efficacy endpoint using the longitudinal repeated measures analysis model as described in Section 7.1.6.1 and in Section 7.5.1 with subgroup, subgroup-by-week, subgroup-by-treatment group and subgroup-by-week-by-treatment group interaction as 4 additional effects. Models for subgroup analyses which evaluate baseline HbA1c level will include terms for the categorized baseline HbA1c level and not (continuous) baseline values. Models for subgroup analyses which evaluate a randomization variable will include term(s) for that variable in the analysis model (ie, subgroup, subgroup*treatment, subgroup*week, and subgroup*treatment*week) and will include terms for the remaining randomization strata as main effects (ie, subgroup).

For groups with K ($K \geq 2$) subgroups, the subgroup-by-treatment interaction will be tested using a single (K-1)-degree-of-freedom hypothesis. Statistical significance of a Week 24 treatment*subgroup interaction will be assessed at an unadjusted 0.10 level, and Forest plots will be used to evaluate significant interactions. The categories stated in Table 9 will be used to assess the subgroup-by-treatment interaction. The adjusted mean changes from baseline, SEs, and 95% CIs for each subgroup and the nominal p-value for subgroup by treatment interaction will be summarized. Although included in the analysis model, if, in any treatment group, the

number of subjects is less than 10 then only the summary statistics for that subgroup will be presented and the subgroup(s) will not be included in tests for subgroup-by-treatment interaction.
For background therapy subgroup, if the number of subjects within 'insulin only' or 'insulin+metformin' category is less than 10, these 2 categories will be grouped.

7.5.3 Secondary Efficacy Analysis

7.5.3.1 Sequential Testing Methodology for the Secondary Endpoints

The family-wise Type I error rate related to the primary and secondary efficacy endpoints will be controlled at the 2-sided 0.05 level by using a hierarchical closed testing procedure.

For comparison of dapagliflozin 10mg group versus the placebo group, if the primary endpoint is significant, the statistical tests for the secondary efficacy endpoints will be performed. The Type I error rate for comparing dapagliflozin 10mg group to the placebo group for each secondary efficacy endpoint will be controlled at the nominal 0.05 level (2-sided). Secondary efficacy endpoints will be tested in the order that they appear in the study objectives section of the protocol and protocol synopsis, and in Section 4.2 as: firstly the change from baseline in FPG, secondarily the percentage of subjects who require glycemic rescue medication or permanently discontinue treatment due to lack of glycemic control over 24 weeks double-blind treatment period and thirdly the percentage of subjects with baseline HbA1c ≥7% who achieve HbA1c level <7% at Week 24 (note that in the following sections secondary endpoints may appear in an order different than the order that they will be tested). Statistical tests between dapagliflozin 10mg group and the placebo group will be performed, and inference provided, for a given secondary endpoint if all previous sequential tests for that comparison achieve statistical significance. Otherwise, inference from the testing procedure will stop at the secondary endpoint that does not reach statistical significance at the nominal Type I error level.

P-values will be calculated for all comparisons for the secondary endpoints. However, no claim will be based on endpoints for which the statistical testing is not performed for the endpoint as per the testing strategy as described above. No claims can be made based on these p-values. A clear distinction will be made between p-values whereby claims can and cannot be made.

7.5.3.2 Change from baseline in fasting plasma glucose at Week 24

The change in FPG from baseline to Week 24 is the first secondary endpoint. The comparison between dapagliflozin 10mg group and placebo will be performed following the testing procedure outlined in Section 7.5.3.1.

The primary analysis will only include measurements prior to the administration of rescue medication or permanent discontinuation from study drug. MMRM will be performed using a 'direct likelihood' approach, with model terms as outlined in Sections 7.1.6.1 and 7.1.6.2 and will include subjects from the FAS.

Point estimates and 95% CIs for the mean change in FPG for each treatment group, as well as the difference in the estimated mean change between the dapagliflozin treatment group and placebo group, will be presented. In addition, a line plot of LSmean ± 95% CI will be displayed.

To assess the robustness of the analysis for the change in FPG from baseline to Week 24, a similar longitudinal repeated measures analysis will be performed on the FAS using all available data, ie, regardless of rescue therapy initiation or permanent discontinuation from the study drug.

7.5.3.3 Proportion of subjects discontinued due to lack of glycemic control or rescued for failing to achieve pre-specified glycemic targets at or prior to Week 24

The proportion of subjects who require glycemic rescue medication or permanently discontinue treatment due to lack of glycemic control over the 24-week double-blind treatment period is the second secondary endpoint. The comparison between the dapagliflozin treatment group and the placebo treatment group will be performed following the hierarchical testing procedure outlined in Section 7.5.3.1.

The proportion will be analyzed using the methodology outlined in Section 7.1.8. Point estimates and 2-sided 95% CIs for the adjusted proportion within each treatment group, as well as the OR and corresponding p-value will be calculated. The analysis will use subjects in the primary efficacy dataset (ie, FAS). Subjects lost to follow-up will be considered as permanent treatment discontinuation at the time of last assessment.

Additionally the time to glycemic rescue medication initiation or permanent treatment discontinuation due to lack of glycemic control will be presented by treatment group using a Kaplan-Meier curve applying methodology described in Section 7.1.7. A plot will be presented only when there are at least 5 subjects meeting the criteria in 1 treatment group. An accompanying table of the cumulative event probabilities at specific time points during the ST double-blind treatment period will be produced. No p-value will be presented for this analysis. Subjects not rescued and not permanently discontinued from IP due to lack of glycemic control on/before Week 24 will be censored at the Week 24 visit date or the last visit date for those withdrawing from the study before Week 24 visit. Subjects lost to follow-up during the ST period will be censored at their latest assessment date whereas subjects having skipped Week 24 visit will be censored at the latest Week 24 assessment date in either treatment group.

7.5.3.4 Proportion of subjects with baseline HbA1c ≥7% who achieve HbA1c level <7% at Week 24

The proportion of subjects with baseline HbA1c ≥7% who achieve HbA1c level <7% at Week 24 is the third secondary endpoint. The comparison between the dapagliflozin treatment group and the placebo treatment group will be performed following the hierarchical testing procedure outlined in Section 7.5.3.1.

The proportion will be analyzed using the methodology outlined in Section 7.1.8. Point estimates and 2-sided 95% CIs for adjusted proportion within each treatment group, as well as the OR and corresponding p-value, will be calculated. The analysis will use subjects in the primary efficacy dataset (ie, FAS). Subjects who do not achieve a therapeutic glycemic response, are rescued, permanent discontinued from study drug, lost to follow-up, or are missing an assessment at Week 24 will be considered as not achieving glycemic response (counted as treatment failures).

The proportion of subjects having an HbA1c Week 24 value <7% independently of their baseline values will also be analyzed using the same analysis. No statistical testing will be performed to compare the dapagliflozin and the placebo treatment groups. Nominal p-value will be provided.

7.5.4 Exploratory Efficacy Analysis

Although all subjects receive open-label dapagliflozin 10 mg during the LT period, results will be presented by randomized treatment assigned. Statistical testing will not be performed, and p-values will not be generated for exploratory analyses.

7.5.4.1 Change from baseline to Week 52 in HbA1c and fasting plasma glucose

The change from baseline to Week 52 in HbA1c and FPG are exploratory endpoints of the study.

The same analysis as described for primary (see Section 7.5.1) and secondary (see Section 7.5.3.2) efficacy analysis will be used, respectively. They will include all scheduled assessments from baseline to Week 52.

For both HbA1c and FPG the same analysis will be repeated both excluding and including data after administration of rescue medication or permanent study treatment discontinuation (using the FAS).

7.5.4.2 Proportion of subjects discontinued or rescued for failing to achieve pre-specified glycemic targets at or prior to Week 52 and time to Glycemic rescue therapy initiation or withdrawal to study treatment due to lack of glycemic control

The proportion of subjects who require glycemic rescue medication or who permanently discontinue study treatment due to lack of glycemic control during the 52-weeks treatment period is an exploratory endpoints of the study. The same analysis as described for the secondary endpoint (see in Section 7.5.3.3) will be repeated including all data during the ST+LT period.

However, subjects not rescued and not permanently discontinued from IP due to lack of glycemic control on/before Week 52 will be censored at the Week 52 visit date or the last visit date for those withdrawing from the study before Week 52 visit. Subjects lost to follow-up will be censored at their latest assessment date.

7.5.4.3 Proportion of subjects with baseline HbA1c ≥7% who achieve HbA1c level <7% and Proportion of subjects who achieve HbA1c level <7% whatever baseline status at Week 52

The percentage of subjects with baseline HbA1c ≥7% who achieve a HbA1c level <7% at Week 52 as well as the percentage of subjects who achieve a HbA1c level <7% regardless of baseline HbA1c status at Week 52 are exploratory endpoints of the study. The same analyses

as described for the secondary endpoint (see in Section 7.5.3.4) will be repeated including all data during the ST+LT period. Subjects permanently discontinued from study treatment, lost to follow-up, rescued or missed measurements (regardless type of missing) at the specified time point will be considered as not achieving glycemic response.

7.6 Pharmacokinetic Analyses

Pharmacokinetic concentrations for dapagliflozin achieved with the dapagliflozin treatment group at every time point of protocol defined collection will be summarized and listed.

Summaries will include the calculation of arithmetic mean, SD, geometric mean, geometric SD, coefficient of variation, median, minimum and maximum values, and number of subjects having a value below the lower limit of quantification (LLOQ) and will be presented at the time of the 24-week database lock.

The analyses will be performed using the Pharmacokinetic Analysis Dataset.

All PK analyses, including the exposure-response relationship of dapagliflozin, will be described in a separate Pharmacokinetics Analysis Plan and reported separately from the CSR.

7.7 Safety

This safety section describes safety analyses that will be conducted both for ST double-blind treatment period and ST+LT treatment periods. The same analyses will be repeated for both periods. Therefore, in the sections below, the word "period" will refer to either ST double-blind treatment period or ST+LT treatment period, respective on the analysis. Safety analyses will be presented for the ST period at time of 24-week data unblinding and for the combined ST+LT period and the FU periods at the time of the final database lock.

The analysis including all data, regardless of rescue following the first dose of double-blind study medication during the period, for the Treated Subjects data set is the primary safety analysis and will be performed for all safety variables specified below. Sensitivity safety analyses excluding data from subjects after rescue medication initiation during period utilizing the Treated Subjects data set will be performed for selected summaries of Adverse Events as mentioned in Sections 7.7.1 and 7.7.2.1. Measurements obtained after start of administration of rescue medication will be excluded in sensitivity analyses. The Treated Subjects Data Set will be used in all summaries of safety data.

7.7.1 Adverse Events

Adverse Events will be classified by primary SOC and PT according to the MedDRA. Summaries of AEs will use the version of MedDRA that is current at the time of database lock for each study period.

No statistical test will be performed to compare AE rates between treatment groups. This policy was adopted to recognize the lack of power and the potential for misleading interpretation based on repeated statistical tests which increase the family wise Type I error level.

Counting rules for AEs are described in Section 8.7.

In summaries by SOC and PT, AEs will be sorted by decreasing frequency within each SOC and PT according to the Dapagliflozin treatment group. In summaries by PT, AEs will be sorted by decreasing frequency within PT according to the dapagliflozin treatment group.

Separate pages to capture events of hypoglycemia or DKA are contained within the CRF. Hypoglycemia or DKA events as well as discontinuation due to hypoglycemia or DKA would not be reported on an AE CRF page unless the event fulfilled criteria for a Serious AE (SAE) in which case an SAE form would be completed. Hypoglycemia and/or DKA events that are reported as SAEs will be included in all summaries of AEs or SAEs (see in Section 7.7.1.1). Separate summaries will be provided including hypoglycemia events reported on that special CRF pages (see in Section 7.7.1.8) or adjudicated DKA events (see in Section 7.7.1.6).

7.7.1.1 All Adverse Events

All AEs (serious and non-serious, excluding hypoglycemic or DKA events that are not reported as SAEs) with onset during the ST period and, separately, during the combined ST+LT period, will be summarized by SOC, PT, and treatment group in safety analyses. In addition, subject listings of all reported AEs will be produced for the ST+LT period (including pre-treatment and post-treatment events). Listings will utilize flags to identify AEs with off-treatment onset dates.

All AEs (serious and non-serious) including all serious hypoglycemic events and serious DKA events will also be summarized by treatment group.

Adverse events and SAEs with an onset from Day 1 of the ST double-blind treatment period up to and including 4 days and 30 days respectively, after the last dose date in the period (or up to and not including the start date of the LT treatment period, whichever comes first, for analysis of the ST double-blind treatment period) will be considered as occurring during the ST period.

For subjects treated during the LT period, all AEs & SAEs occurring on or after start of the open-label treatment will be considered as occurring during the LT period. In case of premature end of treatment during the LT period, only AEs or SAEs with onset between start of the open label treatment period up to 4 or 30 days after last dose will be considered occurring during the LT period. All AEs and SAEs occurring during LT period will be summarized in ST + LT period and some for LT period.

Due to the counting rules, for subjects who completed the on-treatment ST + LT period, all SAEs with onset on or after Day 1 in the ST period up to end of the study will be summarized as occurring during the combined ST+LT period.

An overall AE summary will be provided for the ST period and the combined ST+LT period presenting the number and percentage of subjects by treatment group reporting at least 1 AE (excluding hypoglycemia events and DKA events that are not reported as SAE) for the categories presenting below. The summary will be provided for both primary and sensitivity analyses for all treated subjects:

- at least 1 AE,

- at least 1 SAE of hypoglycemia,
- at least 1 AE or SAE of hypoglycemia,
- at least 1 adjudicated and confirmed DKA event reported as an SAE,
- at least 1 related AE,
- deaths,
- at least 1 SAE,
- at least 1 related SAE,
- SAE leading to discontinuation of study medication,
- AE leading to discontinuation of study medication,
- SAE of hypoglycemia leading to discontinuation of study medication,
- DKA event leading to treatment discontinuation of study medication reported as an SAE.

The following summaries will be provided for the ST period and the combined ST+LT period (excluding hypoglycemic and/or DKA events that are not reported as SAEs):

- Proportion of subjects with AEs in subgroups of subjects defined by age category (≥10 and ≤15 yrs, >15 and <18 yrs, ≥18 and <25 yrs), gender, race (white vs. non-white) and antidiabetic background medication (metformin only, insulin only, combination of metformin and insulin); with age, gender and antidiabetic background medication category being defined based on randomization strata.
- AEs by SOC and PT per subgroup category defined by age category (≥10 and ≤15yrs, >15 and <18yrs, ≥18 and <25 yrs), gender, race (white vs. non-white) and antidiabetic background medication (metformin only, insulin only, combination of metformin and insulin); with age, gender and antidiabetic background medication category being defined based on randomization strata.
- Most common AEs by PT and treatment group (ie, reported by >5% of subjects in any treatment group).
- AEs by SOC, PT, maximum intensity (mild, moderate, severe) and treatment group.
- AEs related to study medication by SOC, PT, and treatment group.
- SAEs by SOC, PT, and treatment group.
- Non-serious AEs by SOC, PT, and treatment group.

The total number of occurrences for each AE will be added to the summaries of AEs and SAEs by SOC and PT.

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

7.7.1.2 Deaths

All deaths recorded on the status 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 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 will be produced. For the combined ST+LT period, this listing will present the period of occurrence.

7.7.1.3 Serious Adverse Events

All SAEs (including hypoglycemic events and DKA events reported as SAE) will be described in narratives, regardless of investigator assessment of causality. SAEs with an onset from Day 1 of the ST double-blind treatment period up to and including 30 days after the last dose date in the period (or up to and not including the start date of the LT treatment period, whichever comes first, for the ST double-blind period) will be considered as occurring during ST double-blind treatment period. For subjects treated during the LT period, all SAEs with an onset from on or after Day 1 of the ST double-blind treatment period will be considered as occurring during the combined ST +LT period. In case of premature end of treatment during the LT period, only SAEs with onset between start of the open label treatment period up to 30 days after last dose will be considered occurring during the combined ST+LT period.

SAEs will be summarized by SOC, PT, and treatment group for both the primary and sensitivity safety analyses presenting the number and percentage of subjects with at least 1 SAE along with the number of corresponding SAEs. In addition, the proportion of subjects with related SAEs will be presented by SOC, PT, and treatment group. A listing of all SAEs will be produced, displaying all SAEs that occurred during the study. This listing for the combined ST+LT period will present the period of onset.

7.7.1.4 Adverse Events Leading to Discontinuation of Study Medication

Adverse events with an onset during the period reported with an action taken of discontinuation of study medication will be summarized by SOC, PT, and treatment group for both the primary and sensitivity safety analyses. This summary will include all hypoglycemia events and all DKA events that are reported as SAEs. When summarizing AEs leading to discontinuation, no upper cutoff day windows (ie, 4 days and 30 days from last dosing date for AEs and SAEs respectively) are applied.

In addition, a subject listing of discontinuation due to AEs will be provided, displaying all events that led to discontinuation.

7.7.1.5 Hepatic adverse events

An independent Hepatic Adjudication Committee, blinded to the treatment of the subjects, will determine the probability that DILI is the cause of liver-related abnormalities, including but not limited to, hepatic disorders leading to death, and liver laboratory abnormalities such as elevated AST and/or ALT with or without TB elevations.
To facilitate monitoring of liver safety, a list of PTs will be selected before database lock to form the Standard MedDRA Query (SMQ) for events of hepatic disorders. The number and percentage of subjects with events of hepatic disorders will be summarized by PT and treatment group for the ST period, and will be summarized separately for the combined ST+LT period.

7.7.1.6 Diabetic Ketoacidosis

A DKA Adjudication Committee, blinded to the treatment of the subjects, will independently adjudicate all the DKA events reported by the investigators and those identified based on pre-defined algorithm during the study period. A separate Adjudication Manual will define and describe the procedure for the handling, reporting, and classification of these cases.

All adjudicated DKA events with an onset from Day 1 of the ST double-blind treatment period (up to and not including the start date of the LT treatment period or up to and including 4 days

after last dose, whichever comes first, for ST double-blind period) will be considered as occurring during the ST period. The proportion of subjects with adjudicated DKA events will be tabulated by treatment group per adjudication category for the ST period after data unblinding and for the combined ST +LT period at the time of the final database lock. Furthermore, signs and symptoms and, separately, risk factors for DKA events will also be presented by treatment group.

When summarizing DKA events leading to discontinuation, no upper cutoff day windows are applied.

Serious DKA events will also be presented by treatment group per adjudication category and PT.

A listing of subjects will be produced, and it will display all confirmed adjudicated DKA events with an onset date/time from the start date/time of double-blind treatment period. This listing will present the period of onset.

7.7.1.7 Self-monitoring Blood Ketone

Separate pages to capture SMBK are contained within the CRF.

The mean number of measurements as well as the mean number of measurements per day and per subject will be summarized using descriptive statistics by treatment group for the ST period and the combined ST + LT period.

- From start of the ST period (defined as the day following 1st dosing [ie, Day 2]) through Week 4 (defined as the earliest between Week 4 visit date and last dosing date during the ST period + 4 days),
- From after Week 4 (defined as the day following Week 4 visit date) to the end of the ST period (defined as the earliest between the beginning of the LT period and last dosing date + 4 days during the ST period),
- From start of the LT period (defined as the day following Week 24 visit date) to Week 28 (defined as the earliest between Week 28 visit date and last dosing date during the LT period + 4 days),
- From after Week 28 (defined as the day following Week 28 visit date) to Week 52 (defined as the earliest between Week 52 visit date and the end of the LT period (last dosing date of the LT period + 4 days).

The number of subject with at least 1 SMBK value:

- >0.6 mmol/L,
- >3.8 mmol/L,

Will also be presented by treatment group for the intervals described above.

7.7.1.8 Hypoglycemia

Separate pages to capture events of hypoglycemia are contained within the CRF.

Hypoglycemic events with an onset from Day 1 of the ST double-blind treatment up to and including 4 days (30 days for serious events) after the last dose date in the period (or up to and but not including the start date of the LT treatment period, whichever comes first) will be considered as occurring during the ST period.

All hypoglycemic events occurring during LT period will be summarized under ST + LT period.

Hypoglycemic events will also be summarized for ST and ST+LT periods for subjects on background insulin antidiabetic medication and/or requiring glycemic rescue.

Hypoglycemic events will be categorized using the following classes following ADA recommendations[18] :

- **Severe hypoglycemia.** "An event requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration."[18]
- **Documented symptomatic hypoglycemia. "**An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L)." [18]
- **Asymptomatic hypoglycemia. "**An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L). Since the glycemic threshold for activation of glucagon and epinephrine secretion as glucose levels decline is normally 65–70 mg/dL (3.6-3.9 mmol/L) (24–26) and since antecedent plasma glucose concentrations of ≤70 mg/dL (3.9 mmol/L) reduce sympathoadrenal responses to subsequent hypoglycemia (1,11,20), this criterion sets the lower limit for the variation in plasma glucose in nondiabetic, nonpregnant individuals as the conservative lower limit for individuals with diabetes."[18]
- **Probable symptomatic hypoglycemia.** "An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤70 mg/dL [3.9 mmol/L]). Since many people with diabetes choose to treat symptoms with oral carbohydrate without a test of plasma glucose, it is important to recognize these events as "probable" hypoglycemia. Such self-reported episodes that are not confirmed by a contemporaneous low plasma glucose determination may not be suitable outcome measures for clinical studies that are aimed at evaluating therapy, but they should be reported." [18]
- **Relative hypoglycemia. "**An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration >70 mg/dL (3.9 mmol/L). This category reflects the fact that patients with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels > 70 mg/dL (3.9 mmol/L) as plasma glucose concentrations decline toward that

> level (27,28). Though causing distress and interfering with the patient's sense of well-being, and potentially limiting the achievement of optimal glycemic control, such episodes probably pose no direct harm and therefore may not be a suitable outcome measure for clinical studies that are aimed at evaluating therapy, but they should be reported." [18]

Additionally, hypoglycemic events will be categorized using the following classes following ISPAD (International Society of Pediatric and Adolescent Diabetes) recommendations for subjects below 18-years-old of age[19]:

- Severe hypoglycemia: The child is having altered mental status and cannot assist in their care, is semiconscious or unconscious, or in coma± convulsions and may require parenteral therapy (glucagon or intravenous glucose).
- Mild/moderate hypoglycemia: The child or parent is aware of, responds to, and treats the hypoglycemia orally after documenting a blood glucose level of ≤3.9 mmol/L (70 mg/dL), where the ADA has suggested using the terminology of 'Documented Symptomatic Hypoglycemia' for this category. Or the child is not symptomatic with hypoglycemia but the blood glucose is documented to be ≤3.9 mmol/L (70 mg/dL), where the ADA has suggested using the terminology of 'Asymptomatic Hypoglycemia' for this category.

All analyses of hypoglycemic events will be performed both overall and by class of events as per the categorization presented above.

The proportion of subjects with hypoglycemic events will be tabulated by treatment group using both classification systems, both regardless of rescue, excluding data after rescue and for subjects under insulin therapy used either as background or as rescue antidiabetic medication.

Hypoglycemic events with an onset during the period and those leading to discontinuation of study medication will be summarized by treatment group. When summarizing hypoglycemic events leading to discontinuation no upper cutoff day windows are applied.

A listing will be produced displaying all hypoglycemic events with their period of onset.

7.7.2 Laboratory Evaluation

Unless otherwise specified, laboratory data obtained after the start of study medication dosing up to and including 4 days (30 days for liver function laboratory tests) after the last dosing date (or up to and not including the start of the LT treatment period, whichever comes first) will be considered as obtained during ST period. Laboratory data that is summarized for the ST period will also be summarized, for ST+LT period. Some summaries will be produced for LT period if deemed appropriate.

All liver function laboratory tests assessment occurring on or after the start of the LT period will be included for ST+LT period summaries. However, in case of premature permanent discontinuation during the LT period only those collected up to 30 days after last open-label dosing will be included in the ST+LT period summaries.

For liver safety, a summary of proportion of subjects with elevated liver function tests including elevated aminotransferases (ALT and/or AST) and total bilirubin will be provided. In addition, a summary of proportion of subjects with elevated liver tests and/or reported AE of hepatic

disorder will also be provided. For liver safety summaries, liver function tests data will be summarized as described above.

7.7.2.1 Laboratory Abnormalities

Laboratory abnormalities will be evaluated based on pediatric marked abnormality values for AST, ALT, total bilirubin, and creatine kinase. The pre-defined criteria for marked abnormalities are detailed in APPENDIX 2.

In addition, laboratory abnormalities (as detailed in APPENDIX 3) will be evaluated on laboratory values using shift tables of Treated Subjects Data Set subjects with laboratory values in categories of lower the lower limit of normal (LLN) (at least 1 value lower the LLN during the period), normal (all values within reference ranges during the period), and higher the upper limit of normal (ULN) (at least 1 value upper the ULN during the period) according to baseline status; based on LLN and ULN range defined of laboratory).

For both analyses described above, laboratory abnormality data will be summarized, by treatment group, for the ST and, separately ST+LT periods using the Treated Subjects Data Set. The summaries will be presented for both the primary and sensitivity safety analyses.

The direction of change (high or low) in laboratory abnormality will be indicated in the tables.

Additionally, for each subject with a post baseline out of reference range value for a parameter, all the subject's values of that parameter over the treatment period and the FU period, where applicable, will be listed.

7.7.2.2 Change from Baseline for Selected Laboratory Parameters Over Time

All analyses of laboratory data will use observed data regardless rescue that occurs post-randomization.

Visit windows are provided in Section 8.3 in order to link each laboratory test to a scheduled visit. Change from baseline during the treatment period for the following selected laboratory parameters will be summarized by treatment group and visit using descriptive statistics:

- hematocrit,
- hemoglobin,
- platelet count,
- white blood cell count,
- total bilirubin,
- ALT,
- alkaline phosphatase,
- AST,
- uric acid,
- eGFR
  - using the Modified Diet in Renal Disease (MDRD) equation for subjects ≥18 years of age:

    eGFR (mL/min/1.73m^2) = 175 x (Scr)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if African-American),
  - using Schwartz equation for subjects <18 years of age:

eGFR (mL/min/1.73 m^2) = 41.3 x (ht/Scr),

- creatine kinase (creatine phosphokinase) (CK),
- creatinine, serum (S_{cr}),
- electrolytes - sodium, potassium, bicarbonate, chloride, magnesium and calcium,
- total protein, serum,
- albumin,
- inorganic phosphorus,
- albumin to creatinine ratio,
- fasted glucose:creatinine ratio,
- spot urine for fasted glucose,
- fasting lipid: total cholesterol.

Additionally, eGFR will also be described by age group: ≥10 and ≤15 years-old; >15 and <18 years-old ≥18 and <25 years- old.

7.7.2.3 Additional Laboratory Data Summaries

For the 24-week ST double-blind treatment period and respectively the 52-week ST+LT treatment period, the following summaries will be provided. (regardless of post-randomization rescue).

Shift Tables for Electrolytes (Sodium, Potassium, Calcium, Phosphate, and Magnesium) Categories.

Shift tables of Treated Subjects Data Set subjects with electrolytes values in categories of low, normal, and high (based on normal range of central laboratory) will be summarized by treatment group using the highest (for sodium, calcium, phosphate, and magnesium) and lowest (for sodium, potassium, and calcium) values obtained during the period.

Shift Tables for Urine Albumin Excretion Categories

Shift tables of Treated Subjects Data Set subjects with urine albumin to creatinine ratios in 0 - <30 mg/g (3.4 mg/mmol) [normoalbuminuria], 30 mg/g (3.4 mg/mmol) - <300 mg/g (33.9 mg/mmol) [microalbuminuria], and ≥ 300mg/g (33.9 mg/mmol) [macroalbuminuria] will be summarized by treatment group using the Week 24 values and Week 52 values, for each period respectively.

For both shift tables described above, the last observation, regardless of post-randomization rescue, prior to Week 24 or Week 52 will be used if no Week 24 or Week 52 measurement is available, respectively.

7.7.3 Vital Signs

Vital signs data obtained after the start of study medication dosing up to and including 4 days after the last dosing date (or up to and including the start of the LT treatment period, whichever comes first, for ST double-blind treatment period) will be considered as obtained during the period..

Visit windows are provided in Section 8.3 in order to link each vital sign measurement to a scheduled visit.

Vital signs summary will be produced using all available data regardless of rescue for subjects in the Treated Subjects Data Set.

7.7.3.1 Systolic blood pressure, diastolic blood pressure, and heart rate

Measured values and changes from baseline in systolic blood pressure, diastolic blood pressure and heart rate will be summarized by treatment group at each scheduled visit using descriptive statistics (using available data regardless of rescue for subjects in the Treated Subjects Data Set).

7.7.3.2 Height, Weight, and BMI

Measured values and absolute change from baseline in height, weight and BMI will be summarized by treatment group at each scheduled visit using descriptive statistics. In addition, standardized height, weight and BMI (see details in Section 8.15) expressed as a z-score adjusted for age (see details in Section 8.13) and gender using the CDC growth chart[20] will be also be summarized using the same approach.

7.7.4 Electrocardiograms

The normality/abnormality of the electrocardiogram (ECG) tracing, as determined by the investigator, will be summarized using frequency tables on number of subjects who have a normal/abnormal ECG tracing at Week 24 of the ST double-blind treatment period and at Week 52 of the ST+LT treatment period, overall and by the ECG tracing at baseline. When the data at Week 24 or Week 52 is not available for a discontinued subject, then the last observation before discontinuation of that subject (regardless of rescue) will be used for summary, for each period respectively.

7.7.5 Pregnancy Test Results

By-subject listing of pregnancy test results will be provided using the Treated Subject Data Set.

7.7.6 Other Safety Observations

7.7.6.1 Tanner Staging

The Tanner Scale (also known as Tanner Staging) is a measure of pubertal development (sexual maturation) in children and adolescents with components described for each sex, rates rated separately on a scale of stage 1 to stage 5. The stages define physical measurement of development based on external primary and secondary sexual characteristics. Females are classified with regard to breast and pubic hair characteristics. Males are classified with regard to genitalia and pubic hair characteristics.

A qualitative determination of the subject's sexual maturity rating on a scale of 1 to 5 will be determined according to those criteria established by Tanner (see Table 10 and Table 11). Based on the level of comfort by the Investigator, caregiver, or study subject, the measure of sexual maturity may be obtained by 1) visually observing the level of development after the subject disrobes or 2) requesting the caregiver or subject point to the level of maturity from a description or selection of pictures that exhibit the various stages of maturity.

Table 10: Classification of Sex Maturity Stages in Girls

Stage	Pubic Hair	Breasts
1	Preadolescent	Preadolescent
2	Sparse growth of long, slightly pigmented downy hair, straight or only slightly curled, appears chiefly along the labia	Breast bud stage; elevation of breast and papilla as a small mound; enlargement of areola diameter
3	Dark, beginning to curl, increased amount	Further enlargement of breast and areola with no separation of their contours
4	Resembles adult type but the area covered is still considerably smaller than in most adults; no spread to the medial surface of the thighs	Projection of areola and papilla form a secondary mound above the level of the breast
5	Adult in quantity and type, spread to medial surface of thighs	Mature; projection of papilla only due to recession of the areola to the general contour of the breast

Table 11: Classification of Sex Maturity Stages in Boys

Stage	Pubic Hair	Genitalia
1	None	Preadolescent
2	Sparse growth of long, slightly pigmented downy hair, straight or only slightly curled; appears chiefly at the base of the penis	Scrotum and testes have enlarged; change in texture of the scrotal skin with some reddening
3	Darker, coarser, and more curled; spreads sparsely over the junction of the pubes	Growth of the penis, mainly in length but with some increase in breadth; further growth of testes and scrotum
4	Resembles adult type but the area covered is still considerably smaller than in most adults; no spread to the medial surface of the thighs	Penis further enlarged in length and breadth with development of glans. Testes and scrotum further enlarged with further darkening of the scrotal skin
5	Adult in quantity and type, spread to medial surface of thighs	Adult size and shape. No further enlargement of testes and scrotum

The Tanner Stages will be summarized by treatment group and age category (≤10,15), [15,18) and ≥18 years- old) using shift tables. These analyses will be performed for the ST double-blind treatment period and for the combined ST+LT treatment period based respectively on Week 24 and Week 52 value.
Additionally, the evolution of tanner stage per visit will be summarized using count and percentage:

- during the ST double-blind period at Week 24 according to baseline status and overall,
- during the LT period at Week 24 according to baseline status and overall and at Week 52 according to baseline and Week 24 status and overall.

When the assessment at Week 24 or Week 52 is not available for a discontinued subject, then the last observation before discontinuation of that subject (regardless of rescue therapy initiation) will be used for summary, respectively for each study period.

7.7.6.2 Growth and Maturation Markers

The values for thyroid-stimulating hormone [TSH], free thyroxine, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, total testosterone, insulin-like growth factor-1 [IGF-1], insulin-like growth factor binding protein-3 [IGFBP3], calcitonin, 25-hydroxy vitamin D and parathyroid hormone (PTH), will be summarized by treatment group and by either age category (≥10 and ≤15, >15 and <18) and ≥18 and < 25 year old). A summary will also be produced by treatment group and puberty status (pre-puberty, early puberty, mid puberty, late puberty and young adults) and another one by treatment group and gender (Male, Female) , as described in Section 8.16. These analyses will be performed for Week 24 of the ST period and for Week 52 of the combined ST+LT period. When the assessment at Week 24 or Week 52 is not available for a discontinued subject, then the last observation before discontinuation of that subject (regardless rescue therapy initiation) will be used for summary, respectively for each study period.

A listing of the growth/maturation markers along with the Tanner Stages by subject will be provided.

7.7.6.3 Bone Biomarkers

The values for bone alkaline phosphatase and osteocalcin will be summarized by treatment group and age category (≥10 and ≤15; >15 and <18; and ≥18 and <25-year-old) at each scheduled time of assessment. A summary will also be produced by treatment group and puberty status (pre-puberty, early puberty, mid puberty, late puberty and young adults and another one by treatment group and gender (Male, Female), as described in Section 8.16.

These analyses will be performed for Week 24 of the ST period and for Week 52 of the combined ST+LT period. When the assessment at Week 24 or Week 52 is not available for a discontinued subject, then the last observation before discontinuation of that subject (regardless rescue therapy initiation) will be used for summary, respectively for each study period.

A listing of the bone biomarkers along with the Tanner Stages by subject will be provided.

8 CONVENTIONS

8.1 Duration of Type 2 Diabetes

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

(1 + consent date - diagnosis date) / 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 subject will be excluded from all summaries related to duration of T2DM.
- Missing day, month and year: No imputations will occur, and the subject 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.

8.2 Missing and Multiple Measurements

For listings of efficacy, safety, PK, outcome research measures, missing values will be represented as not reported.

For all analyses and summaries of efficacy, safety, outcome research measures, missing values will not be imputed, unless otherwise specified.

Some laboratory samples may be inadvertently analyzed multiple times for the same test, producing multiple lab results on the same collection date and time for the same subject. The selection of laboratory result for analysis for this subject will follow rules as detailed in Section 8.3.

If the blood pressure measurements are taken at a wrong position, eg, sitting instead of standing, then these measurements will be excluded from the summary/analysis.

8.3 Longitudinal Assessments

Day 1 for the ST double-blind treatment period is the start date of double-blind treatment medication. The observation closest to the target day (and time where applicable) is the measurement used in the analysis for each scheduled visit.

The following visit window will apply for all laboratory parameters, vital signs and physical measurements. In particular, for efficacy endpoints (HbA1c, FPG), windowing applies whether subjects are on-treatment or off-treatment.

Table 12: Longitudinal assessment – Visit window for subjects not discontinuing treatment during the LT period

Visit	Target Day (LT day)	Day Range by type of assessment						
		Vital signs **Standard safety laboratory panel** **HbA1c**	**FPG**	**Height, Body Weight**	**Spot Urine glucose**	**ECG** **Tanner stage** **Growth maturation marker & bone biomarker** **Fasting lipid panel**	**PK-Concentration**	**AE and concomitant medications**
Week 4	29	2-43	2-85		2-85			
Week 8	57	44-85		2-85				
Week 16	113	86-141	86-141	86-141	86-141		86-141	
Week 24	169 (-1)	142-LDST*	142-LDST*	142-LDST*	142-LDST*	2- LDST*	142-LDST*	2- LDST*
Week 32	225 (56)	FDLT-85	FDLT-85	FDLT-85*	FDLT-85			
Week 40	281 (112)	FDLT + 86 - FDLT + 154	FDLT + 86 - FDLT + 154	FDLT + 86 - FDLT + 154	FDLT + 86 - FDLT + 154			
Week 52	365 (196)	≥ FDLT+ 155	≥ FDLT +155	≥ FDLT +155	≥ FDLT +155	≥ FDLT+155		≥ FDLT + 155
Week 56 (Follow-up visit)**	393							≥ LDLT + 1

Day 1 is the first day of double-blind IP administration

LDST refers to last day of the short term-period

FDLT refers to the first day of the long-term period, defined as the day following the end of the Short-term period.

LDLT refers to last day of the long term period

** for subjects discontinuing the study during the ST period LDST refers to Day 169*

*** For subjects discontinuing the study during the ST period Week 56 FU will begin the day following LDST*

Table 13: Longitudinal assessment – Off-treatment visit window applying to subjects discontinuing IP during LT Period

Visit	Target Day	Day Range by type of assessment					
		Vital signs **Standard safety laboratory panel** **HbA1c**	**FPG**	**Height, Body Weight**	**Spot Urine glucose**	**ECG** **Tanner stage** **Growth maturation marker & bone biomarker** **Fasting lipid panel**	**AE and concomitant medications**
Week 4	29	2-43	2-85		2-85		
Week 8	57	44-85		2-85			
Week 16	113	86-141	86-141	86-141	86-141		
Week 24	169	142-197*	142-197*	142-197*	142-197*	2-197*	2-197*
Week 32	225	198-253	198-253	198-253	198-253		
Week40	281	254-323	254-323	254-323	254-323		
Week 52**	365	≥354	≥354	≥354	≥354		≥198*
Week 56 (Follow-up visit)***	393						≥ LDLT +1

Day 1 is the first day of double-blind IP administration

LDLT refers to last day of the long term period

**Week 24 visit is to be considered as the end of the ST period whether patient are off-treatment or on-treatment. The day following Week 24 visit being the first day of the LT period. Consequently, if Week 24 visit is occurring after D197 the day of Week 24 visit will be used instead of D197 and the day following Week 24 visit day will be used instead of D198.*

*** Week 52 Visit is the end of the LT period even if occurring after D393*

**** For subjects discontinuing the study during the ST period Week 56 FU will begin the day following last day of the short term period.*

For analysis of the ST double-blind period (ST), the study treatment refers to the double-blind treatment. For analysis of the ST+LT treatment period (ST+LT), the study treatment refers to double-blind or open-label treatment.

For Week 24, the upper cut off is the last day of ST double-blind study treatment for analysis of the ST double-blind period (ST), unless study medication is stopped earlier, in which case this the upper cut off is the last day of study treatment + x days. However, for patient continuing in the long term the period and not having permanently discontinued IP, all Week 24 assessment will be considered as occurring during the ST period even if the subject is receiving open-label IP treatment the day of Week 24 visit.

For early treatment discontinuation visit, rescue visit as well and non-treatment visits, the same visit windows will be applied.

The use of post treatment observations is specified in Section 8.4.

For all safety laboratory parameters, the use of post-double-blind treatment observations is specified in Section 7.7.2.

For laboratory and non-laboratory parameters, if a subject has more than 1 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 (ie, more than 1 value for the same day but different time), the value with the earlier entry date/time will be used. However, measurements obtained on-treatment and post-treatment will be differentiated, and measurements obtained prior to rescue therapy initiation and after rescue therapy initiation will also be differentiated. Samples collected the same day of rescue medication initiation will be assumed to have been collected prior to rescue medication initiation

In addition, if many assessments are collected at the same date and time (if any), the worst one will be chosen (eg, the lowest for eGFR and the highest for the other parameters).

For the shift tables for nominal ECG parameter of normal/abnormal the following rules apply. If more than 1 ECG measurement is performed within a specified time window, an abnormal ECG value will be chosen over a normal ECG value. If more than 2 abnormal or 2 normal ECG values are within the same time window, the one closest to the target date will be used.

8.4 Post-Treatment Efficacy and Safety Observations

While efficacy and safety observations will be listed regardless of whether the subject was taking blinded study drug, observations may not contribute to summaries/analyses if they are measured after the last dose of study medication as indicated below:

For efficacy (using on-treatment assessments) and safety parameters:

- HbA1c, height, body weight, BMI, Tanner staging, lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fasting triglycerides), free fatty acids will be summarized/analyzed only if measured on or prior to the 8^{th} day after the last dose of study medication.

- Vital signs (blood pressures and pulse rate) as safety parameters, will be summarized/analyzed only if measured on or prior to the 4th day after the last dose of study medication.
- FPG, spot urinary glucose to creatinine ratio will be summarized only if measured on or prior to the first day after the last dose of study medication.

For other safety parameters:

Unless otherwise specified, safety data obtained after the start of study medication dosing up to and including 4 days (30 days for SAEs and liver function laboratory tests) after the last dosing date (or up to and not including the start of the LT treatment period, whichever comes first) will be considered as obtained during ST period.

All safety and liver function laboratory tests assessment occurring on or after the start of the LT period will be included in the ST+LT period summaries. However, in case of premature permanent discontinuation during the LT period only those collected up to 30 days after last open-label dosing will be included in the ST+LT period summaries.

All other safety events and measurements obtained from the day after the last study medication (with appropriate windows) up to the last visit date of the FU period will be considered as obtained during the FU period.

For analysis of the ST double-blind period, the study treatment refers to the double-blind treatment but also to the open-label treatment if initiated the day of Week 24 visit.

For analysis of the ST+LT treatment period, the study treatment refers to double-blind or open-label treatment.

8.5 Assignment of Doses to Adverse Events and Laboratory Assessments

In case of missing dates and/or times, 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:

For AEs, a missing or incomplete onset date will be imputed according to the following conventions:

- If the onset date for an AE is missing or incomplete, an imputed date will be derived to assigned the event to an appropriate analysis period. 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 missing, the derived onset date will be calculated as the first non-missing valid date from the following list (in order of precedence):
  - First active study medication date
  - Consent date
  - Visit date corresponding to the visit at which the event was reported.
  - 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
  - Visit date corresponding to the visit at which the event was reported
  - 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 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 3 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.

A drug treatment file will be created, containing any starting and stopping dose as well as intermediate dose changes within each study period, with dates and times as recorded on the CRF. In this context,

- The date of the first dose of study medication is defined as the earliest start date with number of tablets >0 reported on the study medication page. However, if for any reason the 1st dosing date is unknown it will be imputed to the randomization date.
- the date of the last dose of study medication is defined as the latest start or stop date with number of tablets >0 reported on the study medication page. However, if for any reason the last dosing date is unknown, it will be imputed to earliest date between date of death, the latest Week 24 assessment date (unblinding for ST assessment) or last contact date (final database lock),
- if a dosing time is missing for a starting dose of study drug in a study period or a dose change, then it is defaulted to 9:00 if there are AM and BID dosing in the study, and it is defaulted to 19:00 if there is only PM dosing in the study.
- if there's a gap in the dosing information, then the dosing time corresponding to the start date of the gap, is defaulted to 00:00.

If a dosing time is missing for a last stop dosing date for the study drug in a study period, then it is defaulted to 23:59 when there is no study medication in the next study period, or is

defaulted to 1 minute before the starting dose time of the study medication in the next study period when available.

8.5.1 Treatment at Onset of an Adverse Event

Both onset date and (if requested) onset time of an AE will be compared to the dosing information. Treatment will then be the dose at the last observation for a subject in the dosing file where the AE onset date/time is not earlier than the dose date/time.

However, if last dosing information is not known, for example, because a subject is lost to follow up or, at time of unblinding for ST data the Week 24 visit is skipped, the subject will be assumed to be on-treatment up to the earliest date between death date, latest Week 24 assessment date (at time of unblinding for ST data) or last contact date at the time of unblinding or final database lock).

8.5.2 Treatment at the Time of a Laboratory Assessment

Laboratory draw date and time will both be compared to the dosing information. Treatment at the time of the laboratory assessment will then be the dose at the last observation for a subject in the dosing file where the laboratory date/time is not earlier than the dose date/time.

8.6 Concomitant Medications

Start and stop date of all concomitant medications (including rescue insulins) are collected on the CRF. In order to classify medication as prior, current or concomitant, partial, missing or invalid start and stop dates will be imputed where possible as follows:

Rescue insulin medications are determined by the investigator and reported using the "Rescue insulin dosing" eCRF page which is identified at database level.

Start and stop dates for all concomitant medications are collected on the CRF. However, in case of missing or partial information in these dates, the following rules will be used:

If start date is missing or partial:

- if month is missing, use January (01),
- if day is missing, use the 1st (01),
- if year is missing, use year of the entry visit (consent date for those missing entry visit),
- if entire date is missing, use consent date.

If stop date is missing, partial or "continuing":

- if month is missing, use December (12),
- if day is missing, use the last day of the month under consideration,
- if year or the entire date is missing or if "continuing", we leave the date as missing.

Imputed dates

- will not appear on the tables of non-study medication.
- will be reviewed within the study team and agreed by the study team prior to the study data being unblinded.

8.7 Counting Rules for Adverse Events

8.7.1 At Subject Level

Where a subject has the same AE, based on preferred terminology, reported multiple times in a single analysis period, the subject will only be counted once at the PT level in AE frequency tables.

Where a subject has multiple AEs within the same SOC in a single analysis period, the subject will only be counted once at the SOC level in AE frequency tables.

When a subject has the same AE, based on preferred terminology, reported multiple times in a single analysis period, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Relationship to study medication
- Intensity of event
- Onset date and time
  a) When assessing relationship to study medication, relationship as reported by the investigator, events will be reported as related or not to study medication. Related events will take precedence over unrelated events in determining the event to include in summary tables.
  b) More intense events will take precedence over less intense events in determining the event to include in summary tables.
  c) Earlier onset date-time events will take precedence over late onset date-time events in determining the onset to include in summary tables.

When reporting AEs by intensity, in addition to providing a summary table based on the event selection criteria detailed above, summary tables will also be provided based on the most intense event during the analysis period - independent of relationship to study medication.

8.7.2 At Event Level

At event level, each unique AE record will be counted.

8.8 Fasting State

Lipid parameters listed in the protocol include TG, LDL-C, HDL-C, total-C. For TG, calculated LDLC, only data collected in fasting state will be used for analysis.

For FPG, fasting insulin, and fasting C-peptide, only assessments documented with the subject in fasting state will be summarized and listed.

8.9 Percent Compliance Calculation

A subject should take 1 tablet a day, each day from the first treatment dose date (eCRF) to the last treatment dose date. Consequently, the compliance (%) is defined as 100 X the number of tablets taken divided by the number of tablets that should have been taken and is derived as follows:

- The number of tablets taken is the total number of tablets dispensed minus the number entered on the CRF as returned, where the number dispensed is: 70 x the number of kits dispensed (since there are 70 tablets per kit/bottle),
- The number of tablets that should have been taken is calculated as:
  [the number of days from the first treatment period dose recorded in the "Record of Study Medication" to the last expected treatment dose in the study period – the number of days of unaccounted + days of interruption] x [the prescribed daily dose (ie, 1 tablet per day)].

The number of unaccounted days is defined by the number of days the exposure to treatment is unknown because either missing or partial exposure date, or unknown or unreliable (e.g., returned greater than dispensed) returned number of tablets. The number of days of interruption is defined as 'number of exposure days interrupted' recorded in the eCRF.

The last expected treatment dose in the period is defined as:

- the date of Week 24 visit or end of treatment date (whichever is earliest) for the ST treatment period,
- the date of Week 52 visit or end of treatment date (whichever is earliest) for the combined ST+LT treatment period.

Compliance will be derived based only on complete dispensed and returned information. For instance, no imputation will be done, especially on last dose date, or unknown number of return tablets, meaning that the compliance will only be derived based on last known return date and quantity.

8.10 Strip Sign for Selected Laboratory Data

For selected laboratory test values that have been received with an operator sign as a part of the result (>,≥, ≤, <), a process to strip the operator sign will be applied and the resulting numeric values will be used for data analysis. The raw value with operator will remain as such on the CRF (or in the electronic record) and in the database.

The applicable impacted laboratory tests and applicable operator signs will be identified during the course of the study and study monitoring. For laboratory parameters not included in any statistical analyses, operator signs will not be stripped and the value will be counted as missing. However, while displaying laboratory parameters in individual data listings the sign will be presented.

The list of tests identified with an operators are presented in Table 17 APPENDIX 4.

8.11 United States Conventional Units and Standard International Units for Laboratory Data

Unless otherwise specified, all analyses of laboratory data (independently of being safety or efficacy) will be performed in Standard International Units (SI).

However, analysis of HbA1c, will be performed only in United States Conventional Unit as this unit is accepted by Health Authorities in other countries.

8.12 Laboratory evaluations

All laboratory evaluations as specified in Section 7.7.2 performed by central laboratories and/or local laboratories will be included in summaries and listings.

8.13 Age presented in growth and maturation marker and bones biomarkers individual listings

For baseline assessment age from IXRS will be used.

At Week 24, Week 52 or premature end of treatment visit, the age will be derived as:

(Visit date - birth date +1) / 365.25;

If only year date of birth is available, this will be imputed to 30th of June.

8.14 Age Used to Derive Normalized Height, Weight, and BMI Expressed as z-Score

Age will be presented in months.

At date of sampling, age in months will be derived as: (Visit date - birth date) / 30.5;

If only year date of birth is available, age in months will be derived as: (assessment date – year of birth)*12 + 6

If subject's age is greater or equal to 20 years old, age will be change to 239,5 months[20].

8.15 BMI Used to Derive Normalized BMI Expressed as z-Score

BMI will be derived from weight and height obtained at the same visit using the following formula:

BMI (kg/m^2) = Weight (kg) / [Height (cm)*0.01]^2

If either weight or height is missing at a given visit, no imputation will be performed.

8.16 Puberty Status and Height Velocity Used to Categorize Growth and Maturation Markers as well as Bones Biomarkers

8.16.1 Height Velocity

The height velocity is defined as the absolute change from baseline to Week 24 in height regardless of rescue therapy initiation or discontinuation from study drug. In case of missing Week 24 height the last observation during the ST period (regardless of rescue) will be carried forward provided that this observation occurs at least 3 months (91 days) after baseline weight.

8.16.2 Puberty Status

Puberty status will be defined, by visit, using tanner stage at that visit (regardless rescue therapy initiation or discontinuation from study drug) along with height velocity (as defined Section 8.16.1) as follow:

- Pre-puberty: Tanner stage 1,
- Early puberty: Tanner stage 2,
- Mid puberty: Tanner stage 3 or Tanner stage 4 with height velocity ≥1.5 cm,
- Late puberty and young adult: Tanner stage 4 with height velocity <1.5 cm or tanner stage 5.

9 CONTENT OF REPORTS

The analysis results will be obtained in two steps.

The study will be unblinded after completing ST period assessments (Week 24) and all baseline characteristics, demographics and efficacy results and relevant safety parameters from ST period will be reported in the CSR. All ST period individual data listings and safety summaries by visit dedicated for ST period will be produced for informative purposes, but will not be included in the CSR.

After the final database lock (Week 56), efficacy and safety results from the ST plus LT periods will be produced and included in the CSR.

10 CHANGES OF ANALYSIS FROM PROTOCOL

Section of SAP Affected (If applicable)	Change	Rationale
Secondary and third objectives	Odds ratios will be presented instead of differences in proportions between Dapagliflozin and placebo (as specified in the protocol) for comparison of the percentage of subjects with baseline HbA1c ≥7% who achieve a HbA1c level <7.0% requiring rescue medication or discontinuing study medication due to lack of glycemic control	Logistic regression reports ORs, not differences in proportions
Demographics and other baseline characteristics as well as efficacy	The Randomized Subjects Data Set will consist on all patients randomized by IXRS and represent the Full Analysis Subject Set	Primary and secondary endpoints as well as sensitivity analyses on primary endpoint and FPG, using on ITT estimand are analyzed using the Full Analysis Subject Set

APPENDIX 1 GEOGRAPHIC REGIONS

Table 14: Geographic regions

Geographic Region	Countries
North America	United States
Latin America	Mexico
Europe	Russia United Kingdom Hungary, Romania, Israel
Asia/Pacific	

APPENDIX 2 UNITS AND MARKED ABNORMALITY CRITERIA FOR SAFETY LABORATORY VARIABLES

Clinical laboratory variables will be summarized and listed using the units listed here. The criteria for marked abnormality for each variable are listed in the following table. Note that a post-baseline laboratory value will be considered a marked abnormality only if it satisfies the specified criteria and is more extreme (farther from the limit) than is the baseline value.

Table 15: Marked abnormality criteria for safety laboratory variables

Clinical Laboratory variables	Units	Marked Abnormality Criteria	
		Low	High
Blood Chemistry			
ALP	U/L		>3 X ULN
ALT	U/L		>3 X ULN
AST	U/L		>3 X ULN
ALT	U/L		>5 X ULN
AST	U/L		>5 X ULN
ALT	U/L		>10 X ULN
AST	U/L		>10 X ULN
ALT	U/L		>20 X ULN
AST	U/L		>20 X ULN
Total Bilirubin	µmol/L		>1.5 X ULN if PreRx ≤ULN; >2 X ULN if PreRx >ULN
CK (Creatine Kinase)	U/L		>5 X ULN
CK (Creatine Kinase)	U/L		>10 X ULN

Conventional (US) unit being identical to standard international unit except for bilirubin expressed in mg/dL

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

The following 3 criteria will be summarized in examination of elevated AT (ALT and/or AST) and total bilirubin:

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

APPENDIX 3 ABNORMALITY CRITERIA FOR SAFETY LABORATORY VARIABLES OUT OF REFERENCE RANGE VALUES

Table 16: Abnormality criteria for safety laboratory variables out of reference range values

Clinical Laboratory variables	Units SI (US conventional)	Marked Abnormality Criteria	
		Low	High
Hematology			
HCT males/females	vol (%)	<1X LLN	>1X ULN
Hemoglobin males/females	g/L (g/dL)	<1X LLN	>1X ULN
Blood Chemistry			
Albumin	g/L (g/dL)	<1X LLN	>1X ULN
Total protein	g/L (g/dL)		>1X ULN
ALP	U/L		>1X ULN
ALT	U/L		>1X ULN
AST	U/L		>1X ULN
Total Bilirubin	µmol/L (mg/dL)		>1X ULN
Glucose, Plasma Unspecified	mmol/L (mg/dL)	<1X LLN	>1X ULN
Na (Sodium)	mmol/L (mEq/L)	<1X LLN	>1X ULN
K (Potassium)	mmol/L (mEq/L)	<1X LLN	>1X ULN
HCO3 (Bicarbonate)	mmol/L (mEq/L)	<1X LLN	
BUN / Urate	mmol/L (mEq/L)		>1X ULN
Creatinine	µmol/L (mg/dL)		>1X ULN
CK (Creatine Kinase)	U/L		>1X ULN
Calcium	mmol/L (mg/dL)	<1X LLN	>1X ULN
Magnesium	mmol/L	<1X LLN	>1X ULN
Inorganic phosphorus	mmol/L (mg/dL)	<1X LLN	>1X ULN
Urine			
UACR (Urinary Albumin to Creatinine Ratio)	mg/mmol (mg/g)		>1X ULN

APPENDIX 4 LABORATORY DATA IDENTIFIED WITH AN OPERATOR

Clinical laboratory variables identified by signs are described below.

Table 17: Laboratory data identified with an operator

:

Test code	Laboratory test	Laboratory category	Laboratory unit	Operator Signs and limit of quantification
BILI	Bilirubin	CHEMISTRY	umol/L	<
K	Potassium	CHEMISTRY	mmol/L	>
LH	Luteinizing Hormone	ENDOCRINOLOGY	IU/L	<
PTHI	Parathyroid Hormone, Intact	ENDOCRINOLOGY	pmol/L	<
LKM1IGAB	Liver Kidney Microsomal Type 1 IgG Ab	IMMUNOLOGY	U	<
SMUSCGAB	Smooth Muscle IgG Antibody	IMMUNOLOGY	U	<
GLUC	Glucose	SELF MONITORING BLOOD GLUCOSE	mmol/L	>
EBCIGGAB	Epstein-Barr Capsid IgG Antibody	SEROLOGY	Index	<
VITDIT	25-Hydroxyvitamin D	SPECIAL CHEMISTRY	nmol/L	<
V25HD2	25-Hydroxyvitamin D2	SPECIAL CHEMISTRY	ng/mL	<
CLCTONN	Calcitonin	SPECIAL CHEMISTRY	pg/mL	<
ESTRDIOL	Estradiol	SPECIAL CHEMISTRY	pmol/L	<
GADAB	Glutamic Acid Decarboxylase Antibody	SPECIAL CHEMISTRY	U/mL	<
GADAB	Glutamic Acid Decarboxylase Antibody	SPECIAL CHEMISTRY	U/mL	>
IC512AB	Islet Cell 512 Antibody	SPECIAL CHEMISTRY	kU/L	<
IC512AB	Islet Cell 512 Antibody	SPECIAL CHEMISTRY	kU/L	>
TESTOS	Testosterone	SPECIAL CHEMISTRY	nmol/L	<
TTGIGAAB	Tissue Transglutaminase IgA Antibody	SPECIAL CHEMISTRY	U/mL	<
VITD3	Vitamin D3	SPECIAL CHEMISTRY	ng/mL	<
ALBCREAT	Albumin/Creatinine	URINE CHEMISTRY	mg/mmol Creatinine	<
GLUCCRT	Glucose/Creatinine	URINE CHEMISTRY	mmol/mmol Creatinine	<
Additional laboratory parameters with an operator might be part of time of Week 24 unblinding ST assessment or final database lock. Concerned safety summary tables using strip signs will be identified.				

APPENDIX 5 OVERVIEW OF PRIMARY AND SENSITIVITY ANALYSES FOR EFFICACY ANALYSES

Endpoint	Endpoint ref, analysis type*	Analysis	Brief description
Change from baseline in HbA1c at Week 24	P1, Primary	Longitudinal repeated measures analysis	Repeated measures model, no imputation. MAR assumption. Prior rescue therapy initiation or discontinuation from study drug
	P1, SA1	Longitudinal repeated measures analysis	Repeated measures model, no imputation. MAR assumption. regardless rescue or discontinuation from study drug
	P1, SA2	Longitudinal repeated measures analysis	Same methodology as primary but population is Per Protocol Subjects set
	P1, SA3	MI followed by ANCOVA at Week 24	MNAR assumptions used for imputation: - MI-washout (placebo-based imputation),. Regardless rescue or discontinuation of study drug.
	P1, SA4	MI followed by ANCOVA at Week 24	Tipping Point analysis MNAR assumption for MI: Subjects who discontinue the study early have worse HbA1c values (by amount δ) than would have been assumed under a MAR model. The values of δ that will be examined using a grid search method until a p-value >0.05 is obtained Regardless rescue or discontinuation of study drug.
	P1, SA5	ANCOVA at Week 24	LOCF imputation, BOCF imputation for subjects with no post baseline assessment.

Endpoint	Endpoint ref, analysis type*	Analysis	Brief description
	P1, Subgroup	Longitudinal repeated measures analysis	Subgroup analyses. Based on same Repeated measures model as for primary endpoint
Change from baseline in FPG at Week 24	S1	Longitudinal repeated measures analysis	Same methodology as primary
	S1, supportive	Longitudinal repeated measures analysis	Repeated measures model, no imputation. MAR assumption. regardless rescue or discontinuation from study drug.
Analysis of subjects requiring glycemic rescue medication or discontinuing study medication due to lack of efficacy at or prior to Week 24	S2	Logistic regression (replaced by Fisher exact test if less the 5 responder in any group)	Binary response analysis, LOCF imputation
Time to glycemic rescue medication or discontinuation of study medication due to lack of efficacy at or prior to Week 24	S2, supportive	Kaplan Meier	Time-to-event analysis
Comparison of the percentage of subjects with baseline HbA1c ≥7% who achieve an HbA1c level <7.0% at Week 24	S3	Logistic regression (replaced by Fisher exact test if less the 5 responder in any group)	Binary response analysis, LOCF imputation
Comparison of the percentage of subjects who achieve an HbA1c level <7% at or prior Week 24	S3, supportive	Logistic regression (replaced by Fisher exact test if less the 5 responders in any group)	Same methodology as E3 but independently to baseline HbA1c value

Endpoint	Endpoint ref, analysis type*	Analysis	Brief description
Change from baseline in HbA1c at Week 52	E1	Longitudinal repeated measures analysis	Repeated measures model, no imputation. MAR assumption. Prior rescue therapy initiation or discontinuation from study drug
	E1, supportive	Longitudinal repeated measures analysis	Repeated measures model, no imputation. MAR assumption. Regardless rescue or discontinuation of study drug.
Change from baseline in FPG at Week 52	E2	Longitudinal repeated measures analysis	Same methodology as for E1
	E2, supportive	Longitudinal repeated measures analysis	Same methodology as for E1, supportive.
Analysis of subjects requiring glycemic rescue medication or discontinuing study medication due to lack of efficacy at or prior to Week 52	E3	Logistic regression (replaced by Fisher exact test if less the 5 responder in any group)	Binary response analysis
Time to glycemic rescue medication or discontinuation of study medication due to lack of efficacy at or prior to Week 52	E3, supportive	Kaplan Meier	Time-to-event analysis
Comparison of the percentage of subjects with baseline HbA1c ≥7% who achieve an HbA1c level <7.0% at Week 52	E4	Logistic regression (replaced by Fisher exact test if less the 5 responder in any group)	Binary response analysis, LOCF imputation

Endpoint	Endpoint ref, analysis type*	Analysis	Brief description
Comparison of the percentage of subjects who achieve an HbA1c level <7.0% at or prior Week 52	E4, supportive	Logistic regression (replaced by Fisher exact test if less the 5 responders in any group)	Same methodology as E3 but independently to baseline HbA1c value

*P=Primary. S=Secondary. SA=Sensitivity Analysis. E=Exploratory.
Unless otherwise specified, all analyses are based on the Full Analysis subjects data set.G

11 REFERENCES

[1] Alberti G, Zimmet P, Shaw J, Bloomgarden Z, Kaufman F, Silink M, et al. Type 2 diabetes in the young: the evolving epidemic. Diabetes Care 2004;27:1798-811

[2] International Diabetes Federation Clinical Guidelines Task Force. Global guideline for type 2 diabetes. Brussels: International Diabetes Federation; 2005. Available from: http://www.idf.org/webdata/docs/IDF%20GGT2D.pdf. Accessed on 13 February 2008.

[3] American Diabetes Association. Type 2 diabetes in children and adolescents. Diabetes Care 2000;23:381-9.

[4] American Diabetes Association. Standards of medical care in diabetes 2008. Diabetes Care 2008;31(Suppl 1):S12-54.

[5] Goran MI, Ball GDC, Cruz ML. Obesity and risk of type 2 diabetes and cardiovascular disease in children and adolescents. J Clin Endocrinol Metab 2003;88:1417-27.

[6] Krakoff J, Hanson RL, Kobes S, Knowler WC. Comparison of the effect of plasma glucose concentrations on microvascular disease between Pima Indian youths and adults. Diabetes Care 2001;24:1023-8.

[7] Dean HJ, Sellers EAC. Comorbidities and microvascular complications of type 2 diabetes in children and adolescents. Pediatr Diabetes 2007; 8 (Suppl 9):35-41.

[8] Eppens MC, Craig ME, Cusumano J, Hing S, Chang AKF, Howard NJ, et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. Diabetes Care 2006;29:1300-6.

[9] Bloomgarden, ZT. Type 2 diabetes in the young. The evolving epidemic. Diabetes Care 2004;27:998-1010.

[10] Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. N Engl J Med 1993;329:977- 86.

[11] Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. J Pediatr 1996;128(5 Pt 1):608-15.

[12] Bingley P, Bonifacio E, Ziegler A, Schatz D, Atkinson M, Eisenbarth G and the Immunology of Diabetes Society. Proposed Guidelines on Screening for Risk of Type 1 Diabetes. Diabetes Care 2001;24(2):398.

[13] Ehtisham S, Hattersley AT, Dunger DB, Barrett TG. First UK survey of pediatric type 2 diabetes and MODY. Arch Dis Child 2004;89:526-9.

[14] Neu A, Feldhahn L, Ehehalt S, Hub R, Ranke M. Type 2 diabetes mellitus in children and adolescents is still a rare disease in Germany: A population-based assessment of the prevalence of type 2 diabetes and MODY in patients aged 0-20 years. Peds Diabetes 2009;10(7):468-73.

[15] Zachrisson I, Tibell C, Bang P, Ortquist E. Prevalence of type 2 diabetes among known cases of diabetes aged 0-18 years in Sweden. J Pediatr Endocrinol Metab 2003;16:919-55.

[16] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of American Statistical Association. 1958; 53:457-481.

[17] Greenwood M. The natural duration of cancer. Reports on public health and medical subjects. 1926; 33:1-26.

[18] Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005 May;28(5):1245-9.

[19] Global IDF/ISPAD Guideline for Diabetes in Childhood and Adolescence, available at https://www.idf.org/sites/default/files/Diabetes-in-Childhood-and-Adolescence-Guidelines.pdf.

[20] Centers for Disease Control and Prevention

Available at https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm