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Clinical Protocol MB102138
(AZ study number: D1690C00017)

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.

Revised Protocol Number: 03
Incorporates amendments: 01 & 02 & 03

Medical Monitor

[redacted]

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

[redacted]

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	20-Sep-2017	Incorporates Amendment 03
Amendment 03	20-Sep-2017	The purpose of this protocol amendment is to increase the number of subjects randomized in the study to ensure that at least 50 subjects will complete the 24-week treatment period on investigational product and the Week 24 assessment.
Revised Protocol 02	13-Feb-2017	Incorporates Amendment 02
Amendment 02	13-Feb-2017	The purpose of this protocol amendment is 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 has been 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 have been clarified. The 24-hour emergency telephone numbers and SAE reporting details have been updated to PRA numbers.
Revised Protocol 01	15-Jan-2016	Incorporates Amendment 01
Amendment 01	15-Jan-2016	The purpose of this amendment is to incorporate new safety information related to diabetic ketoacidosis (DKA) as reflected in Dapagliflozin IB version 12, and correct typographical errors and discrepancies within the protocol.
Original Protocol	09-Nov-2015	Not applicable

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SYNOPSIS

Clinical Protocol MB102138 (AZ study number: D1690C00017)

Protocol Title: 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.

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Dapagliflozin 10 mg or placebo tablets administered orally once daily for the 24-week double-blinded short-term treatment period and dapagliflozin 10 mg tablets administered orally once daily for the 28-week open-label safety extension.

Study Phase: 3b

Research Hypothesis: Dapagliflozin results in a greater mean reduction from baseline in glycated hemoglobin (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.

Objectives:

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.

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 discontinuation 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.

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 diabetic ketoacidosis (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.

Exploratory Objectives:

- To explore the pharmacokinetics (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 discontinuation 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.

Study Design: The study will be 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 release (IR) or extended release (XR) (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. 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.

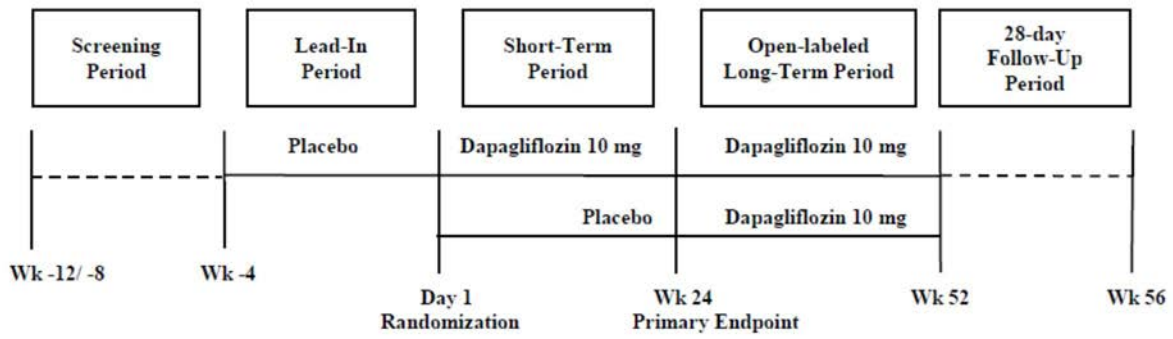
After the lead-in period, at least 66 subjects with HbA1c ≥ 6.5% and ≤ 11% at screening will be randomized 1:1 to receive oral blinded dapagliflozin 10 mg or placebo, stratified by gender, age (< 18 vs. ≥ 18 years and ≤ 15 years vs. > 15 to < 18 years) and baseline medication (metformin alone, insulin ± metformin). After completion of the 24-week short-term 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 period.

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

Safety measures will be collected throughout the study. This will include regular self-monitored blood glucose (SMBG) levels, self-monitored blood ketone 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.

Study Schematic:



During the course of the trial, subjects may be eligible for the addition of open-label rescue medication to their blinded treatment regimen in order to treat ongoing hyperglycemia. Insulin will be initiated or up-titrated as rescue.

Pre-specified glycemic criteria (see Table 1 below), based upon SMBG FPG, or single central laboratory FPG and repeat confirmatory FPG have been established during the treatment period, starting at Day 1, and up to the Week 52 visits to determine eligibility for open-label rescue medication. For subjects on baseline insulin, persistently increased doses of insulin 20% or more above baseline dose, despite advice and counsel to keep the insulin dose stable, may be considered another potential manifestation of poor glycemic control, and should be evaluated for rescue. Any permanent changes in dose of basal insulin should be done after evaluation of rescue criteria, including both SMBG and central laboratory FPG values.

Table 1: Lack of Glycemic Control Criteria for Initiation of Rescue Medication

Study week	Rescue criterion
From Day 1 visit up to and including Week 24 visit	FPG > 13.3 mmol/L (240 mg/dL) based on SMBG for 3 consecutive days followed by a confirmatory central laboratory FPG or Single central laboratory FPG followed by a confirmatory central laboratory FPG
Following Week 24 visit up to and not including Week 52 visit	FPG > 10 mmol/L (180 mg/dL) based on SMBG for 3 consecutive days followed by a confirmatory central laboratory FPG or Single central laboratory FPG followed by a central laboratory FPG or HbA1c > 8.0%

Study Population: For entry into the study, the following criteria MUST be met. The full inclusion/exclusion criteria are found in Section 3.3 of the protocol.

Key Inclusion Criteria:

- Provision of informed consent prior to any study-specific procedures
- Males and females, ages 10 years of age, up to but not including 25 years of age at the time of randomization
- Previously diagnosed as having T2DM for at least 2 months by World Health Organization (WHO)/ADA diagnostic criteria
- HbA1c ≥ 6.5% and ≤ 11% obtained at screening visit

- Currently on diet and exercise and a stable dose of metformin (at least 1000 mg daily) for a minimum of 8 weeks, or stable dose of insulin for a minimum of 8 weeks, or a stable combination of metformin (at least 1000 mg daily) and insulin for a minimum of 8 weeks prior to screening
- FPG ≤ 255 mg/dL (≤ 14.2 mmol/L) obtained at screening visit

Key Exclusion Criteria:

- Previous diagnosis of Type 1 diabetes
- Diabetes ketoacidosis (DKA) within 6 months of screening
- Current use of the following medications for the treatment of diabetes, or use within the specified timeframe prior to screening for the main study:
  - Eight weeks: sulfonylureas, alpha glucosidase inhibitors, metiglinide, oral or injectable incretins or incretin mimetics or other antidiabetes medications not otherwise specified
  - Sixteen weeks: thiazolidinediones
  - Any previous history or current use of a sodium glucose cotransporter-2 (SGLT-2) inhibitor, including dapagliflozin
- Initiation or discontinuation of prescription or non-prescription weight loss drugs within 8 weeks of screening. Use of prescription or non-prescription weight loss drugs must be stable during the study.
- Pregnant, positive serum pregnancy test, planning to become pregnant during the clinical trials, or breastfeeding
- History of unstable or rapidly progressive renal disease
- History of unresolved vesico-ureteral reflux
- Replacement or chronic systemic corticosteroid therapy, defined as any dose of systemic corticosteroid taken for > 4 weeks within 3 months prior to the Day 1 visit

  Note: Topical, nasal, or inhaled corticosteroids are allowed
- Abnormal renal function, which is defined in subjects < 18 years of age as an estimated glomerular filtration rate (eGFR) calculated by the Schwartz Formula < 80 mL/min/1.73 m^2 (1.33 mL/s), and in subjects ≥ 18 years as an eGFR calculated by the Modified Diet in Renal Disease (MDRD) Formula < 60 mL/min/1.73 m^2 (1.33 mL/s)
- Presence of either: antibodies to glutamic acid decarboxylase (GAD) or protein tyrosine phosphatase-like protein antibodies (IA-2)
- An abnormal thyroid stimulating hormone (TSH) value at screening will be further evaluated for free T4. Subjects with abnormal free T4 values will be excluded.
- Hematuria (confirmed by microscopy at screening) with no explanation as judged by the Investigator up to randomization
- Anemia of any etiology defined as hemoglobin ≤ 10.7 g/dL (107 g/L) for females and ≤ 11.3 g/dL (113 g/L) for males. Subjects who are considered to have anemia according to local guidelines should be excluded.
- Volume-depleted subjects. Subjects at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, should carefully monitor their volume status.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for BMS-512148		
Medication	**Potency**	**IP/Non-IP**
Dapagliflozin	10 mg	IP
Placebo Matching Dapagliflozin	0 mg	IP

Study Assessments:

Dose and Treatment Regimens

Dapagliflozin 10 mg tablets or matching placebo tablets, administered orally once daily, will be provided for the 24-week blinded treatment period. Dapagliflozin 10 mg tablets administered orally once daily, will be provided for the 28-week site and subject blinded long-term extension.

During the study, diet and exercise will be reinforced at each visit.

Safety Assessments

Self-monitored blood glucose (SMBG) and reporting of hypoglycemia

Glucose meters will be supplied to each study site. Subjects should be asked to self-monitor their blood glucose at least once per day and when symptoms suggestive of hypoglycemia occur. The Investigator may require more frequent readings based on local clinical practice. The glucose values should be reviewed by the site to identify any unusual high or low values.

Self-monitored blood ketones and reporting of DKA

Subjects and their family members must be aware of the possibility that DKA may occur, the signs and symptoms and the dangers associated with DKA. Subjects will receive a combined glucose and ketone meter and sufficient supplies for testing at the entry into Lead-In (Week -4 visit). Subjects will also be trained in the procedure of conducting blood ketone testing according to the manufacturer's specifications. The blood ketone values should be recorded and will be reviewed by the site to identify any unusual high values.

Assessment of growth and maturation

Growth and maturation will be assessed through the collection of relevant physical measurements and specific laboratory tests,

Laboratory Safety Assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the protocol.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities.

Statistical Considerations:

Sample Size:

Given the anticipated challenges to recruitment with this population, a partial extrapolation approach was used to better inform the sample size determination.

A probability estimate was determined using clinical trial simulation from a non-linear mixed effects model for the relationship between dapagliflozin 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 (PD) 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. 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 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 two-sided alpha level of 5 percent. To ensure that at least 50 subjects will complete the 24-week treatment period on investigational product and the Week 24 assessment, at least 66 subjects will be randomized.

Endpoints:

Primary endpoint

1. Change from baseline in HbA1c at Week 24

Secondary endpoints

2. The change from baseline in FPG at Week 24
3. The percentage of subjects who require glycemic rescue medication or discontinuation due to lack of glycemic control over 24 weeks double-blind treatment
4. The percentage of subjects with baseline HbA1c > 7% who achieve HbA1c level < 7% at Week 24

Safety endpoints

The assessment of safety will be based on the analyses of adverse events (AEs), vital signs, physical examinations, electrocardiograms (ECGs), hypoglycemia, elevated plasma ketone level, and clinical laboratory evaluations. All safety analyses will be performed using the Treated Subjects Data Set.

Analyses:

Statistical Approach and Assumptions

The primary analysis of the primary endpoint, change in HbA1c from baseline to Week 24, will be based on a mixed model with repeated measures (MMRM) including all scheduled time points following randomization up to and including Week 24. The primary analysis will only include measurements prior to the administration of rescue medication. Measurements made following rescue administration will be included in sensitivity analysis. Various sensitivity analyses will be specified in the Statistical Analysis Plan to assess the robustness of the primary analyses, including sensitivity analyses of all data pre-and post-rescue.

Point estimates and 95% confidence intervals 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.

Safety Analyses

Safety analyses will include treatment group summaries of the incidence of AEs and marked laboratory abnormalities, the percentages of subjects experiencing hypoglycemia as well as the number and severity of hypoglycemic events, the incidence of elevated plasma ketone level, vital signs, and laboratory test parameters.

Summaries will include the number of patients with events by specified system organ classes and preferred terms.

1 INVESTIGATIONAL PLAN

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 T2DM, 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 glycosylated 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 UK 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 sodium glucose cotransporter-2 (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.

1.1 Study Rationale

This protocol will be performed to meet the requirements of the European Union (EU) Pediatric Investigations Plan (PIP) 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 (OAD) 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 (UK), 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 model for the relationship between dapagliflozin pharmacokinetics (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 (PD) 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.

1.2 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.

1.3 Objectives(s)

1.3.1 Primary Objectives

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.

1.3.2 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 discontinuation 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.

1.3.3 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 diabetic ketoacidosis (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.

1.3.4 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 discontinuation 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.

1.4 Product Development Background

Dapagliflozin is a rationally designed, stable, competitive, reversible, highly selective and orally active inhibitor of SGLT-2, the major transporter responsible for renal glucose reabsorption. Dapagliflozin inhibits human SGLT-2 (Ki = 0.55 nM) selectively (1400-fold selective), and is also highly selective vs. other facilitative glucose transporters. Dapagliflozin's mechanism of action is different and complementary to the mechanisms of currently available medicines, resulting in the direct and insulin-independent elimination of glucose by the kidney. Further, as SGLT-2 is almost exclusively expressed in the kidney, the highly selective nature of dapagliflozin minimizes the risk of off target (i.e., non-kidney) effects. As such, dapagliflozin offers an important additional strategy for improving glycemic control in patients with T2DM.

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 OAD medications. Results from secondary glycemic efficacy endpoints (including FPG, 2-hour postprandial glucose [PPG], and change in HbA1c in patients with baseline HbA1c ≥ 9.0%) are consistent with the main HbA1c results and further support the role of dapagliflozin as a glucose lowering agent. Importantly, dapagliflozin has been shown to improve glycemic control with a low intrinsic risk for hypoglycemia. Furthermore, the steady excretion of glucose due to SGLT-2 inhibition results in a continual loss of calories that ultimately leads to a decrease in weight and adiposity. The inhibition of sodium and glucose transport in the proximal tubule also causes a mild diuretic effect, leading to a modest lowering of blood pressure (BP). Overall, 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.

1.5 Overall Risk/Benefit Assessment

Dapagliflozin is approved for use in adults in approximately 40 countries including the United States (US) and EU. Prior to approval, dapagliflozin was evaluated in 5 core Phase 2b studies, 16 core Phase 3 studies, and 3 regional Phase 3 studies. These studies established that dapagliflozin is effective in reducing HbA1c in a broad range of adult subjects, regardless of disease progression/duration or concomitant use of antidiabetic therapies. Dapagliflozin consistently demonstrated statistically and clinically significant mean reductions in HbA1c versus placebo among the three doses typically studied (2.5, 5, and 10 mg). Overall, the dose of 10 mg provided better efficacy than the two lower doses. Effects on secondary glycemic efficacy parameters, including FPG and PPG, support the primary HbA1c efficacy findings. Dapagliflozin also resulted in a modest reduction in total body weight relative to placebo or comparator, largely attributable to a decrease in body fat mass, as well as reductions in systolic BP. Placebo-controlled data for up to 2 years indicate that the beneficial effects on glycemic and non-glycemic parameters were maintained.

Overall, dapagliflozin has been well tolerated in clinical studies.

For an overall risk/benefit assessment of dapagliflozin, see the Investigator's Brochure (IB).

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying EU Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other written information to be provided to subjects. The

Investigator or Sponsor (or designee) should also provide the IRB/IEC with a copy of the IB or product labeling information to be provided to subjects and any updates.

The Investigator or Sponsor (or designee) should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

Sponsor or designee will provide the Investigator with an appropriate (i.e., Global or Local) sample informed consent form (ICF) which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC’s written approval/favorable opinion of the written ICF and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject’s legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The Investigator, or a person designated by the Investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects’ signed Health Insurance Portability and Accountability Act of 1996 (HIPAA) Authorization.

The consent form must also include a statement that the Sponsor or designee and regulatory authorities have direct access to subject records.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the ICF approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information, to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the Investigator.

Minors who are judged to be of an age of reason must also give their written assent.

Subjects unable to give their written consent may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the Investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

The study will be 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 release (IR) or extended release (XR) (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 Section 3.3. 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 vs. ≥ 18 years and ≤ 15 years vs. >15 to < 18 years) and baseline medication (metformin alone, insulin ± metformin). After completion of the 24-week short-term 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 period. The study will end when all evaluable subjects complete the 56 weeks of study.

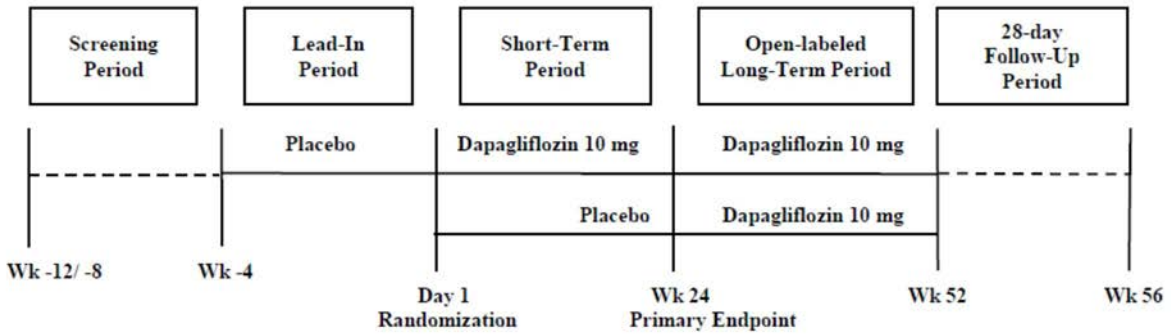
Subjects who discontinue study drug before the end of the study treatment period will enter a non-treatment, follow-up phase, in which subjects will follow their visit schedules with modified assessments until study completion. Discontinued subjects will not be replaced.

Glycemic rescue parameters are included for subjects who meet the criteria for lack of glycemic control in both the 24-week short-term treatment period and the 28-week safety extension period. Investigators will use insulin as rescue. Rescued subjects will continue treatment on study drug.

Safety measures will be collected throughout the study. This will include regular self-monitored blood glucose (SMBG) levels, self-monitored blood ketone 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 3.1-1.

Figure 3.1-1: Study Design Schematic



3.2 Post Study Access to Therapy

At the end of the treatment period (at Week 52 visit) or early discontinuation, the Sponsor or designee will not continue to provide Sponsor supplied study drug to subjects/investigators unless the Sponsor or designee chooses to extend the study. The Investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects (or designee) must be willing and able to give signed and dated written informed consent. Minor's parents or legally acceptable representatives must give fully informed

written consent. Assent should be obtained according to local regulations and if child is capable.

2. Target Population

a) Previously diagnosed with T2DM by World Health Organization (WHO)/ADA diagnostic criteria

b) HbA1c ≥ 6.5% and ≤ 11% obtained at screening visit

c) Currently on diet and exercise and a stable dose of metformin (at least 1000 mg daily) for a minimum of 8 weeks, or stable dose of insulin for a minimum of 8 weeks, or a stable combination of metformin (at least 1000 mg daily) and insulin for a minimum of 8 weeks prior to screening

d) FPG ≤ 255 mg/dL (≤ 14.2 mmol/L) obtained at screening visit

e) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (i.e., subject has not been randomized / has not been treated).

Note: If re-enrolled, the subject must be re-consented. All screening procedures will be repeated. Subjects may only be re-enrolled once.

3. Age and Reproductive Status

a) Males and females, ages 10 years of age, up to but not including 25 years of age at the time of randomization.

i) Recruitment (randomization) of subjects ≥ 18 and < 25 years old will be limited to < 40% of subjects.

ii) Recruitment (randomization) of subjects ≥ 10 and ≤ 15 years old will include at least 20% of subjects.

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta-human chorionic gonadotrophin) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding

d) Women of childbearing potential must agree to follow instructions for method of contraception for the duration of treatment with study drug, plus 5 half-lives of study drug or 30 days (whichever is longer), plus 30 days (duration of ovulatory cycle), for a total of 60 days post-treatment completion.

e) Women of childbearing potential who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to use one highly effective OR one less effective method of contraception as listed below:

A. HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. Women of childbearing potential are expected to use one of the highly effective methods of contraception listed below. Contraception methods are as follows:

1. Progestogen-only hormonal contraception associated with inhibition of ovulation
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3. Nonhormonal IUDs, such as ParaGard®
4. Bilateral tubal occlusion
5. Vasectomised partner with documented azoospermia 90 days after procedure
    a. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
6. Intrauterine hormone-releasing system
7. Complete abstinence
    a. Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms).
    b. Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).
    c. It is not necessary to use any other method of contraception when complete abstinence is elected.
    d. Subjects who choose complete abstinence must continue to have pregnancy tests.
    e. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
    f. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

B. LESS EFFECTIVE METHODS OF CONTRACEPTION

1. Diaphragm with spermicide
2. Cervical cap with spermicide
3. Vaginal sponge with spermicide
4. Male or female condom with or without spermicide.[16,17] A male and a female condom must not be used together.
5. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

C. UNACCEPTABLE METHODS OF CONTRACEPTION

a) Periodic abstinence (calendar, symptothermal, post-ovulation methods)
b) Withdrawal (coitus interruptus)
c) Spermicide only
d) Lactation amenorrhea method

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Previous diagnosis of Type 1 diabetes

b) Previous diagnosis of monogenic etiology of T2DM such as maturity onset diabetes of the young (MODY), genetic disorders with strong associations with insulin resistance/diabetes and/or obesity such as Turner's Syndrome and Prader-Willi, or secondary diabetes (steroid use, Cushing's disease, acromegaly)

c) Diabetic ketoacidosis within 6 months of screening

d) Current use of the following medications for the treatment of diabetes, or use within the specified timeframe prior to screening for the main study:

i) Eight weeks: sulfonylureas, alpha glucosidase inhibitors, metiglinide, oral or injectable incretins or incretin mimetics or other antidiabetes medications not otherwise specified

ii) Sixteen weeks: thiazolidinediones

iii) Any previous history or current use of an SGLT-2 inhibitor, including dapagliflozin

e) Initiation or discontinuation of prescription or non-prescription weight loss drugs within 8 weeks of screening. Use of prescription or non-prescription weight loss drugs must be stable during the study.

2. Medical History and Concurrent Diseases

a) Pregnant, positive serum pregnancy test, planning to become pregnant during the clinical trials, or breastfeeding

b) History of unstable or rapidly progressive renal disease

c) History of unresolved vesico-ureteral reflux

d) History of hemoglobinopathy, with the exception of sickle cell trait or thalassemia minor; or chronic or recurrent hemolysis

e) Malignancy within 5 years of the screening visit (with the exception of treated basal cell or treated squamous cell carcinoma)

f) Significant co-morbidity that, in the opinion of the investigators, will increase the risk to the subject such as coronary artery disease, any heart disease that increases risk associated with exercise, or immune-suppression

g) Replacement or chronic systemic corticosteroid therapy, defined as any dose of systemic corticosteroid taken for > 4 weeks within 3 months prior to the Day 1 visit

NOTE: Topical, nasal, or inhaled corticosteroids are allowed

3. Physical and Laboratory Test Findings

a) Abnormal renal function, which is defined in subjects < 18 years of age as an estimated glomerular filtration rate (eGFR) calculated by the Schwartz Formula < 80 mL/min/1.73 m^2 (1.33 mL/s)[18], and in subjects ≥ 18 years as an eGFR calculated by the Modified Diet in Renal Disease (MDRD) Formula < 60 mL/min/1.73 m^2 (1.33 mL/s)[19]

b) Presence of either: antibodies to glutamic acid decarboxylase (GAD) or protein tyrosine phosphatase-like protein antibodies (IA-2)

c) An abnormal thyroid stimulating hormone (TSH) value at screening will be further evaluated for free T4. Subjects with abnormal free T4 values will be excluded.

Note: In subjects who have had a prior diagnosis of a thyroid disorder and who are currently receiving thyroid replacement therapy, a one-time retest of TSH may be allowed, as determined by the Investigator, after a minimum of 6 weeks following the adjustment of thyroid hormone replacement therapy. Such cases should be discussed with the Sponsor prior to re-testing. The subject must have all enrollment procedures and laboratory assessments performed as part of this re-test, and all of these must meet enrollment eligibility criteria. The subject's number will however remain the same as initially assigned.

d) Hematuria (confirmed by microscopy at screening) with no explanation as judged by the Investigator up to randomization.

e) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2× upper limits of normal (ULN), or clinically significant hepatic disease.

f) Serum total bilirubin (TB) ≥ 2x ULN, unless exclusively caused by Gilbert's syndrome

g) History of positive serologic evidence of current infectious liver disease including anti-hepatitis A virus (HAV) (Immunoglobulin M [IgM]), hepatitis B surface antigen (HBsAg), or anti-hepatitis C virus (HCV). Patients who may have isolated positive hepatitis B surface antibodies may be included.

h) Anemia of any etiology defined as hemoglobin ≤ 10.7 g/dL (107 g/L) for females and ≤ 11.3 g/dL (113 g/L) for males. Subjects who are considered to have anemia according to local guidelines should be excluded.

i) Volume-depleted subjects. Subjects at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, should carefully monitor their volume status.

j) Clinically significant abnormalities in any pre-randomization laboratory analyses or electrocardiogram (ECG) that, in the Investigator's opinion, would preclude randomization.

4. Allergies and Adverse Drug Reaction

a) Known allergy, sensitivity or contraindication to any study drug or its excipient/vehicle.

5. Other Exclusion Criteria

a) Subject is currently abusing alcohol or other drugs or has done so within the last 6 months prior to the screening visit.

b) Prisoners or subjects who are involuntarily incarcerated

c) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness

d) Psychiatric or cognitive disorder that will, in the opinion of investigators, limit the subject's ability to comply with the study medications and monitoring.

e) Subjects who have contraindications to therapy as outlined in the dapagliflozin IB or local package inserts

f) Participation and receiving investigational product (IP) in another clinical study during the prior 3 months

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

A woman of childbearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

- Once consented, subjects may not receive any prescription antihyperglycemic medication other than study drug, metformin and/or insulin.
- Once consented, subjects should not begin treatment with any systemic corticosteroid therapy lasting ≥ 5 days (inhaled and topical are allowed). Subjects who require systemic corticosteroid therapy should be discussed with the medical monitor prior to starting therapy whenever possible.
- Once consented, subjects should not commence or modify therapy with any prescription or over the counter weight loss medications.
- Once consented, subjects should not undergo any bariatric surgery.

3.4.2 Other Restrictions and Precautions

- Subjects must comply with their prescribed dosing regimen to preserve study integrity and ensure subject safety.
- Subjects should be cautioned that any new prescription, over-the-counter or herbal/nutritional therapies should be discussed thoroughly with the Investigator as concomitant use could result in alterations to their glycemic control and may place them at risk for significant hypoglycemic episodes.

- Medication other than those which are protocol prohibited as described above, considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and must be recorded in the appropriate sections of the case report form (CRF).
- Subjects must make every attempt to adhere to the diet and exercise counseling and to the study flow chart/time and events schedule (see Section 5.1).
- Women of childbearing potential must immediately contact the Investigator if they suspect they might be pregnant and if they have changed or plan to change their birth control method.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue IP (and non-investigational product [non-IP] at the discretion of the Investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Sponsor
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Unblinding a subject for any reason (emergency or non-emergency)
- Severe non-compliance to protocol, as judged by the Investigator and/or Sponsor
- Safety reasons as judged by the Investigator and/or Sponsor
- Pregnancy
- Subjects experiencing decreased renal function must be evaluated as per Investigator's discretion.
    - Subjects with eGFR < 50 mL/min/1.73 m^2 (by Schwarz formula[18] for subjects < 18 years and by MDRD formula[19] for subjects ≥ 18 years) for a sustained period of time (12 to 16 weeks) must be discontinued.
- Subjects with a central laboratory ALT and/or AST > 3xULN will be scheduled for a follow-up visit within 3 days following the receipt of the result (see Appendix 1 and Appendix 2 for further guidance). Subjects should be discontinued from study drug if the initial repeat laboratory tests meet any of the following criteria:
    - ALT and/or AST are > 3x ULN and TB > 2x ULN.
    - ALT and/or AST are > 5x ULN for ≥ 14 consecutive days, at any time after initial confirmatory results.
    - ALT and/or AST are ≥ 10x ULN.

In the case of pregnancy, the Investigator must immediately notify the Sponsor's Medical Monitor/designee of this event. The study drug will be permanently discontinued in an appropriate manner.

All subjects who discontinue study drug should comply with protocol-specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject

withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.

3.5.1 Procedures for handling patients incorrectly enrolled or randomized

Subjects who fail to meet the inclusion/exclusion criteria must not, under any circumstances, be enrolled or randomized. There can be no exceptions to this rule.

Subjects who are incorrectly enrolled, but are not yet randomized, should be withdrawn from the study. The procedures included in the protocol for the discontinuation of such subjects must be followed. Study medication should be permanently stopped and the subject should be further treated according to the Investigator's judgment and local therapy tradition.

If a subject not meeting the study criteria is randomized in error, and if the error is identified after randomization, a discussion must occur between the Sponsor Medical Monitor or designee and the Investigator regarding whether to continue or discontinue the subject from the study drug. If agreement to continue in the study is reached, the subject should complete the study unless there are safety concerns or if the subject withdraws the consent. In situations in which an agreement cannot be reached, the subject should have the randomized therapy stopped and be discontinued from the study. The procedures included in the protocol for the discontinuation of such subjects must be followed. The Sponsor Medical Monitor is to ensure all such contacts with the Investigator and such decisions are appropriately documented.

Withdrawn subjects will not be replaced.

3.5.2 Rescue Guidelines for Subjects with Protocol-Defined Lack of Glycemic Control

During the course of the trial, subjects may be eligible for the addition of open-label rescue medication to their blinded treatment regimen in order to treat ongoing hyperglycemia. Insulin will be initiated or up-titrated as rescue.

Pre-specified glycemic criteria (see Table 3.5.2-1), based upon SMBG FPG, or single central laboratory FPG and repeat confirmatory FPG have been established during the treatment period, starting at Day 1, and up to the Week 52 visit, to determine eligibility for open-label rescue medication. For subjects on baseline insulin, persistently increased doses of insulin 20% or more above baseline dose, despite advice and counsel to keep the insulin dose stable, may be considered another potential manifestation of poor glycemic control, and should be evaluated for rescue. Any permanent changes in dose of basal insulin should be done after evaluation of rescue criteria, including both SMBG and central laboratory FPG values.

Table 3.5.2-1: Lack of Glycemic Control Criteria for Initiation of Rescue Medication

Study week	Rescue criterion
From Day 1visit up to and including Week 24 visit	FPG > 13.3 mmol/L (240 mg/dL) based on SMBG for 3 consecutive days followed by a confirmatory central laboratory FPG or Single central laboratory FPG followed by a confirmatory central laboratory FPG
Following Week 24 visit up to and not including Week 52 visit	FPG > 10 mmol/L (180 mg/dL) based on SMBG for 3 consecutive days followed by a confirmatory central laboratory FPG or Single central laboratory FPG followed by a central laboratory FPG or HbA1c > 8.0%

Subjects must be rescued following one of these scenarios:

- Subjects with a SMBG FPG value meeting the lack of glycemic control criterion at any time during the pre-specified study period will be instructed to repeat FPG measurements on 2 further consecutive days. If all 3 daily values meet the relevant lack of glycemic control criterion subjects should be scheduled for a follow-up visit (within 1 - 5 days) to obtain a central laboratory FPG value and review of the subject's glucose meter readings. If the central laboratory FPG value meets the criterion, the subject must be rescued.
- Subjects with a central laboratory FPG value meeting the lack of glycemic control criterion at a pre-specified visit will be scheduled for a follow-up visit (within 3 - 5 days) to obtain a second central laboratory FPG value and review of the subject's glucose meter readings. If the second central laboratory FPG value also meets the criterion, the subject must be rescued.
- Subjects with a central laboratory HbA1c value meeting the lack of glycemic control criterion following the pre-specified Week 24 visit must be rescued.

Subjects who meet rescue criteria must first complete the Rescue Visit procedures before receiving open-label rescue medication to ensure that important trial endpoint measurements are collected.

Following completion of the Rescue Visit, rescued subjects will either initiate or up-titrate open-label insulin as rescue medication. Insulin should be initiated at the lowest starting dose and titrated in accordance with the approved product label in the applicable country at the discretion of the Investigator, in addition to their study medication. Additional visits for titration of rescue medication should be scheduled as per the Investigator's judgment in accordance with the approved product label for that country and by the subject's glycemic response. Rescued subjects will then continue in the study according to their original visit schedule.

Note: Rescue medication will NOT be provided by the Sponsor in this study.

3.5.3 Discontinuation Guidelines due to Protocol-Defined Hypoglycemia Episodes

Subjects should not be discontinued from any treatment phase based on single episodes of hypoglycemia or symptoms of hypoglycemia unless clinically indicated. The assessment of a

single finger-stick or central laboratory glucose value should not be the sole assessment used to determine subject discontinuation for hypoglycemia. Clinical indications for discontinuation because of hypoglycemia may include the following:

- Multiple occasions of episodes outlined below that, in the opinion of the Investigator, indicate that continued treatment with study therapy is not in the best interest of the subject. This includes, but is not limited to:
    - Recurrent symptoms suggestive of hypoglycemia (e.g., sweating, shakiness, increased heart rate (HR), confusion, dizziness, light-headedness, or hunger) in the absence of environmental factors known to contribute to hypoglycemia (i.e., excess physical activity, concurrent illness, or missed or delayed meal).
    - Recurrent documented capillary or plasma blood glucose values < 54 mg/dL (< 3.0 mmol/L).
- A subject may also be discontinued from the study because of severe hypoglycemia as determined by the Investigator.

Down-titration of blinded study drug and/or background antihyperglycemic agent during the study

Down-titration of blinded study drug and/or background metformin will not be allowed at any time during the study.

Subjects on background insulin treatment who experience multiple or severe episodes of hypoglycemia may down-titrate insulin treatment during the study. The down-titration should be minimized, but is at the Investigator's discretion.

3.5.4 Discontinuation Guidelines due to Diabetic Ketoacidosis (DKA)

There have been post-marketing reports of ketoacidosis, including DKA, in patients with type 1 and T2DM taking dapagliflozin and other SGLT-2 inhibitors, although a causal relationship has not been established.

Patients treated with dapagliflozin who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise, and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL).

A subject with any symptoms that may be consistent with an event of DKA should measure blood ketone levels, using the provided ketone and glucose meter, interrupt study drug and contact the Investigator. Treatment with the study drug may resume when the symptoms resolve or at the Investigator's discretion. In the case of an established DKA, study drug should be interrupted until the event has resolved.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements due to infections, illness or surgery and alcohol abuse.

3.6 Post Study Drug Study Follow-up

In this study, safety is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

Please note that after the discontinuation of study drug, the management of the subject's diabetes will be under the care and direction of the Investigator.

The only exception to any of these follow-up methods is when a subject withdraws consent for all study procedures, including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the Investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be destroyed, and the action documented. If samples are already analyzed, the Sponsor is not obliged to destroy the results of this research.

The Investigator must ensure:

- Subject's withdrawal of informed consent to the use of donated samples is notified immediately to the Sponsor.
- Biological samples from that subject, if stored at the study site, are immediately identified, destroyed, and the action documented.
- The laboratory holding the samples is informed about the withdrawn consent immediately and that samples are destroyed, and the action documented.
- The subject and Sponsor are informed about the sample disposal.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up

is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If the Investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the Investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other vital status data necessary to complete the follow-up portion of the study. The site staff and representative will conduct searches in a legally permissible manner that may include public records and database research, social media research and genealogical research. Physical research of local municipal resources, as allowed by local laws and regulations, may be conducted. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the subject's medical records.

3.6.3 Survey of Subject Vital Status

Subjects who prematurely discontinue from the study may be contacted after discontinuation from the study to collect vital status and safety information.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/ Non-IMP) and can consist of the following:

Table 4-1: Study Drugs for MB102138: Product Description: Short-term Double-Blind Treatment and Long-term Open Label Treatment Period

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Manufacturer	Storage Conditions (per label)
Dapagliflozin Film Coated Tablet	10 mg	IP	Blinded	AstraZeneca	Storage conditions (per label), printed on IP bottles
Placebo for Dapagliflozin Film Coated Tablets	0 mg	IP	Blinded	AstraZeneca	Storage conditions (per label), printed on IP bottles
Dapagliflozin Film Coated Tablet	10 mg	IP	Open-Label	AstraZeneca	Storage conditions (per label), printed on IP bottles

4.1 Investigational Product

An IP also known as investigational medicinal product (IMP) in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The IP should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that IP is only dispensed to study subjects. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, the IP is dapagliflozin 10 mg and placebo (also described in Table 4-1). Background therapy metformin and/or insulin (as appropriate) will not be provided by the Sponsor, since it is part of patients' standard of care prior to enrollment.

Dapagliflozin 10 mg and corresponding placebo tablets may contain lactose, which may cause discomfort in lactose-intolerant individuals.

Labeling: Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language according to the regional regulatory requirements.

4.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-IPs.

Subjects are expected to be on background medication of metformin IR or XR and / or insulin. Insulin, as per local labeling and standard of care, will be used for rescue as described in Section 3.5.2.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Sponsor or designee. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and the sponsor or designee should be contacted immediately. All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage.

Study drug not supplied by the Sponsor or designee will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by the Sponsor or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets).

4.4 Method of Assigning Subject Identification

At the screening visit each subject will be assigned a unique sequential subject number by the Interactive Web / Voice Response System (IWRS). 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 IWRS in a 1:1 ratio. Randomization will be stratified by gender, age (< 18 vs. ≥ 18 years and ≤ 15 years vs. > 15 to < 18 years) and baseline medication (metformin alone vs. insulin ± metformin).

Subjects entering the 4-week placebo lead-in period

Following completion of the Screening activities, subjects who meet all the inclusion and none of the exclusion criteria will be registered by the IWRS 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 IWRS at the Day 1 Randomization visit, to one of the following two double-blind treatment arms in a 1:1 ratio:

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

Subjects entering the 28-week long-term extension period

Following completion of the 24-week double-blinded treatment period, subjects will enter the long-term open-label treatment period. All subjects will receive open-label dapagliflozin 10 mg, i.e., 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.

At all study visits when study drug is dispensed, each subject will be assigned one or several Kit ID numbers by the IWRS. 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). The IWRS will be available 24 hours per day, 7 days a week.

4.5 Selection and Timing of Dose for Each Subject

Subjects successfully completing the lead-in period and meeting all eligibility criteria will be randomized (1:1) to receive either dapagliflozin 10 mg or placebo for the 24-week double-blinded short-term treatment period. All subjects completing the 24-week double-blind treatment period will then receive open-label dapagliflozin 10 mg for the subsequent 28-week long-term extension period.

Dapagliflozin 10 mg tablets or matching placebo tablets, will be administered orally once daily for the duration of the study.

4.6 Blinding/Unblinding

Blinding of treatment assignment is critical to the integrity of this clinical study.

Methods used to ensure blinding include:

- Investigational product will be labeled using a unique material kit ID, which is linked to the randomization code
- The IWRS will assign the bottle of study material to be dispensed to each patient
- This is a double-blind study wherein each patient will receive either the active drug or matching placebo. The active drug and placebo tablets will be identical and presented in identical packaging to ensure blinding of the medication

However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the IP is critical to the subject's management, the blind for that subject may be broken by the Investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the Investigator should determine that the unblinded information is necessary, i.e., that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the Investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

For this study, the method of unblinding for emergency purposes is via the IWRS.

Any request to unblind a subject for non-emergency purposes should be discussed with the Medical Monitor.

The exception is for those personnel analyzing the PK data, the AstraZeneca Supply Chain Study Management (SCSM) 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.

4.7 Treatment Compliance

Each time study medication is dispensed, compliance will be reinforced. When study medication is returned, compliance will be assessed based upon subject's interview and a count of the tablets returned. Compliance should be between ≥ 70% and ≤ 130% of that prescribed. The Investigator (or designee) will record the amounts of study medication dispensed and returned at each visit, as well as document reasons for non-compliance in the source document. The dates of all study medication dosing, including interruptions, missed doses or overdose, must be recorded on the eCRF.

If the subject is not ≥ 70% compliant with study drug doses during the study, then the period of non-compliance should be noted as a significant protocol deviation and the sponsor should be notified. The subject should be re-educated regarding the importance of study drug compliance.

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by the Sponsor or sourced by the Investigator) such as partially used study drug containers, vials and syringes are to be destroyed locally at a site approved by the local regulatory authority in accordance with local regulations.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to the Sponsor/designee upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study drug to a designated facility for destruction.

4.9 Return of Study Drug

It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.10 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (MB102138)

Procedure	Screening Week -12 / -8[a]	Lead-In Week -4[b]	Notes
Eligibility Assessments			
Informed Consent	X		
Obtain written Assent (If applicable)	X		
Inclusion/Exclusion Criteria	X		
Medical History	X		
Review Concomitant Medication	X	X	
ECG		X	
Safety Assessments			
Physical Examination		X	
Targeted Physical Examination	X		
Tanner Staging (Investigator determined/Self-reported)		X	See Appendix 3
Vital Signs	X	X	
Height	X		
Body Weight	X		
BMI	X		
Serious Adverse Events Assessment	X	X	
Adverse Events Assessment		X	

Table 5.1-1: Screening Procedural Outline (MB102138)

Procedure	Screening Week -12 / -8[a]	Lead-In Week -4[b]	Notes
Laboratory Tests			
Standard Safety Laboratory Panel (Blood/Urine)	X		See Appendix 1
GAD/IA2 Autoantibodies	X		
Fasting Plasma Glucose (FPG)	X		
HbA1c	X		
Pregnancy Test (WOCBP only)	X		For WOCBP only urine test with reflex serum test, if positive.
TSH, (reflex to FT4)	X		
Hepatitis Screening Panel	X		Includes hepatitis screen panel (anti-HAV [IgM], HbsAg, and anti-HCV)
Study Drug / IWRS			
Contact IWRS	X	X	
Dispense Study Drug		X	
General			
Provide Dietary and Exercise Counseling		X	
Provide glucose meter and supplies / instructions		X	
Provide logs / instructions		X	
Assessment of signs and symptoms of hypoglycemia episodes		X	

[a] The range in duration of the screening period, from Week -12 to Week -8, is due to the possibility of considerable delays in the performance and delivery of results of GAD/IA2 antibodies testing in some countries. Therefore, if all other screening procedures have been completed during the first 4 weeks of screening, but a final decision cannot be made due to a delay in results of GAD/IA2 testing, up to 4 additional weeks, i.e, up to a total of 8 weeks for all screening procedures, will be allowed until a decision of compliance with inclusion/exclusion criteria is made.

[b] Lead-in visit can be performed as soon as screening laboratory results have been reviewed, but within ≤ 56 days from Screening visit.

Table 5.1-2: Short-term Procedural Outline (MB102138)

Procedure	Day 1[a]	Wk 2[a,b]	Wk 4[a]	Wk 8[a]	Wk 12[a,b]	Wk 16[a]	Wk 20[a,b]	Week 24 / ETD (early treatment discontinuation) / Rescue[a]	Notes
Eligibility Assessments									
Inclusion/Exclusion Criteria	X								
Review concomitant medications / procedures	X	X*	X	X	X*	X	X*	X	*Assessed by Phone
Safety Assessments									
Physical Examination								X	
Targeted Physical Examination	X		X	X		X			
Tanner Staging (Investigator determined/Self-reported)								X	See Appendix 3
Vital Signs	X		X	X		X		X	
Height	X			X		X		X	
Body Weight	X			X		X		X	
ECG								X	
Assessment of signs and symptoms of hypoglycemia episodes	X	X*	X	X	X*	X	X*	X	*Assessed by Phone
DKA Assessment	X	X*	X	X	X*	X	X*	X	*Assessed by Phone
Serious Adverse Event Assessment	X	X*	X	X	X*	X	X*	X	*Assessed by Phone
Adverse Events Assessment	X	X*	X	X	X*	X	X*	X	*Assessed by Phone
Laboratory Tests									
Standard Safety Laboratory Panel (Blood/Urine)	X		X	X		X		X	See Appendix 1

Table 5.1-2: Short-term Procedural Outline (MB102138)

Procedure	Day 1[a]	Wk 2[a,b]	Wk 4[a]	Wk 8[a]	Wk 12[a,b]	Wk 16[a]	Wk 20[a,b]	Week 24 / ETD (early treatment discontinuation) / Rescue[a]	Notes
Fasting Lipid panel	X							X	Total cholesterol, triglycerides, HDL, and LDL
Fasting Plasma Glucose (FPG)	X		X			X		X	
HbA1c	X		X	X		X		X	Results masked
Pregnancy Test (WOCBP only)	X*		X	X	X**	X	X**	X	*To be performed prior to administration of first dose. **If appropriate, parent will provide result over the phone. Home pregnancy kits will be provided
Spot Urine Glucose	X		X			X		X	Results masked
Growth / maturation markers / Bone biomarkers	X							X	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, bone alkaline phosphatase, and osteocalcin, parathyroid hormone (PTH).
Blood PK Sampling									
PK Panel						X		X*	Samples to be taken pre-dose and 2 hours post-dose (± 1 hour) *Not to be collected at ETD visits
Study Drug / IWRS									
Contact IWRS	X			X		X		X	

Table 5.1-2: Short-term Procedural Outline (MB102138)

Procedure	Day 1[a]	Wk 2[a,b]	Wk 4[a]	Wk 8[a]	Wk 12[a,b]	Wk 16[a]	Wk 20[a,b]	Week 24 / ETD (early treatment discontinuation) / Rescue[a]	Notes
Randomize	X								
Dispense Study Drug	X			X		X		X*	*No drug dispensed during ETD or Rescue visit Rescued subjects will continue with their current assigned IP regimen.
Study Drug Compliance Review	X			X		X		X	
General									
Provide diet and exercise counseling	X		X	X		X		X	
Dispense Meter Supplies	X		X	X		X		X	
Review daily diary of finger-stick glucose values	X	X*	X	X	X*	X	X*	X	*Assessed by Phone
Provide logs / instructions	X		X	X		X		X	
Assess Rescue			X	X	X*	X	X*	X	*Assessed by Phone

[a] Visits may be scheduled ± 7 days (of original schedule) to allow flexibility of scheduling.

[b] Phone assessments

Table 5.1-3: Long-term Procedural Outline (MB102138)

Procedure	Wk 28[a,b]	Wk 32[a]	Wk 36[a,b]	Wk 40[a]	Wk 46[a,b]	Week 52 / ETD / Rescue[a]	Wk 56 Follow -up	Notes
Eligibility Assessments								
Review concomitant medications / procedures	X*	X	X*	X	X*	X	X*	*Assessed by Phone
Safety Assessments								
Physical Examination						X		
Targeted Physical Examination		X		X				
Tanner Staging (Investigator determined/Self-reported)						X		See Appendix 3
Vital Signs		X		X		X		
Height		X		X		X		
Body Weight		X		X		X		
ECG						X		
Assessment of signs and symptoms of hypoglycemia episodes	X*	X	X*	X	X*	X		*Assessed by Phone
DKA Assessment	X*	X	X*	X	X*	X		*Assessed by Phone
Serious Adverse Event Assessment	X*	X	X*	X	X*	X	X*	*Assessed by Phone
Adverse Events Assessment	X*	X	X*	X	X*	X	X*	*Assessed by Phone
Laboratory Tests								
Standard Safety Laboratory Panel (Blood/Urine)		X		X		X		See Appendix 1

Table 5.1-3: Long-term Procedural Outline (MB102138)

Procedure	Wk 28[a,b]	Wk 32[a]	Wk 36[a,b]	Wk 40[a]	Wk 46[a,b]	Week 52 / ETD / Rescue[a]	Wk 56 Follow -up	Notes
Fasting Lipid panel						X		Total cholesterol, triglycerides, HDL, and LDL
Fasting Plasma Glucose (FPG)		X		X		X		
HbA1c		X		X		X		
Pregnancy Test (WOCBP only)	X*	X	X*	X	X*	X		*If appropriate, parent will provide result over the phone. Home pregnancy kits will be provided.
Growth/ maturation markers / Bone biomarkers						X		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, bone alkaline phosphatase, and osteocalcin , parathyroid hormone (PTH).
Study Drug / IWRS								
Contact IWRS		X		X		X		
Dispense Study Drug		X		X				*No drug dispensed during ETD or Rescue visit Rescued subjects will continue with their current assigned IP regimen.
Study Drug Compliance Review		X		X		X		
General								
Provide diet and exercise counseling	X*	X	X*	X	X*			*Assessed by Phone
Dispense Meter Supplies		X		X				
Review daily diary of finger-stick glucose values	X*	X	X*	X	X*	X		*Assessed by Phone

Table 5.1-3: Long-term Procedural Outline (MB102138)

Procedure	Wk 28[a,b]	Wk 32[a]	Wk 36[a,b]	Wk 40[a]	Wk 46[a,b]	Week 52 / ETD / Rescue[a]	Wk 56 Follow -up	Notes
Provide logs / instructions		X		X				
Assess Rescue	X*	X	X*	X	X*	X		*Assessed by Phone

[a] Visits may be scheduled ± 7 days (of original schedule) to allow flexibility of scheduling.

[b] Phone assessments

Table 5.1-4: Early Treatment Discontinuation (ETD) Follow-up - Non-Treatment Phase

Procedure	Non-treatment Short-term Follow-up (up to and including Week 24) Office Visit[a,b]	Non-treatment Longterm Follow-up (after Week 24, up to and including Week 52) Office Visit[a,b]	Short-term and Long-term Non-treatment Follow-up Phone Assessment[b,c]	Notes
Safety Assessments				
Targeted physical examination	X	X		
Vital signs	X	X		
Body weight and height	X	X		
Review concomitant medications	X	X	X	
AE assessment	X	X	X	
Standard safety laboratory panel (Blood/Urine)	X	X		Appendix 1
HbA1c	X	X		

[a] In-office assessments to occur at time points corresponding to originally scheduled Short-term (up to and including Week 24) and Long-term (after Week 24, up to and including Week 52) visits

[b] Visits may be scheduled ± 7 days (of original schedule) to allow flexibility of scheduling

[c] Phone assessments only to occur at time points corresponding to originally scheduled that is not identified above as an in office visit

5.1.1 Retesting During Screening or Lead-in Period

The laboratory parameters listed below may be repeated once in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Retesting of screening laboratory tests will only be allowed under the following circumstances, and must be performed within ≤ 10 days from the original screening visit:

- Repeat HbA1c testing if results fall ± 0.3% from inclusion range
- Repeat FPG testing if results fall + 9 mg/dL (0.5 mmol/L) from inclusion range

Any new result will override the previous result (i.e., the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Other individual laboratory screening tests for which the results are in error, borderline, or indeterminate for inclusion in the study may be repeated once for confirmation during the Screening period if they are within 25% of the exclusion limit. Upon retesting, subjects whose results remain outside this threshold should not be randomized.

5.2 Study Materials

The Sponsor or designee will supply the sites with the following materials:

- Blood glucose and ketone meters. One (1) meter will be provided to each study subject at enrollment and one (1) meter will be provided to each investigative site.
- Glucose and ketone test strips
- Lancets
- Glucose control solutions
- Subject education and site support materials
- Electronic case report forms (eCRFs) [Serious Adverse Event (SAE) Forms, Pregnancy Surveillance Forms]
- Subject Alert Cards
- Study Drug inventory control forms
- Subject Diary:
  - Full diary review by site staff is required for this study
  - Use of subject diaries is mandatory for the study and will be maintained by each study subject for documentation of SMBG results, ketone results, study medication dosing, hypoglycemia episodes (if applicable), symptoms potentially associated with DKA and relevant risk factors, WOCBP urine pregnancy test results (if applicable).
    - eCRF pages will be provided to the sites so they can record the relevant data obtained from the diaries into the study database.
    - Subjects are to record any hypoglycemic symptoms and symptoms potentially associated with DKA they may experience and SMBG and ketone values if they

conducted the test when they have symptoms in their diaries. All events recorded in subject diary are to be reviewed by site staff according to Section 5.3.1

- Any other materials as locally required or agreed.

The central laboratory will provide all laboratory-related materials including home pregnancy testing kits for WOCBP to the study sites.

5.3 Safety Assessments

Safety assessments will include AE reporting as well as marked abnormalities in clinical laboratory tests. Please refer to Appendix 1 for details on central laboratory assessments.

The procedures described in the sections that follow will also be completed to ensure subject's safety.

It is the Investigator's responsibility to report, as applicable based on the Investigator's judgment and the subject's medical history, related AEs as defined in Section 6. Additional information, including but not limited to completion of supplemental eCRFs or questionnaires may be requested for certain AEs and/or laboratory abnormalities which are reported/identified during the course of the study.

5.3.1 Self-Monitored Blood Glucose (SMBG), Self-Monitored blood Ketones and Guidance on Management and Reporting of Hypoglycemia Episodes

5.3.1.1 Self-Monitoring of Blood Glucose (SMBG)

Glucose meters will be supplied to each study site. At the entry into Lead-In (Week -4 visit), subjects will receive a glucose meter, supplies and instruction on their use. Supplies will be provided to allow for approximately 60 blood glucose assessments per month for the duration of the study. Subjects should be encouraged to measure and record fasting blood glucose levels at least once per day. The Investigator may require more frequent readings based on local clinical practice. Subjects should bring their glucose meter with them to each study visit to ensure that it is functioning properly. Subjects may keep the glucose meters at the end of the study, but the Sponsor will not continue to provide glucose meter supplies once the study is complete.

In the occurrence of hypoglycemic symptoms or in the event of an unusually high or low blood glucose value, subjects should contact the Investigator. In addition, study subjects should comply with site's instructions with regard to self-monitoring of blood glucose and should report to the site blood glucose values and/or signs and symptoms suggestive of a hypoglycemia episode.

The memory of the glucose meter should be reviewed to compare with the subject's hypoglycemia episode log, as applicable. The glucose values should be reviewed by the site to identify any unusual high or low values, and to confirm that the values (from the glucose meter's memory and/or from the subject's hypoglycemia log) were obtained for the subject. If finger-stick glucose values are discordant from glycemic control assessed by the central laboratory or with clinical symptoms, the subject's glucose meter should be tested and the procedure for using it reviewed with the subject.

5.3.1.2 Self-Monitored Blood Ketone Testing and Guidance on Management and Reporting of Diabetic Ketoacidosis Episodes

Diabetic ketoacidosis has been identified as a potential risk in subjects with diabetes receiving SGLT-2 inhibitors. Subjects and their family members must be aware of the possibility that DKA may occur, the signs and symptoms and the dangers associated with DKA. Subjects will receive a combined glucose and ketone meter and sufficient supplies for testing at the entry into Lead-In (Week -4 visit). Subjects will also be trained in the procedure of conducting blood ketone testing according to the manufacturer's specifications.

Subjects will be instructed to measure their blood ketones using the glucose and ketone meter provided by the Sponsor **at least** at the following frequency:

- Between Randomization (Day 1 visit) and Week 4 visit: once a day
- Between Week 4 visit and Week 24 visit: at least once every 2 weeks
- Between Start of open-label extension period (Week 24 visit) and Week 28 visit: once a day
- Between Week 28 visit and Week 52 visit: at least once every 2 weeks
- When experiencing potential symptoms/signs of DKA, including but not limited to; excessive thirst, nausea and vomiting, frequent urination, weakness or fatigue, fever, fruity-scented breath, confusion, and/or consistently elevated blood glucose: at least once a day
- During an acute illness: at least once a day

Blood ketone test results, symptoms potentially associated with DKA and relevant risk factors (e.g., missed insulin injection, infection, etc) should be recorded in the subject diary. As DKA may present differently and occur at lower glucose values than expected, particular attention should be paid to episodes of nausea and vomiting as indicative DKA symptoms, particularly in subjects requiring insulin therapy. Subjects should contact the site for assistance with diabetes management in the event that they develop such symptoms or when the blood ketone reading is 0.6 mmol/L or above, even if their blood glucose levels are not elevated at that time.

The action, follow-up and monitoring plan will be at the discretion of the Investigator and will depend on their judgment of severity based on signs/symptoms of DKA, risk factors, relevant contributing factors, and blood glucose (with the caveat that the blood glucose may be lower than would be otherwise expected given elevated ketone levels).

The blood ketone values should be recorded and will be reviewed by the site to identify any unusual high values, and to confirm that the values (from the glucose and ketone meter's memory and/or from the subject's diary) were obtained from the subject. If finger-stick blood values are discordant from glycemic control assessed by the central laboratory or with clinical symptoms, the subject's glucose and ketone meter should be tested and the procedure for using it reviewed with the subject. Investigators will examine if any of the elevated ketone values from the subject's diary are associated with a DKA event. If yes, investigators will document all DKA related symptoms, relevant risk factors, and available laboratory test results (including blood ketone values and blood glucose values measured by the glucose/ketone meter) on the DKA eCRF pages and report this event to the Sponsor. Signs and symptoms associated with DKA events should not be reported on

the AE eCRF page, unless the event fulfills protocol criteria for an SAE (see Section 6.1.1), in which case an SAE form must be completed in addition to the DKA eCRF pages.

5.3.1.3 Guidance on Management and Reporting of Hypoglycemia Episodes

Hypoglycemia may be an expected event in subjects who are treated for diabetes. Subjects and their family members must be aware of the possibility that hypoglycemia may occur and of the dangers associated with low blood sugar. Study subjects must be properly instructed on the recognition and management of hypoglycemia. Subjects should record in their log books any hypoglycemic symptoms. They should be encouraged to measure, when possible, their blood glucose values when they have symptoms of hypoglycemia. Subjects should carry with them easily ingestible forms of carbohydrate at all times in order to treat an event of hypoglycemia should it occur.

During clinical trials, subjects frequently report symptoms of hypoglycemia when asked, even when treated with placebo or medications not otherwise associated with hypoglycemia. As hypoglycemia is an important event associated with diabetes therapy, all episodes which could be consistent with the clinical definition of hypoglycemia as assessed by the Investigator should be documented and reported on the appropriate eCRF page.

The Investigator is responsible for questioning the subject about all symptoms reported on the hypoglycemia log and for determining if they meet the clinical definition of hypoglycemia. Only symptoms and/or blood glucose values deemed by the Investigator to meet the definition of hypoglycemia should be reported on the hypoglycemia eCRF pages. Signs and symptoms of hypoglycemia, hypoglycemia episode or discontinuation due to hypoglycemia should not be reported on the AE eCRF page, unless the event fulfills protocol criteria for an SAE (see Section 6.1.1), in which case an SAE form must be completed in addition to the hypoglycemia eCRF pages for hypoglycemia.

Hypoglycemia episodes will be classified in the clinical study report (CSR) according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) criteria[20] and the ADA criteria.[21]

5.3.2 Guidance on Assessment of Urinary Tract Infections & Hematuria

5.3.2.1 Guidance on Assessment of Urinary Tract Infections

The following is presented to assist in the classification and management of urinary tract infections (UTIs). It is not intended to supplant investigators' clinical judgment:

Study drug should be withheld in subjects with clinical evidence of upper tract UTI (e.g., pyelonephritis) or presumed urosepsis until the course of treatment of the infection has been completed and clinical recovery has occurred.

It is recommended that a follow-up urine culture be obtained within 7 days of clinical recovery from all urinary tract infections. Whether or not additional therapy is prescribed because of culture results should be determined by Investigator judgment, after consultation with the Medical Monitor.

It is the Investigator's responsibility to report, as applicable based on Investigator's judgment and subject's medical history, related AEs as defined in Section 6.

Additional information, including but not limited to completion of supplemental eCRFs or questionnaires may be requested for certain AEs and/or laboratory abnormalities which are reported/identified during the course of the study.

Asymptomatic bacteriuria

During enrollment, treatment, and follow-up of patients in this trial, the Investigator may discover a patient with asymptomatic bacteriuria. Asymptomatic bacteriuria is defined as the presence of $\geq 10^5$ colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to UTI. In this study, the central laboratory will report urinary dipstick test results for hemoglobin but will not routinely report the results of urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

5.3.2.2 Guidance on Assessment of Hematuria

All events of hematuria (microscopic and/or macroscopic) during the study should be worked up for a possible cause as per local guidelines.

5.3.3 Guidance on Assessment of Hepatic Laboratory Abnormalities

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 events related or leading to death (occurring within 30 days before death)
- Liver laboratory abnormalities such as:
    - elevated AST and/or ALT ≥ 3x ULN and TB ≥ 2x ULN (within 14 days of the AST and/or ALT elevation)
    - AST and/or ALT ≥ 10x ULN

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

The following is presented to assist in the evaluation and management of hepatic laboratory values. It is not intended to supplant Investigator's clinical judgment. Subjects who experience ALT and/or AST values > 3X ULN confirmed with a repeated test will have the following performed within 3 days of the confirmed laboratory results:

- Adverse event assessment
- Physical examination for jaundice and other signs of liver diseases
- Review of relevant risk factors and current history focusing on possible causes of the increased ALT and/or AST and/or TB, including:
    - Use of suspect concomitant medication (including over-the-counter [i.e., acetaminophen/paracetamol], herbal and vitamin preparations)

- Recent alcohol consumption or recreational drug/narcotic use
- Recent unaccustomed physical exertion
- Occupational or environmental exposure to hepatotoxins
- Other conditions which may cause liver diseases or which may cause abnormal test results
- Specialized Liver Laboratory Panel (see Appendix 1)

Additional information, including but not limited to completion of supplemental eCRFs or questionnaires, may be requested for certain AEs and/or laboratory abnormalities which are reported /identified as part of the hepatic safety surveillance.

For subjects who are discontinued from study medication as a result of sustained elevated liver safety abnormalities, as described in Section 3.5, additional blood sampling must be done within 3 days of the confirmed laboratory results (see Appendix 2), in conjunction with an Early Treatment Discontinuation (ETD) visit, in addition to the procedures noted above. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained. **Any additional tests and/or examinations should be carried out at the discretion of the Investigator. Any further investigations and laboratory results for subjects with abnormal laboratory values at the follow-up visit should be made available to the Sponsor upon request.**

5.3.4 Physical Examination

- A targeted physical examination should include cardiovascular, lungs, abdomen, and extremities, and any organ systems pertinent to the subject's signs, symptoms, or AEs
- A full physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal

The individual performing the physical examinations must be licensed by state law (or applicable local law) to perform this procedure.

5.3.5 Blood Pressure and Heart Rate

Blood pressure and HR measurements must be taken consistently throughout the study. Only use either the right or the left arm when measuring these parameters. Document which arm was used along with the observer's initials; the same arm and position should be used at each visit. The subject should be allowed at least 5 minutes of rest before measurement. Blood pressure should be measured with the subject's arm resting on a table, and with the subject's back supported and feet flat on the floor.

Blood pressure and HR will be determined from three replicate measurements obtained at least 1 minute apart. The average BP and HR will be determined from these 3 replicate measurements and reported in the eCRF.

All measurements should occur at least 8 hours after the last ingestion of caffeine, alcohol, or nicotine.

It is critical that the BP and HR measurements are obtained prior to the administration of blinded study medication.

5.3.6 Guidance on Volume Depletion

Dapagliflozin has a modest diuretic effect. The risk of volume depletion is enhanced when two diuretics are used in combination and in patients that otherwise are at risk for volume depletion. Therefore, caution should be exercised when administering to patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics. These patients should be carefully monitored for volume status, electrolytes, and renal function.

5.3.7 Supplemental Visits

5.3.7.1 Rescue or Early Treatment Discontinuation Visit

Any subject who qualifies for rescue or discontinues during the study periods must have all Rescue/ETD visit procedures performed at the time of study discontinuation or rescue. The IWRS must be called to record the subject status (i.e., rescue, or discontinuation status). All subjects who are rescued or who discontinue study drug should remain in the study and follow the visit schedule.

- For subjects qualifying for rescue: Rescue procedures will be performed and the subject will then continue in the treatment period according to the regular visit schedule. The Rescue/ETD supplemental eCRF will need to be completed to collect Rescue-related endpoint data.
- Subjects who discontinue study medication should have all ETD procedures performed (Rescue/ETD visit) and recorded in the Rescue/ETD supplemental eCRF. Subjects will then continue in the study and undergo non-treatment follow-up visit assessments according to their original visit schedule (Table 5.1-4).

5.3.7.2 Other Supplemental (Unscheduled) Visits

At any time during the trial, the Investigator may at his/her discretion arrange for a subject to have an unscheduled (supplemental) assessment(s), especially in the case of AEs that require follow-up. If a subject is seen for an unscheduled assessment, the appropriate Supplemental Pages of the eCRF must be completed.

5.3.8 Imaging Assessment for the Study

Not applicable.

5.4 Efficacy Assessments

Assessments consist of the central laboratory measurement of the HbA1c, and other relevant laboratory tests collected during the study.

5.5 Pharmacokinetic Assessments

Blood samples for determination of the level of dapagliflozin in plasma will be taken at the times presented in Table 5.5-1. Samples will be collected, labeled, stored and shipped as detailed in Laboratory Manual.

Samples for determination of drug concentration in plasma will be analyzed by appointed laboratory on behalf of the Sponsor or designee using appropriate bioanalytical methods. Full

details of the analytical methods used will be described in a separate bioanalytical report. Only samples from patients on relevant active study drug will be analyzed. Samples from patients not dosed with the relevant active study treatment will only be analyzed on a 'for cause' basis, for example, if there is a suspicion that a patient has been dosed incorrectly.

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. All samples still within the known stability of the analyses of interest at the time of receipt by the bioanalytical laboratory will be analyzed. Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

Table 5.5-1: Sampling Schedule

Study Day	Time (Relative to Dosing) Hour	Time (Relative to Dosing) Hour: Min	PK Blood Sample
Week 16	0 (predose)	2 hours post-dose (± 1 hour)	X
Week 24	0 (predose)	2 hours post-dose (± 1 hour)	X
Rescue visit[a]	0 (predose)	2 hours post-dose (± 1 hour)	X

[a] If applicable during the short-term treatment period only.

5.6 Biomarker Assessments

Not applicable

5.7 Outcomes Research Assessments

Not applicable

5.8 Other Assessments

5.8.1 Diet and Exercise Counseling

Starting at entry into Lead-In (Week -4), subjects will be instructed on a diet and exercise program in accordance with the ADA or similar local guidelines to be followed for the study duration.

A Registered Dietitian, Registered Nurse, Physician, Certified Diabetes Educator, Nutritionist, or other qualified member of the study team who has appropriate documented training, will provide this counseling.

5.8.2 *Weight and Height*

Body weight and height will be measured according to the schedule presented in the study flow chart/time and event schedule (see Section 5.1) and will be recorded in the eCRF.

The study-site staff should use a digital precision scale if possible, and record the weight to the first decimal point (e.g., 69.3 kg). The subject should wear a standard hospital-type gown or equivalent light indoor clothing, shoes removed, and bladder empty for the body weight measurement at each visit. Subjects should be weighed on the same scale at all visits.

Measurement of height should be performed with the subject's shoes removed. The subject's knees should be straightened, head held erect and eyes forward.

Method of Body Mass Index (BMI) calculation:

- Use actual height and weight
- To calculate BMI:
    - Convert pounds (lbs) to kilograms (kg = lb / 2.2)
    - Convert inches (in) to centimeters (cm = in X 2.54)
    - BMI = (weight in kg) / (height in $cm/100)^2$
    - Round to one decimal place (if 0.05 or greater, round up)

5.9 Results of Central Assessments

Blood and urine samples will be obtained at specified time points for laboratory evaluations (see Appendix 1). The central laboratory for this study will perform the analysis of all scheduled laboratory tests and will provide reference ranges for these tests. The central laboratory will provide specific instructions for collection, processing, packaging, and shipping of all samples.

For the duration of the 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 (after the Week 24 visit to Week 52), the above measurements will be unmasked and available to the Sponsor and the Investigator.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE
- Not related: There is not a reasonable causal relationship between study drug administration and the AE

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of 1 or more AEs.)

The Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and Food and Drug Administration (FDA) Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential DILI is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as an SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in the Sponsor's clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 28 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

The Investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the Investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to the Sponsor within 24 hours of awareness of the event.

All SAEs will be recorded in the CRF. If any SAE occurs in the course of the study, then investigators or other site personnel must inform the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up must be undertaken immediately. Investigators or other site personnel must inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Serious adverse events must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: [redacted]

USA

SAE Telephone Number: [redacted]

SAE Facsimile Number: [redacted]

Europe

SAE Telephone Number: [redacted]

SAE Facsimile Number: [redacted]

For studies capturing SAEs through electronic data capture, electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to the Sponsor using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

Intensity will be graded according to the following definitions:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.1. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.1.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the Investigator must immediately notify the Medical Monitor or appropriate AstraZeneca representatives of this event and complete and forward a Pregnancy Surveillance Form to AstraZeneca or designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

If pregnant the study drug shall be immediately discontinued.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential DILI is defined as:

1. Aminotransferases (AT) (ALT or AST) elevation > 3 times ULN
   AND
2. Total bilirubin (TB) > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECG, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER COMMITTEES

7.1 Data Monitoring Committees

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.

7.2 Hepatic Adjudication Committee

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 (see Section 5.3.3 for more details).

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

7.3 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.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

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 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 two-sided alpha level of 5 percent. To ensure that at least 50 subjects will complete the 24-week treatment period on IP and the Week 24 assessment, at least 66 subjects will be randomized.

8.2 Populations for Analyses

- The Enrolled Subjects Data Set will consist of all subjects who sign informed consent.
- The Randomized Subjects Data Set will consist of all randomized subjects who receive at least one dose of study medication during the treatment period. This is also known as the Intent to Treat population. This will be the primary efficacy data set. Data in this data set will be analyzed based on randomized treatment group.
- The Evaluable Subjects Data Set will be a subset of the Randomized Subjects, with all data points collected after relevant protocol deviations are excluded from the data set. Relevant protocol deviations are defined as deviations that could potentially affect the interpretability of the study results. This is also known as the per-protocol population. This data set will be used for sensitivity analyses of the primary efficacy endpoint if > 10% of subjects in any treatment group have relevant protocol deviations.
- The Treated Subjects Data Set will consist of all subjects who receive at least one dose of study medication during the treatment group. This will be the primary safety data set. Data in this data set will be analyzed based on randomized treatment, except in cases where a subject received a different treatment for the entire course of his/her participation in the treatment period. In this case, safety data for such a subject will be analyzed based on the first treatment the subject actually received**.**
- Pharmacokinetic Analysis Data Set will include all patients who received a dapagliflozin dose and have collected at least 1 PK sample.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

Change from baseline in HbA1c at Week 24.

8.3.2 Secondary Endpoint(s)

- The change from baseline in FPG at Week 24
- The percentage of subjects who require glycemic rescue medication or discontinuation due to lack of glycemic control over 24 weeks double-blind treatment.
- The percentage of subjects with baseline HbA1c > 7% who achieve HbA1c level < 7% at Week 24.

8.3.3 Exploratory Endpoint(s)

- 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 discontinuation due to lack of glycemic control during 52 weeks treatment period.
- The percentage of subjects with baseline HbA1c > 7% who achieve a HbA1c level < 7% at Week 52

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized using frequency distributions and descriptive statistics using the Randomized Subjects Data Set, for each treatment group as well as for all subjects combined. No statistical tests will be performed to compare treatment groups at baseline.

8.4.2 Efficacy Analyses

8.4.2.1 Primary Analysis

The primary analysis of the primary endpoint, change in HbA1c from baseline to Week 24, will be based on a mixed model with repeated measures (MMRM) including all scheduled time points following randomization up to and including Week 24. This model will include patients in the Randomized Subjects Data Set who have a baseline measurement and at least one post-baseline measurement. The primary analysis will only include measurements prior to the administration of rescue medication. Measurements made following rescue administration will be included in sensitivity analysis. Various sensitivity analyses will be specified in the Statistical Analysis Plan to assess the robustness of the primary analyses, including sensitivity analyses of all data pre-and post-rescue.

The SAS procedure PROC MIXED will be used for primary analyses. The primary analysis model will include the fixed categorical effects of treatment, week, randomization stratification factor (as warranted), and treatment-by-week interaction as well as the continuous fixed covariates of

baseline measurement and baseline measurement-by-week interaction. An unstructured matrix for the within-patient error variance-covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method. A number of back-up models will be defined in the Statistical Analysis Plan in case of non-convergence of the preferred model or other issues.

Point estimates and 95% confidence intervals 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.

8.4.2.2 Secondary Analyses

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.

Specifically, if the primary comparison in change in HbA1c between the dapagliflozin 10 mg treatment group and the placebo group is significant at the 0.05 level, then the statistical testing for the secondary efficacy endpoints will be performed. In order to control the family-wise Type I error rate across the primary and secondary endpoints, the interpretation of the statistical significance of treatment comparison for each secondary efficacy endpoint will be done using a hierarchical closed testing procedure which will be defined in the Statistical Analysis Plan, prior to unblinding of the treatment assignments.

Similar methods to the primary analysis will be used in analyses of continuous secondary endpoints. The methodology of Zhang, Tsiatis and Davidian[22] and Tsiatis, Davidian, Zhang, and Lu[23] with adjustment for baseline measurement and randomization strata will be used in analyses of categorical secondary endpoints, and details will be provided in the Statistical Analysis Plan.

8.4.2.3 Exploratory Analyses

Similar methods to the primary and secondary analyses will be used for analyses of exploratory endpoints. Between group differences in the mean change from baseline for continuous exploratory variables (HbA1c and FPG) will not be generated for the long-term (LT) period in short-term (ST) + LT analyses, and statistical comparisons will not be performed. Similarly, between group differences in proportions of dichotomous exploratory variables will not be generated for the LT period in ST + LT analyses, and statistical comparisons will also not be performed.

Analysis of the PK endpoint is described in Section 8.4.4.

8.4.3 Safety Analyses

Safety analyses will include treatment group summaries of the incidence of AEs and marked laboratory abnormalities, the percentages of subjects experiencing hypoglycemia as well as the number and severity of hypoglycemic events, the incidence of elevated plasma ketone level, vital signs, and laboratory test parameters.

The assessment of safety will be based on the analyses of AEs, vital signs, physical examinations, ECGs, hypoglycemia, elevated plasma ketone level, and clinical laboratory evaluations. All safety analyses will be performed using the Treated Subjects Data Set.

The number and percent of patients with at least one AE will be summarized by treatment group, including summaries of AEs, SAEs, AEs leading to discontinuation of study medication, and AEs of special interest. Summaries will include the number of patients with events by specified system organ classes and preferred terms.

Summary statistics will be presented at each assessment visit for the continuous safety parameters. Descriptive statistics of changes from baseline by study visits will also be presented. A frequency table of results of categorical safety parameters will be produced. Furthermore, laboratory/ECG abnormalities will be analyzed by shift tables. The number and percent of subjects with values meeting marked/notable abnormality criteria will be summarized for each treatment group for vital signs, lab, and ECG parameters.

8.4.4 Pharmacokinetic Analyses

Dapagliflozin plasma concentration will be listed and summarized by sample collection day and time. The analyses will be performed using the Pharmacokinetic Analysis Data Set.

8.4.5 Biomarker Analyses

Not applicable

8.4.6 Outcomes Research Analyses

Not applicable

8.4.7 Other Analyses

Not applicable

8.5 Interim Analyses

Not applicable

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, the Sponsor or designee. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion

- the Sponsor/Designee
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to the Sponsor or designee.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

The Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of the Sponsor or designee must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by the Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. The Sponsor or designee audit reports will be kept confidential.

The Investigator must notify the Sponsor or designee promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the Sponsor or designee.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), AE tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

AstraZeneca or designee will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The Investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the Sponsor or designee, whichever is longer. The Investigator must contact the Sponsor or designee prior to destroying any records associated with the study.

The Sponsor or designee will notify the Investigator when the study records are no longer needed.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to the Sponsor or designee.

9.2.2 Study Drug Records

It is the responsibility of the Investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include IP and the following non-IP(s). Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (e.g., lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the Sponsor or designee
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for IP dispensing/accountability, as per the Delegation of Authority Form

The Sponsor or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor's electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If an electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The Investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the Investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the Sponsor's electronic data capture tool. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet the Sponsor's training requirements and must only access the Sponsor or designee's electronic data capture tool using the unique user account provided by the Sponsor. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the CSR.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (e.g., among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to the Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to the Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	aminotransferases
AZ	AstraZeneca
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
CFR	Code of Federal Regulations
CRF	case report form
CSR	Clinical Study Report
CTA	Clinical Trial Agreement
DILI	drug-induced liver injury
DKA	diabetic ketoacidosis
dL	deciliter
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EU	European Union
ETD	early treatment discontinuation
FDA	Food and Drug Administration
FPG	fasting plasma glucose
g	gram
GAD	glutamic acid decarboxylase
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HAV	hepatitis A virus

Term	Definition
HbA1c	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HR	heart rate
IA-2	protein tyrosine phosphatase-like protein antibodies
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IP	investigational (medicinal) product
IR	immediate release
IRB	Institutional Review Board
IU	international unit
IUD	intrauterine device
IWRS	Interactive Web / Voice Recognition System
kg	kilogram
L	liter
LT	long-term
MDRD	Modified Diet in Renal Disease, study equation
mg	milligram
min	minute
mL	milliliter
MMRM	Mixed effect Model Repeat Measurement
MODY	maturity onset diabetes of the young
non-IMP	non-investigational medicinal product
non-IP	non-investigational (medicinal) product
OAD	oral antidiabetic
PD	pharmacodynamics
PK	pharmacokinetics

Term	Definition
PPG	postprandial glucose
SAE	serious adverse event
SGLT-2	sodium glucose cotransporter-2
SMBG	self-monitored blood glucose
ST	short-term
TB	total bilirubin
T2DM	type 2 diabetes mellitus
TSH	thyroid stimulating hormone
UK	United Kingdom
ULN	upper limit of normal
UKPDS	UK Prospective Diabetes Study
UTI	urinary tract infection
US	United States (of America)
WHO	World Health Organization
WOCBP	women of childbearing potential
XR	extended release

12 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 paediatric 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. Kestelman P. et. al., Efficacy of the Simultaneous Use of Condoms and Spermicides Family Planning Perspectives.Vol 23 (5); October 1991.

17. Gabbay MB, Thomas J, Gibbs A, Hold P. A Randomized Crossover Trial of The Impact of Additional Spermicide on Condom Failure Rates. Sex Transm Dis 2008; 35: 862-8.

18. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New Equations to Estimate GFR in Children with CKD. JASN 2009; 20: 629-637.

19. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. Clin Chem. 2007 Apr;53(4):766-72.

20. 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

21. http://care.diabetesjournals.org/content/early/2013/04/12/dc12-2480.full.pdf

22. Zhang M., A.A. Tsiatis, and M. Davidian, Improving efficiency of inferences in randomized clinical trials using auxiliary covariates. Biometrics, 2008. 64(3): 707-715.

23. Tsiatis, A.A., et al., Covariate adjustment for two-sample treatment comparisons in randomized clinical trials: a principled yet flexible approach. Stat Med, 2008. 27(23): 4658-4677.

APPENDIX 1 CENTRAL LABORATORY ASSESSMENTS

Blood and urine samples will be obtained at specified time points for laboratory evaluations. The central laboratory for this study will perform the analysis of all scheduled laboratory tests and will provide reference ranges for these tests. The detailed methods for specimen collection, handling, processing, shipping, and storage will be supplied in the Investigator's Laboratory Manual provided by the Central Laboratory. All clinical laboratory tests will be performed by the Central Laboratory or designated reference laboratory.

For the duration of the 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 (after the Week 24 visit to Week 52), the above measurements will be unmasked and available to the Sponsor and the Investigator.

The following sections indicate the laboratory tests required for this study. For countries using conventional units, the results will be reported using conventional units. For countries using SI units, the results will be reported using SI units. In cases of differences in the units as listed in this protocol compared to the units on the central laboratory reports, the units from the central laboratory reports will be used.

PROTOCOL-SPECIFIC CENTRAL LABORATORY ASSESSMENTS:

- HbA1c (%, mmol/mol)
- Fasting plasma glucose (FPG) (mg/dL, mmol/L)
- Fasting serum lipid profile:
  - Total-C (mg/dL, mmol/L)
  - Calculated LDL-C (mg/dL, mmol/L)
    - *Except screening period, reflex testing will occur for Direct LDL-C if TG > 400 mg/dL (4.52 mmol/L)*
  - HDL-C (mg/dL, mmol/L)
  - TG (mg/dL, mmol/L)

Enrollment-Specific Reflex Testing

- Thyroid stimulating hormone (TSH)
  - *Reflex Testing: abnormal TSH value at enrollment will be further evaluated by free T4.*
- Hepatitis Screen Panel:
  - Anti-hepatitis C virus antibody
  - Hepatitis B surface antigen
  - Anti-hepatitis A virus IgM
    - *Reflex Testing: Low positive and positive results require confirmatory testing.*

Specialized Liver Panel:

For subjects who are being monitored frequently as a result of confirmed aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3X upper limit of normal (ULN), additional central laboratory tests will be performed within 3 days of receipt of confirmatory results. These laboratory tests will study the possible causes of the increased ALT and/or AST and/or TB, and may include, but are not limited to, the following tests:

- Hepatitis A IgM
- Hepatitis BsAg
- Hepatitis B Core Ab IgM
- Hepatitis C virus RNA or RIBA
- Hepatitis C Ab
- Hepatitis E IgM
- Epstein-Barr virus (EBV) IgM Ab
- Lactate dehydrogenase (LDH)
- Gamma-glutamyl-transpeptidase (GGT)
- Carbohydrate deficient transferrin (CDT)
- Prothrombin time (PT/INR)
- Iron panel - iron, ferritin, total iron binding capacity (TIBC)
- Immunology panel including antinuclear antibody (ANA), anti-smooth muscle antibody (SMA) and anti-liver/kidney microsomal antibody (Anti-LKM)
- Anti-tissue transglutaminase antibody

Liver Discontinuation Panel:

For subjects who are discontinued from the study as a result of sustained elevated liver safety abnormalities, additional central laboratory tests will be performed at the time of Early Termination (End-of-Treatment) visit. Similar to the Specialized Liver Panel, these laboratory tests will study the possible causes of the increased ALT and/or AST and/or TB, and may include, but are not limited to, the following tests:

- Cytomegalovirus (CMV) IgM Ab
- Herpes simplex virus (HSV) 1 and 2
- Ceruloplasmin
- Toxoplasmosis
- Alpha-1 antitrypsin

For specific details regarding the Specialized Liver Panel and the Liver Discontinuation Panel laboratory tests, refer to the Central Laboratory Manual for this study.

Standard Safety Laboratory Panels:

Table Appendix 1: Standard Safety Laboratory Panels

Hematology

- Hemoglobin (g/dL, g/L)
- Hematocrit (%, V/V)
- Red blood cell (RBC) ($x10^6$/UL, $x10^{12}$/L)

RBC count indices:

- Mean Cell Volume (MCV) (fL)
- Mean Cell Hemoglobin (MCH) (pg/cell)
- Mean Cell Hemoglobin Concentration (MCHC) (gHb/dL, gHb/L)
- White blood cell Count and Differential
- Platelet count (x109/L)

Serum Chemistry

- AST (IU/L)
- ALT (IU/L)
- ALK-P (IU/L)
- Total Bilirubin (mg/dL, µmol/L)
- Serum Creatinine (Scr) used to calculate estimated glomerular filtration rate (eGFR) according to the following:
  - In subjects < 18 years of age: Schwarz formula[1] eGFR (mL/min/1.73 m^2) = 0.413 *(height (cms)/serum creatinine (mg/dL)
  - In subjects ≥ 18 years of age: MDRD Equation[2] GFR (mL/min/1.73 m^2) = 175 × (Serum creatinine)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American)

  Results will be reported to the sites and the Sponsor.
- Sodium (mEq/L, mmol/L)
- Potassium (mEq/L, mmol/L)
- Chloride (mEq/L, mmol/L)
- Calcium (mg/dL, mmol/L)
- Magnesium (mEq/L, mmol/L)
- Phosphorus (mg/dL, mmol/L)
- Total Protein (g/dL, g/L)
- Uric acid (mg/dL, µmol/L)

Urine Analyses

- Creatinine
- Calculated Urinary albumin:creatinine ratio (UACR)
- Urine HCG pregnancy test for WOCBP (HCG minimum sensitivity of 25 IU/L; performed at site or at home). *If a urine HCG test is positive, a blood specimen will be obtained and a serum pregnancy test will be performed by the central laboratory for confirmation.*

Table Appendix 1: Standard Safety Laboratory Panels

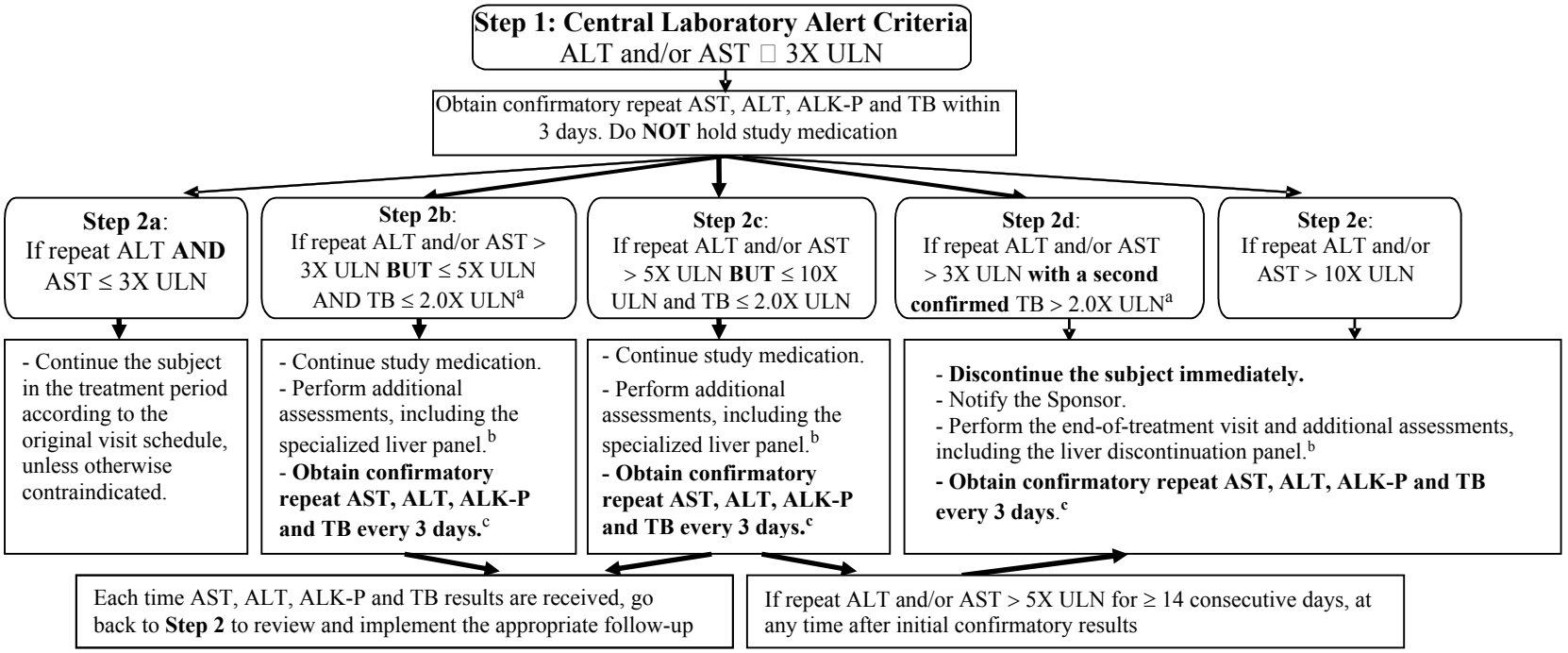
Spot urine:

- Urinary glucose:creatinine ratio

Urinalysis with microscopy:

- Hematuria

APPENDIX 2 SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES FLOW CHART



[a] In subjects with repeat ALT or AST > 3X ULN but ≤ 10X ULN, only subjects with TB ≤ 2.0X ULN at Step 1 should be followed according to Step 2b. Subjects with an initial TB and confirmatory repeat TB > 2.0X ULN should be followed according to Step 2d.

[b] Refer to section 5.3.4 for details on additional assessments to be performed (AE assessment, PE, review of current medical history including focused review of risk factors for liver diseases and collection of blood samples [specialized liver panel or liver discontinuation panel]).

[c] Confirmatory repeat AST, ALT, ALK-P and TB should be obtained every 3 days following receipt of prior laboratory results, until the ALT and AST are ≤ 2X ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic.

APPENDIX 3 TANNER ASSESSMENT SCALE

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, rated separately on a scale of stage one to stage five. 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[3,4] (summarized in Tables 1 and 2 below). 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 1: 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	Darker, 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 2: 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

Additional materials to aid in the Tanner Stage assessment will be provided upon request.