Official Protocol Title:	A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled Clinical Study to Evaluate the Safety and Efficacy of Ertugliflozin (MK-8835/PF-04971729) in Pediatric Participants (ages 10 to 17 years, inclusive) with Type 2 Diabetes Mellitus
NCT number:	NCT04029480
Document Date:	14-Nov-2024

Title Page

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Protocol Title: A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled Clinical Study to Evaluate the Safety and Efficacy of Ertugliflozin (MK-8835/PF-04971729) in Pediatric Participants (ages 10 to 17 years, inclusive) with Type 2 Diabetes Mellitus

Protocol Number: 059-04

Compound Number: MK-8835

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Ertugliflozin (MK-8835/PF-04971729) is being co-developed by MSD and Pfizer.

Regulatory Agency Identifying Number(s):

IND	106,447
EudraCT	2017-003455-35

EU CT: 2022-501085-21-00
UTN: U1111-1279-3984
MSD Protocol Number: 059-00
Pfizer Protocol Number: B1521066

Approval Date: 14 November 2024

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 4	14-NOV-2024	Health Authority feedback to update the primary treatment policy analysis.
Amendment 3	14-MAR-2024	This protocol is being amended to address Health Authority feedback to change the primary analysis methodology.
Amendment 2	16-FEB-2023	To align with EU CTR and update Sponsor's name and address change.
Amendment 1	11-JUN-2020	Amendment created to fulfill requests from regulatory agencies. Changes also include corrections and clarifications.
Original Protocol	01-APR-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 4

Overall Rationale for the Amendment:

Health Authority feedback to update the primary treatment policy analysis.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 9.6.1, Statistical Methods for Efficacy Analysis	Changed the primary analysis from a single value imputation to multiple imputation with a Bayesian Rubin's rule methodology.	CCI [redacted]

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 9.1, Statistical Analysis Plan Summary	Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses: Updated the weight given to the adult prior distribution for the primary hypothesis test.	CCI [redacted]
	Sample Size and Power: Changed TP estimand power measurement from Highest Posterior Density to posterior credible intervals.	
Section 9.4.1, Efficacy Endpoints	Homeostasis Model Assessments were removed as exploratory endpoints.	
Section 9.5.1, Efficacy Analysis Populations	Information on classification of the incorrect stratum for insulin use was added.	
Section 9.6.1, Statistical Methods for Efficacy Analysis	The mixture parameter was changed from 0.299 to 0.134.	
	Changed TP estimand power measurement from highest posterior density to posterior credible intervals.	
	The RD imputation analysis steps were revised based on the new Rubin's rule multiple imputation methodology.	
	Details on the computation of the SD for the WI approach were revised to align with the RD imputation analysis.	
	Updated the analyses for hypotheses H2 and H3 from the bootstrap to Rubin's rule.	

Section Number and Name	Description of Change	Brief Rationale
Section 9.6.2, Statistical Methods for Safety Analyses	Added details on number of days after last dose of therapy for Tanner staging, growth velocity, and safety vital signs.	CCI [redacted]
Section 9.9, Sample Size and Power Calculations	Changed TP estimand power measurement from highest posterior density to posterior credible intervals.	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled Clinical Study to Evaluate the Safety and Efficacy of Ertugliflozin (MK-8835/PF-04971729) in Pediatric Participants (ages 10 to 17 years, inclusive) with Type 2 Diabetes Mellitus

Short Title: Ertugliflozin T2DM Pediatric Study (MK-8835/PF-04971729)

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

In pediatric patients (ages 10 to 17 years, inclusive) with T2DM on a stable dose of metformin ≥1500 mg/day ± stable insulin:

Primary Objectives	Primary Endpoints
- Objective: To compare the addition of ertugliflozin with the addition of placebo on the change from baseline in A1C at 24 weeks. Hypothesis (H1): The addition of ertugliflozin reduces A1C more than the addition of placebo after 24 weeks of treatment.	- A1C
- Objective: To assess the safety and tolerability of ertugliflozin over 24 weeks and 54 weeks.	- Adverse Events (AEs) - Discontinuation of study medication due to AEs
Secondary Objectives	Secondary Endpoints
- Objective: To compare the addition of ertugliflozin, with dosing optimized according to A1C response, to the addition of placebo on the change from baseline in A1C at 24 weeks. Hypothesis (H2): The addition of ertugliflozin, with dosing optimized according to A1C response, reduces A1C more than the addition of placebo after 24 weeks of treatment.	- A1C

- Objective: To compare the addition of ertugliflozin 5 mg with the addition of placebo on the change from baseline in A1C at 24 weeks. Hypothesis (H3): The addition of ertugliflozin 5 mg reduces A1C more than the addition of placebo after 24 weeks of treatment.	- A1C
- Objective: To compare the effect of the addition of ertugliflozin to the addition of placebo on the change from baseline in fasting plasma glucose (FPG) at 24 weeks.	- FPG
- Objective: To assess the within-group (ertugliflozin and placebo) changes from baseline at 54 weeks for A1C and FPG.	- A1C - FPG

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	T2DM
Population	Pediatric patients who are 10 to 17 years of age (inclusive) with T2DM and inadequate glycemic control on metformin ± insulin.
Study Type	Interventional
Intervention Model	Parallel multi-site
Type of Control	Placebo
Study Blinding	Double-blind
Masking	Sponsor Investigator Participant
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 6 years from the time the first participant signs the informed consent/assent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 165 participants will be enrolled.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period	Use
Ertugliflozin 5 mg[a]	Ertugliflozin	5 mg	qd	Oral	Double-blind treatment period	Test Product
Ertugliflozin 15 mg[b]	Ertugliflozin	15 mg	qd	Oral	Double-blind treatment period starting **Visit 5 /Week 12**	Test Product
Placebo[a]	Placebos matching ertugliflozin 5 mg and 15 mg	0 mg	qd	Oral	Double-blind treatment period	Placebo

Abbreviations: mg=milligram; qd= once daily.
a. At the first randomization (R1) participants in the ertugliflozin arm will receive ertugliflozin 5 mg and placebo to ertugliflozin 15 mg. Participants in the placebo arm will receive placebos to both ertugliflozin 5 mg and ertugliflozin 15 mg.
b. At the second randomization (R2), **Visit 5/Week 12,** approximately half of the participants in the ertugliflozin 5 mg arm with A1C ≥7.0% (53 mmol/mol) will up-titrate to receive ertugliflozin 15 mg and placebo to ertugliflozin 5 mg. Participants in the placebo group with A1C ≥7.0% (53 mmol/mol) at **Visit 5/Week 12** will be mock titrated. **Note:** The up-titration criteria for participants on insulin will include a fasting fingerstick glucose (FFSG) of ≥110 mg/dL (6.1 mmol/L) in addition to A1C ≥7.0% (53 mmol/mol) at **Visit 5/Week 12**. Participants who do not meet the threshold(s) for a second randomization will continue on ertugliflozin 5 mg/placebo.

Participants will remain on their background metformin ± insulin treatment throughout the course of the study.

Total Number	2 treatment groups at **Day 1**, changing to 3 treatment groups at **Visit 5/Week 12**.
Duration of Participation	Each participant will participate in the study for approximately 58 weeks from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening period of approximately 1 week and a single-blind placebo run-in period of approximately 1 week, each participant will receive assigned treatment for approximately 54 weeks. Participants will be contacted by telephone 14 days (Week 56) after the last dose of study medication to assess and collect information on AEs, and any other reportable safety events. To minimize missing data, participants who discontinue study medication prior to study completion will remain in the study and complete all remaining scheduled visits.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Internal Ketoacidosis Case Review Committee	Yes
Study governance considerations are outlined in Appendix 1.	

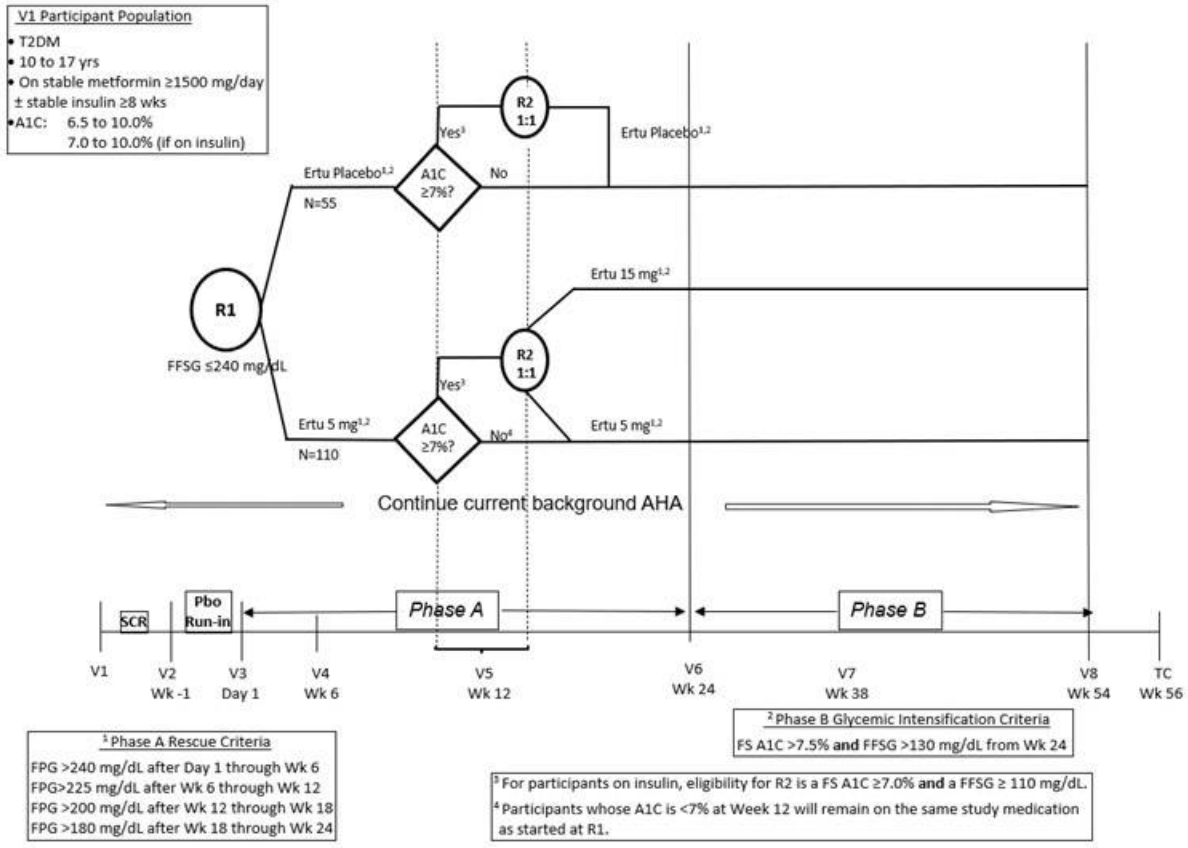
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 14.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



A1C=glycosylated hemoglobin; AHA=anti-hyperglycemic agent; FFSG=fasting fingerstick glucose; FPG=fasting plasma glucose; FS=fingerstick; FSG=fingerstick glucose; Pbo=placebo; R=randomization; SCR=screening; T2DM=type 2 diabetes mellitus; TC=telephone call; V=Visit; Wk=Week.

1.3 Schedule of Activities (SoA)

Schedule of Activities	Screen	Single-Blind Placebo Run-In	Random-ization	Double-Blind Treatment Period Phase A				Double-Blind Treatment Period Phase B				Visit Rescue - Intensific-ation/ Discon	Post-Study Phone Contact	Comment
	Visit 1	Visit 2	Visit 3	Visit 4[a]	Visit 5	TC	Visit 6	TC	Visit 7[a]	TC	Visit 8			
	No earlier than -4 weeks	Week -1	Week 0/ Day 1	Wk 6 ± 1 wk	Wk 12 ± 1 wk	Wk 18 ± 1 wk	Wk 24 ± 1 wk	Wk 30 ± 1 wk	Wk 38 ± 2 wks	Wk 44 ± 1 wk	Wk 54 ± 2 wks		Wk 56 OR 14 days after last dose	**See Note 1 below**
Study Procedures														**See Note 1 below**
Obtain informed consent and assent	X													
Obtain informed consent and assent for Future Biomedical Research	X													Can also be obtained any time prior to collecting the samples.
Assignment of screening number	X													
Evaluate Inclusion/Exclusion criteria	X	X	X											
Dispense participant identification card	X		X											
Collect medical history	X													
Review prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X		
CCI [redacted]														

Schedule of Activities	Screen	Single-Blind Placebo Run-In	Random-ization	Double-Blind Treatment Period Phase A				Double-Blind Treatment Period Phase B				Visit Rescue - Intensific-ation/ Discon	Post-Study Phone Contact	Comment
	Visit 1	Visit 2	Visit 3	Visit 4[a]	Visit 5	TC	Visit 6	TC	Visit 7[a]	TC	Visit 8			
	No earlier than -4 weeks	Week -1	Week 0/ Day 1	Wk 6 ± 1 wk	Wk 12 ± 1 wk	Wk 18 ± 1 wk	Wk 24 ± 1 wk	Wk 30 ± 1 wk	Wk 38 ± 2 wks	Wk 44 ± 1 wk	Wk 54 ± 2 wks		Wk 56 OR 14 days after last dose	**See Note 1 below**
CCI														

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	No earlier than -4 weeks	Week -1	Week 0/ Day 1	Wk 6 ± 1 wk	Wk 12 ± 1 wk	Wk 18 ± 1 wk	Wk 24 ± 1 wk	Wk 30 ± 1 wk	Wk 38 ± 2 wks	Wk 44 ± 1 wk	Wk 54 ± 2 wks		Wk 56 OR 14 days after last dose	**See Note 1 below**
CCI														

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	No earlier than -4 weeks	Week -1	Week 0/ Day 1	Wk 6 ± 1 wk	Wk 12 ± 1 wk	Wk 18 ± 1 wk	Wk 24 ± 1 wk	Wk 30 ± 1 wk	Wk 38 ± 2 wks	Wk 44 ± 1 wk	Wk 54 ± 2 wks		Wk 56 OR 14 days after last dose	**See Note 1 below**
CCI														

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	Visit 1	Visit 2	Visit 3	Visit 4[a]	Visit 5	TC	Visit 6	TC	Visit 7[a]	TC	Visit 8			
	No earlier than -4 weeks	Week -1	Week 0/ Day 1	Wk 6 ± 1 wk	Wk 12 ± 1 wk	Wk 18 ± 1 wk	Wk 24 ± 1 wk	Wk 30 ± 1 wk	Wk 38 ± 2 wks	Wk 44 ± 1 wk	Wk 54 ± 2 wks		Wk 56 OR 14 days after last dose	**See Note 1 below**
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	Visit 1	Visit 2	Visit 3	Visit 4[a]	Visit 5	TC	Visit 6	TC	Visit 7[a]	TC	Visit 8			
	No earlier than -4 weeks	Week -1	Week 0/ Day 1	Wk 6 ± 1 wk	Wk 12 ± 1 wk	Wk 18 ± 1 wk	Wk 24 ± 1 wk	Wk 30 ± 1 wk	Wk 38 ± 2 wks	Wk 44 ± 1 wk	Wk 54 ± 2 wks		Wk 56 OR 14 days after last dose	**See Note 1 below**
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	Visit 1	Visit 2	Visit 3	Visit 4[a]	Visit 5	TC	Visit 6	TC	Visit 7[a]	TC	Visit 8			
	No earlier than -4 weeks	Week -1	Week 0/ Day 1	Wk 6 ± 1 wk	Wk 12 ± 1 wk	Wk 18 ± 1 wk	Wk 24 ± 1 wk	Wk 30 ± 1 wk	Wk 38 ± 2 wks	Wk 44 ± 1 wk	Wk 54 ± 2 wks		Wk 56 OR 14 days after last dose	**See Note 1 below**
CCI														

2 INTRODUCTION

Ertugliflozin (MK-8835/PF-04971729), a sodium glucose co-transporter 2 (SGLT2) inhibitor, is approved for the treatment of T2DM in adults (18 years and older) and is being developed for pediatric patients (10 to17 years of age).

2.1 Study Rationale

The purpose of this 54-week (24 weeks Phase A + 30 weeks Phase B) study is to evaluate the safety and efficacy of ertugliflozin in pediatric patients (10 to 17 years of age, inclusive) with T2DM. The study design uses a dose titration scheme to optimize the dose for participants in a manner consistent with the ertugliflozin label/Investigator's Brochure (IB).

Metformin and insulin remain the only pharmaceutical agents approved for pediatric patients with T2DM. However, both agents may have issues with acceptability (for metformin, difficulty in swallowing tablets and gastrointestinal side-effects, and for insulin, difficulty with accepting injections and hypoglycemia) that limit their use, making it important to develop a more acceptable alternative therapy.

Furthermore, glycemic control on metformin monotherapy is not durable, and insulin is the only agent approved for use in pediatric patients with T2DM and inadequate glycemic control on metformin. Pediatric patients with T2DM on insulin (± metformin) often have poor glycemic control, likely due to poor compliance, as well as difficulty with accepting insulin therapy. Therefore, there is a need to assess additional treatment options for pediatric patients with T2DM, including those who are on metformin ± insulin.

2.2 Background

Ertugliflozin has been approved for use in adults; refer to the IB/approved labeling for detailed background information on ertugliflozin. Refer to product labeling for information on metformin and insulin.

2.2.1 Pharmaceutical and Therapeutic Background

The incidence and prevalence of T2DM in the pediatric population is increasing worldwide. T2DM is associated with the development of microvascular complications, particularly nephropathy [Bogdanovic, R. 2007] [Krakoff, J., et al 2003] [Pavkov, M. E., et al 2006] [Eppens, M. C., et al 2006], as well as the presence of several cardiovascular risk factors that increase the likelihood of early macrovascular complications in this population [Fagot-Campagna, A., et al 2000] [Eppens, M. C., et al 2006] [Petitti, D. B., et al 2007] [Sanders, B. H., et al 2006] [Gungor, N., et al 2005][Fagot-Campagna, A., et al 2000] [Eppens, M. C., et al 2006] [Petitti, D. B., et al 2007] [Sanders, B. H., et al 2006] [Gungor, N., et al 2005]. As in adults, blood glucose levels likely influence the development and progression of both the microvascular and possibly macrovascular complications of T2DM [Bogdanovic, R. 2007] [DCCT/EDIC Study Research Group 2005]. Therefore, given the substantial lifelong cumulative exposure to hyperglycemia for this population, the availability of effective therapies is necessary.

While lifestyle modification is effective [Urakami, T. 2005], it is difficult to implement and maintain, and tends to benefit a relative minority of youths with T2DM [American Diabetes Association 2000] [Urakami, T. 2005]. Metformin is the only broadly approved oral agent for first-line therapy in youths with T2DM [Pinhas-Hamiel, O. and Zeitler, P. 2007] [Bobo, N., et al 2004] [Canadian Diabetes Association 2003]. Although initially effective in lowering A1C, studies suggest that 35 to 50% of pediatric patients need an additional agent within a year of diagnosis [Hannon, T. S., et al 2005]. Since the evolution of T2DM in youths is characterized by a rapid and progressive decrease in insulin secretion and progressive increase in insulin resistance, along with overproduction of hepatic glucose, and excessive levels of glucagon [Weiss, R., et al 2006] [Caprio, S. 2002] [Weiss, R., et al 2005] [Weiss, R., et al 2003] [Yeckel, C. W., et al 2005], an orally administered pharmacological agent that lowers glucose while also reducing other risks factors, represents a major advantage in the treatment of diabetes.

Ertugliflozin is a potent inhibitor of SGLT2 and possesses a high selectivity over glucose transport via SGLT1 and several other glucose transporters (GLUT1-4). Ertugliflozin inhibits renal glucose reabsorption resulting in urinary glucose excretion and thereby reducing plasma glucose and A1C in patients with T2DM with a low risk of hypoglycemia, and without increasing insulin secretory burden on pancreatic beta cells. Adult studies have also shown that ertugliflozin achieves clinically meaningful improvements in body weight and systolic blood pressure (SBP).

The purpose of this study is to evaluate the safety and efficacy of ertugliflozin in pediatric patients with T2DM on metformin ± insulin. Ertugliflozin could potentially represent a valuable therapeutic option across the typical disease progression of T2DM, including those with inadequate glycemic control on metformin with or without insulin.

2.2.2 Information on Other Study-related Therapy

Metformin

Clinical recommendations for treatment of pediatric patients with T2DM are to integrate metformin monotherapy with lifestyle modifications (ie, diet and exercise) [Copeland, K. C., et al 2013]. Close monitoring for glycemic deterioration is also recommended, with the early addition of insulin or another pharmacologic agent as needed.

Insulin

Insulin is approved for use in pediatric patients with T2DM. Use of basal insulin is associated with less hypoglycemia in patients with T2DM compared to intermediate-acting insulin [Klingensmith, G. J., et al 2015]. The procedure and dose for initiation of insulin glargine, and for titration of background insulin, will be at the discretion of the investigator, based on local/regional/country guidelines.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine. However, based on the available ertugliflozin adult data, it is predicted that the benefit/risk will be favorable in the patient population studied.

In adults, ertugliflozin provides the benefit of inhibiting renal glucose reabsorption resulting in urinary glucose excretion and thereby reducing plasma glucose and A1C in patients with T2DM without increasing the risk of hypoglycemia. In adult studies of participants with T2DM, ertugliflozin treatment improved glucose control, and led to reductions in body weight and blood pressure. However, it is not known if these effects will be the same in the pediatric population.

Adverse reactions with ertugliflozin treatment in adults include genital mycotic infections in males and females, increased urination, thirst, vulvovaginal pruritus, volume depletion (particularly in patients with impaired renal function [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2], elderly patients [≥65 years], or patients on diuretics), ketoacidosis, hypoglycemia in combination with insulin and/or insulin secretagogues, and increased low-density lipoprotein cholesterol (LDL-C). In adult studies, use of ertugliflozin was associated with transient increases in serum creatinine and decreases in eGFR. Please refer to the latest version of the ertugliflozin IB/approved labeling for the most current risk information related to ertugliflozin treatment.

A risk to the participants in the placebo group is inadequate glycemic control leading to hyperglycemia. The medical risk of inadequate glycemic control has been considered and efforts to limit this risk will be implemented in this protocol. To ensure that participants (in both treatment groups) will not be exposed to poor glycemic control for an undue period of time, the following have been included in the protocol design: diet and exercise counseling specifically designed for pediatric patients with T2DM, frequent blood glucose monitoring, protocol-specified progressively stricter glycemic rescue/intensification procedures, and glycemic discontinuation criteria.

Participants being treated with glucose lowering medications have the risk of developing hypoglycemia, which is even greater in participants taking insulin. Hypoglycemia will be mitigated by frequent blood glucose monitoring, down-titration, and discontinuation of insulin (if needed).

Additional details regarding specific benefits and risks for participants of this clinical study may be found in the accompanying IB and Informed Consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In pediatric patients (ages 10 to 17 years, inclusive) with T2DM on a stable dose of metformin ≥1500 mg/day ± stable insulin:

Objectives	Endpoints
Primary	
• **Objective:** To compare the addition of ertugliflozin with the addition of placebo on the change from baseline in A1C at 24 weeks. **Hypothesis (H1):** The addition of ertugliflozin reduces A1C more than the addition of placebo after 24 weeks of treatment.	• A1C
• **Objective:** To assess the safety and tolerability of ertugliflozin over 24 weeks and 54 weeks.	• Adverse Events (AEs) • Discontinuation of study medication due to AEs
Secondary	
• **Objective:** To compare the addition of ertugliflozin, with dosing optimized according to A1C response, to the addition of placebo on the change from baseline in A1C at 24 weeks. **Hypothesis (H2):** The addition of ertugliflozin, with dosing optimized according to A1C response, reduces A1C more than the addition of placebo after 24 weeks of treatment.	• A1C
• **Objective:** To compare the addition of ertugliflozin 5 mg with the addition of placebo on the change from baseline in A1C at 24 weeks. **Hypothesis (H3):** The addition of ertugliflozin 5 mg reduces A1C more than the addition of placebo after 24 weeks of treatment.	• A1C

Objectives	Endpoints
• **Objective:** To compare the effect of the addition of ertugliflozin to the addition of placebo on the change from baseline in fasting plasma glucose (FPG) at 24 weeks.	• FPG
• **Objective:** To assess the within-group (ertugliflozin and placebo) changes from baseline at 54 weeks for A1C and FPG.	• A1C • FPG
Tertiary/Exploratory	
• **Objective:** To assess the within-group (ertugliflozin and placebo) mean changes from baseline for A1C at Week 12.	• A1C

• **Objective:** To assess the within-group (ertugliflozin and placebo) proportion of participants at 24 weeks and 54 weeks for the following endpoints:
  • Initiating glycemic rescue/glycemic intensification
  • At the following A1C treatment targets:
  ▪ <7.0% (53 mmol/mol)
  ▪ <6.5% (48 mmol/mol)
  ▪ <7.0% (53 mmol/mol) among participants with baseline A1C ≥7.0% (53 mmol/mol)
  • Acceptability and palatability of ertugliflozin
	• Use of glycemic rescue or glycemic intensification therapy
	• A1C
	• AEs

• **Objective:** Among those who up-titrated from ertugliflozin 5 mg/day to ertugliflozin 15 mg/day, to assess the within-group (ertugliflozin and placebo) proportion of participants with A1C <7.0% (53 mmol/mol) at 24 weeks.	• A1C

Objectives	Endpoints

• **Objective:** To assess the within-group (ertugliflozin and placebo) mean changes from baseline at 24 weeks and 54 weeks for the following endpoints:
  • Body weight and body mass index (BMI) percentile
  • Systolic and diastolic blood pressure
  • Bone biomarkers
	• Body weight and BMI percentile
	• Systolic and diastolic blood pressure
	• Bone biomarkers

• **Objective:** To assess the within-group (ertugliflozin and placebo) mean ertugliflozin exposure at 24 weeks.	• Steady state ertugliflozin exposure levels

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind study of ertugliflozin in pediatric participants (10 to 17 years of age, inclusive) with T2DM, including a randomly assigned up-titration of eligible participants after a second randomization at **Visit 5/Week 12** (Section 8.1.14). Participants will take part in the study for approximately 58 weeks, including an approximately 1-week screening period (**Visit 1/Screening** to **Visit 2/Week -1**), an approximately 1-week single-blind placebo run-in period (**Visit 2/Week -1** to **Visit 3/Day 1/Randomization**), an approximately 54-week double-blind treatment period (including a 24-week Phase A + 30-week Phase B), and a telephone contact 14 days after the last dose of study medication. All participants will continue to receive metformin ± insulin background therapy during the course of the study. The primary efficacy endpoint for the study will be evaluated using data from Phase A. The 30-week Phase B will provide a longer-term evaluation of ertugliflozin safety and efficacy in this pediatric population.

The mitigation strategies for managing participants with poor glycemic control differ between the Phase A and Phase B periods (Section 6.5.1). During the 24-week Phase A period, participants meeting progressively lower FPG thresholds (Table 3) will be rescued. In Phase B, therapy for participants meeting even lower glycemic thresholds will be intensified (Table 4) to prevent prolonged exposure to hyperglycemia.

At **Visit 3/Day 1/Randomization**, eligible participants will be randomized in a 2:1 ratio to ertugliflozin 5 mg or placebo. At **Visit 5/Week 12**, eligible participants in the ertugliflozin 5 mg treatment group (Section 6.1) will undergo a second randomization in a 1:1 ratio to either continue on ertugliflozin 5 mg or up-titrate to ertugliflozin 15 mg. Similarly, eligible participants in the placebo group will be mock-titrated (Section 6.1) to maintain the blind. Participants who do not meet the threshold(s) for a second randomization will continue on

ertugliflozin 5 mg/placebo. Additional details are provided in Section 9. If a participant discontinues study medication before **Visit 5/Week 12**, the second randomization should not be performed.

Approximately 165 participants will be randomized (at **Visit 3/Day 1/Randomization**) such that at least 156 participants are likely to have complete data at **Visit 6/Week 24** as described in Section 9.9. At least 30% of randomized participants will be between the ages of 10 and 14 years of age, and at least 30% of participants will be recruited from European Union (EU) member states, or countries with ethnicity, lifestyle, and diabetes care similar to those in EU countries. Further, at least 1/3 of the participants and not more than 2/3 of the participants will be female.

Sparse sampling to assess the pharmacokinetics (PK) of ertugliflozin will be performed. An interim analysis (IA) is planned to confirm ertugliflozin exposure in this population, and to limit potentially exceeding the exposures observed with the highest dose used in adult Phase 2 clinical studies. The IA will be conducted when ~30 participants on study medication (~20 participants on ertugliflozin) have completed **Visit 4/Week 6**.

If the IA exposure result exceeds the threshold described in Section 9.7, the second randomization will be discontinued, and ongoing participants who have up-titrated to ertugliflozin 15 mg/day will have an **Unscheduled Visit** as soon as possible to be down-titrated to ertugliflozin 5 mg/day in a blinded manner; participants in the placebo group who have been mock up-titrated will also be mock down-titrated. If the ertugliflozin 15 mg dose is continued, the second randomization at **Visit 5/Week 12** will be monitored by the unblinded DMC statistician so that ~30 participants are up-titrated to ertugliflozin 15 mg/day.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

The purpose of this study is to evaluate the safety and efficacy of ertugliflozin in pediatric patients (10 to 17 years of age, inclusive) with T2DM. In addition, the study design incorporates a dose titration scheme through a second randomization at **Visit 5/Week 12**. This design element aligns ertugliflozin administration in the study with clinical practice and the ertugliflozin product label and IB.

Population

Pediatric participants 10 to 17 years (inclusive) of age were selected for evaluation because T2DM does not occur in infants or toddlers and has rarely been reported in prepubertal children less than 10 years of age [Pettitt, D. J., et al 2014] [American Diabetes Association 2000] [Cefalu, W. T. 2015] [NA 2009]. In individuals less than 18 years of age, the onset of T2DM usually occurs during or following the onset of puberty. For this reason, this study will focus on participants 10 to 17 years of age (inclusive).

Primary Endpoint

A1C reflects average glucose concentrations in the past 3 to 4 months and, therefore, will provide a useful index of glycemic control at the end of the 24-week treatment period. A1C is a standard efficacy endpoint used to assess the glycemic efficacy of AHAs, and improvements in A1C correlates with reduction of risk of diabetic complications [Freinkel, N. 2017].

Run-in placebo period

The placebo run-in period has the explicit purpose of familiarizing the participants with the study treatment regimen and excluding participants who are not compliant with the blinded placebo prior to randomization.

Phase A: (Visit 3/Day 1/Randomization to Visit 6/Week 24)

The length of the placebo-controlled Phase A (24 weeks) was chosen to provide the optimal duration to assess the safety and efficacy profile of ertugliflozin versus placebo. An A1C threshold of ≥7.0% (53 mmol/mol) was chosen for up-titration of ertugliflozin at **Visit 5/Week 12** based on the definition of glycemic control in the clinical practice guideline for the management of pediatric patients with T2DM [American Diabetes Association 2018] [DiMeglio, L. A., et al 2018]. The up-titration schema is described in Section 8.1.14.

Phase B: (Visit 6/Week 24 to Visit 8/Week 54)

The 30-week treatment period should provide longer-term safety and efficacy data for the use of ertugliflozin in pediatric patients.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

To assess longer-term glucose-lowering efficacy (weeks to months), A1C will be measured. Since A1C reflects average glucose concentrations over the past 3-4 months, this measure provides a more useful index of the glycemic efficacy of ertugliflozin than FPG alone. Moreover, A1C is the key glycemic parameter which correlates with reduction of risk of diabetic complications. FPG will be measured to characterize the time course of glucose control.

4.2.1.2 Safety Endpoints

General safety and tolerability will be evaluated by clinical review of relevant parameters, including AEs, vital signs, laboratory safety studies (blood chemistry, hematology, lipid panel, urinalysis, and urine pregnancy testing for all females [for exceptions, see Section 10.7]), bone turnover biomarkers, assessment of growth and development, and nephrocalcinosis evaluation. For this study, prespecified AEs of interest (Tier 1) are symptomatic hypoglycemia, hypovolemia, genital mycotic infections (gender specific), and urinary tract infection (UTI).

4.2.1.3 Pharmacokinetic Endpoints

The PK data from this study may be combined with data from other studies for population PK analysis using nonlinear mixed effects modeling. If data permit, estimates of population PK parameters such as apparent oral clearance (CL/F) as well as estimates of inter-individual and residual variability will be determined. In addition, effects of demographic or physiologic factors (eg, age, race, weight, gender, renal function) on PK parameters will be assessed if possible. The results of this population PK analysis will be summarized in a separate report.

4.2.1.4 Pharmacodynamic Endpoints

No pharmacodynamic analysis is being conducted for this study.

4.2.1.5 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 6.

4.2.2 Rationale for the Use of Placebo

The placebo control group is an essential arm in this study, as it supports the evaluation of the safety and efficacy of ertugliflozin in pediatric participants 10 to 17 years of age (inclusive).

Glucose concentrations can change over time related to changes in diet, activity, and other factors, and hence a comparison to pre-treatment baseline glucose concentrations, rather than to glucose levels in another treatment group, would not accurately characterize the glucose-lowering efficacy of ertugliflozin in this population. Non-placebo controlled, active-comparator studies provide important information, but the efficacy profile of a new agent is best characterized by comparison to placebo.

Similarly, the safety profile of any drug is best characterized versus placebo, especially when it is first being studied in a particular population (eg, pediatric participants with T2DM).

4.3 Justification for Dose

The proposed ertugliflozin doses to be evaluated in this study are 5 mg and 15 mg qd to be taken in the morning with or without food.

The 5 mg and 15 mg doses of ertugliflozin were studied in the adult Phase 3 program and have been approved for use in adults. Since pediatric PK and pharmacodynamic responses are anticipated to be comparable to those of adults, the same adult doses were selected for evaluation in this study. Results from the adult Phase 3 program showed that the 5 mg and 15 mg doses of ertugliflozin have similar safety profiles, and both lead to clinically meaningful improvements in glycemia, blood pressure, and body weight. Due to the consistent effects of both doses, primary safety and efficacy analyses for this study will pool results from the 2 ertugliflozin dose groups.

4.3.1 Maximum Dose/Exposure for This Study

Based on 3 Phase 1 PK/Pharmacodynamic studies for canagliflozin, empagliflozin, and dapagliflozin, the PK/pharmacodynamic relationship for SGLT2 inhibitors appears to be similar in pediatric T2DM patients (aged 10-17 years of age) and adult T2DM patients [Tamborlane, W. V., et al 2018] [Laffel, L. M. B., et al 2018] [Tirucherai, G. S., et al 2016]. The maximum dose of 15 mg qd was selected because it was the highest ertugliflozin dose studied in adults with T2DM in the Phase 3 studies and is the higher of 2 approved doses for use in adults. Population PK analysis predicts that ertugliflozin exposure in T2DM pediatric participants would be similar to that of adults when the same dose is administered. For the 15 mg dose, the population PK model predicted a median steady state AUC_{24} of 1207 ng•hr/mL in the T2DM pediatric population, which is comparable to the model predicted steady state AUC_{24} in adults with T2DM (1329 ng•hr/mL). The threshold for stopping the 15 mg dose is described in Section 9.7.

4.3.2 Rationale for Dose Interval

The PK of ertugliflozin in adults supports once daily dosing and the approved dosing regimen in adults is ertugliflozin 5 mg qd or ertugliflozin 15 mg qd without regards to food. Since the population PK model has predicted comparable exposures between adults and pediatric patients 10 to 17 years of age, a similar dosing regimen (dose and dose interval) is proposed for this study.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the informed consent/assent form. End of study will be declared after (1) all participants in the study have completed Week 54 or have discontinued from study prior to Week 54, (2) the database has been locked (after medical and scientific reviews of the data have been completed), and (3) the data have been unblinded. Note: Fifty-six weeks after the last participant is randomized, any participant with an outstanding status will be declared as “lost to follow-up”.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

However, the clinical study may be terminated early if the risk/benefit ratio to the study population is viewed as unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (GCP), and/or other applicable regulatory requirements, procedure-related problems or an unacceptably high number of discontinuations or withdrawals due to administrative reasons.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Male/Female participants with T2DM between the ages of 10 and 17 years (inclusive) will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

All laboratory measures (to determine eligibility) must be performed after an overnight fast ≥10 hours in duration. Participants with laboratory screening values/findings not meeting protocol inclusion criteria may, at the discretion of the investigator, have 1 repeat determination performed by the central laboratory. If the repeat value satisfies the criterion, the participant may continue in the screening process. Only the specific laboratory test not meeting the inclusion criterion should be repeated (not the entire panel).

Note: If the period of time between **Screening Visit/Visit 1** (ie, date when the screening laboratory measurements were obtained) and the **Visit 3/Day 1/Randomization** date exceeds 28 days, participants must have all screening laboratory measurements repeated (this includes participants who have had their metformin and/or insulin doses adjusted). If screening laboratory values are repeated, the last laboratory draw/result should be used to evaluate eligibility.

To be eligible for inclusion in this study, the participant must meet all of the following criteria:

At Screening Visit/Visit 1

1. Have T2DM as indicated by "yes" answers to all of the following:

    i. Participant has diabetes diagnosed by one of the following American Diabetes Association (ADA) criteria, eg:

        a. Laboratory determinations of FPG ≥126 mg/dL (7.0 mmol/L), OR

        b. Random plasma glucose ≥200 mg/dL (11.1 mmol/L), OR

        c. 2-hour oral glucose tolerance test (OGTT) plasma glucose ≥200 mg/dL (11.1 mmol/L), OR

        d. A1C ≥6.5% (48 mmol/mol) test performed using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.

    ii. Participant has BMI ≥85th percentile at screening OR

    participant has a history of being overweight or obese at time of diagnosis of T2DM.

    Note: If the participant does not have a BMI ≥85th percentile at the time of screening, the documentation of overweight or obesity at the time of diagnosis of T2DM must be included in the source documents at the site.

2. Have:

    i. T2DM for ≥2 years, OR

    ii. T2DM for <2 years and a fasting C-peptide value >0.6 ng/mL at **Screening Visit/Visit 1**.

    Note: All participants on background insulin must have a fasting C-peptide value >0.6 ng/mL with a concurrent FPG >100 mg/dL (5.56 mmol/L) at **Screening Visit/Visit 1** regardless of duration of T2DM. If FPG ≤100 mg/dL (5.56 mmol/L) C-peptide levels should be measured at an **Unscheduled Visit/Visit 2/Week -1**, at least 30 minutes, but no longer than 2 hours after a meal. Participants must have a C-peptide value >1.5 ng/mL in the post-meal period.

3. Be:

    i. On stable metformin monotherapy (≥1500 mg/day, for ≥8 weeks prior to **Screening Visit/Visit 1**), OR

    ii. On a stable metformin dose (≥1500 mg/day, for ≥8 weeks prior to **Screening Visit/Visit 1**) and a stable dose of insulin (of any type, variance in dose to be ≤15% of total daily dose for ≥8 weeks prior to **Screening Visit/ Visit 1**). **Note:** This stable dose can include: (1) a stable dose of basal insulin (±15%) AND/OR (2) stable prescribed doses of bolus insulin (±15%) (a) for each fingerstick glucose (FSG) range for participants on sliding scale OR, if applicable, (b) for corrective doses and carbohydrate coverage.

Notes:

a. Participants on stable doses of metformin ≥1000 and <1500 mg/day (± insulin) for ≥8 weeks can participate if there is documentation that they cannot tolerate higher doses of metformin.

b. Participants on metformin doses ≥1000 and <1500 mg/day (± insulin) can have their metformin doses up-titrated to ≥1500 mg/day and be eligible to participate after their dose remains stable for ≥8 weeks, if they meet eligibility criteria when they are rescreened. If up-titration of metformin is not tolerated, it must be documented, and the participant will be eligible if they meet all other **Screening Visit/Visit 1** eligibility criteria.

c. At **Screening Visit/Visit 1**, participants on insulin doses that are not stable can have the insulin doses adjusted and be eligible to participate after their dose remains stable for ≥8 weeks, if they meet eligibility criteria when they are rescreened.

4. Have an A1C ≥6.5% and ≤10.0% (48 mmol/mol and 86 mmol/mol) at **Screening Visit/Visit 1** if on metformin monotherapy, OR an A1C ≥7.0% and ≤10.0% (53 mmol/mol and 86 mmol/mol) at **Screening Visit/Visit 1** if on metformin + insulin.

Demographics

5. Be male or female, ≥10 years and ≤17 years of age, when the informed consent is signed by the legally acceptable representative, and randomization (**Visit** 3/**Day 1/Randomization**) will occur prior to the participant's 18th birthday.

Male Participants

6. Contraceptive use by male participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

7. Contraceptive use by female participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

8. Be a female participant who is unlikely to conceive as indicated by at least 1 "yes" response to the following which will remain consistent for the projected duration of the study and for 14 days after the last dose of study treatment:

    i. Participant is a non-sterilized female who is currently not sexually active and agrees to follow statement "iii" if heterosexual activity is initiated, OR

    ii. Participant is a non-sterilized female who agrees to abstain from heterosexual activity. **Note:** If abstinence (see Appendix 5) is not a locally acceptable method of contraception, then 1 other adequate birth control method must be used, OR

    iii. Participant is a non-sterilized female who agrees to start contraception prior to initiating sexual activity and who agrees to use an adequate method of contraception (Appendix 5). **Note:** Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Participants initiating hormonal contraception during the study should use 1 additional contraceptive method.

Informed Consent/Assent

9. Have a legally acceptable representative who understands the study procedures, alternative treatments available and risks involved with the study, and voluntarily agrees to the child's participation by giving informed written consent, and the participant has an age-appropriate understanding of the same by giving informed written assent. If the legally acceptable representative is illiterate see Section 8.1.1.1 for details. In addition, the legally acceptable representative may also consent to have the child participate in Future Biomedical Research (FBR) by signing a separate consent (Section 8.1.1.2). Otherwise eligible participants will be able to participate in the main study even if they opt to not participate in FBR.

10. Have a family member or adult who, along with the participant, will be closely involved in the participant's daily activities (in the opinion of the investigator) and in the participant's treatment and study procedures (ie, available for telephone calls, study visits and administration of study medication as needed).

At Visit 3/Day 1/Randomization

11. Have ≥80% compliance with placebo treatment during the single-blind run-in as measured by site-performed tablet count.
    Note: The minimum interval between **Visit 2/Week -1** and **Visit 3/Day 1/Randomization** should be 6 days. In this case, 100% compliance with single-blind placebo treatment will be required for randomization. The maximum interval between **Visit 2/Week -1** and **Visit 3/Day 1/Randomization** should be 14 days, with ≥80% compliance with single-blind placebo treatment required for randomization.

5.2 Exclusion Criteria

All laboratory measures (to determine eligibility) must be performed after an overnight fast ≥10 hours in duration. Participants with laboratory screening values outside the ranges described in the protocol may, at the discretion of the investigator, have 1 repeat determination performed by the central laboratory. If the repeat value satisfies the criterion, the participant may continue in the screening process. Only the specific out-of-range value/finding should be repeated (not the entire panel).

Note: If the period of time between **Screening Visit/Visit 1** (ie, date when the screening laboratory measurements were obtained) and the date of **Visit 3/Day 1/Randomization** exceeds 28 days, participants must have all screening laboratory measurements repeated (this includes participants who have had their metformin and/or insulin doses adjusted). If screening laboratory values are repeated, the last laboratory draw/result should be used to evaluate eligibility.

The participant must be excluded from the study if the participant meets any of the following criteria:

At Screening Visit/Visit 1

1. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

Medical Conditions

2. Has known type 1 diabetes mellitus or documented evidence of positive diabetes auto-antibodies performed when participant was diagnosed with diabetes.

3. Has known monogenic diabetes, or secondary diabetes.

4. Has symptomatic hyperglycemia and/or moderate to large ketonuria requiring immediate initiation of another antihyperglycemic agent, including insulin.

5. Has active, obstructive uropathy or indwelling urinary catheter.

6. Has history of malignancy ≤5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer.

   Note (a): A participant with a history of malignancy >5 years prior to signing informed consent should have no evidence of residual or recurrent disease.

   Note (b): A participant with any history of melanoma, leukemia, lymphoma, or renal cell carcinoma is excluded (cannot participate).

7. Has a known hypersensitivity or intolerance to any SGLT2 inhibitor.

8. Has active liver disease (other than non-alcoholic hepatic steatosis) by history, including chronic active hepatitis B or C, primary biliary cirrhosis, or symptomatic gallbladder disease.

9. Has active nephropathy (ie, nephrotic syndrome or glomerulonephritis) or abnormalities of genitourinary tract that predispose to recurrent urinary tract infections. Note: Participants with diabetic nephropathy will be eligible if they meet all other eligibility criteria.

10. Meets any of the following criteria:

    i. Participant is on a weight-loss program and is not weight-stable.

    ii. Participant is on a weight-loss medication (eg, orlistat, phentermine/topiramate, lorcaserin) and is not weight-stable.

    iii. Participant is on other medications associated with weight changes (eg, anti-psychotic agents) and is not weight-stable.

    iv. Participant had bariatric surgery at any time in the past.

    Note: Weight-stable is defined as <5% change in body weight in the last 3 months.

11. Has been previously diagnosed with disorders of growth or bone metabolism.

12. Has a clinically significant hematological disorder (such as aplastic anemia, thrombocytopenia, myeloproliferative or myelodysplastic syndrome).

13. Is pregnant, or breast feeding or is expecting to conceive or donate eggs during the study, including 14 days following the last dose of study medication.

Prior/Concomitant Therapy

14. Has been treated with a sulfonylurea, meglitinide, alpha glucosidase inhibitor, DPP-4 inhibitor, or incretin-based agent in the 8 weeks prior to Screening Visit/Visit 1.

15. Has been treated with a thiazolidinedione in the 16 weeks prior to Screening Visit/Visit 1.

16. Is taking blood pressure medication(s) and will not be on a stable dose for at least 4 weeks prior to Visit 3/Day 1/Randomization.

17. Is currently being treated for hyperthyroidism.

18. Is on, or likely to require treatment with, ≥14 consecutive days or repeated courses of pharmacologic doses of corticosteroids.

    Note: Inhaled, nasal, and topical corticosteroids are permitted.

Prior/Concurrent Clinical Study Experience

19. Has previously taken an SGLT2 inhibitor (such as canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin) or was enrolled in a study for these agents.

    Note: Participants who have been enrolled in single-dose studies with these agents ≥12 weeks prior to screening are eligible to participate.

Diagnostic Assessments

20. Has a Screening Visit/Visit 1 SBP or diastolic blood pressure (DBP) ≥95th percentile for age, height percentile, and gender (see Table 11 and Table 12) and is not considered likely to have values <95th percentile for age, height percentile and gender by Visit 3/Day 1/Randomization even with appropriate antihypertensive therapy.

    Note: Investigators are encouraged to maximize blood pressure control according to current guidelines. Participants may have blood pressure medications adjusted and may be enrolled if the participant's blood pressure no longer meets exclusion criteria.

21. Has fasting serum triglyceride >500 mg/dL (5.65 mmol/L) at Screening Visit /Visit 1, confirmed by a single repeat if deemed necessary. Participants with elevated triglycerides may be rescreened with the permission of the Sponsor's Clinical Director if they have a normal triglyceride level (<150 mg/dL [1.7 mmol/L]) after they have been on a triglyceride-lowering diet or a stable lipid-lowering medication regimen for at least 4 weeks prior to rescreening with no further dose changes during the pre-randomization period.

22. Has an eGFR <45 mL/min/1.73m^2 at Screening Visit/ Visit 1.

    Note: The eGFR cutoff for exclusion should be consistent with the local label for ertugliflozin if it is different from above.

23. Has an aspartate transaminase (AST) or alanine transaminase (ALT) >2.5X the upper limit of normal (ULN) at Screening Visit/ Visit 1, or a total bilirubin >1.5X the ULN unless the participant has a history of Gilbert syndrome.

24. Has hemoglobin levels below normal range for age and sex at Screening Visit/ Visit 1.

25. Has thyroid-stimulating hormone (TSH) levels outside normal range at Screening Visit/ Visit 1. Participants with elevated TSH must be excluded and may be rescreened with the permission of the Sponsor's Clinical Director if they have a normal TSH after they have been on a stable thyroid replacement regimen for at least 6 weeks prior to rescreening with no further dose changes during the pre-randomization period.

    Note: Participants already on thyroid replacement therapy at Screening Visit/Visit 1 should have a normal TSH and be on a stable dose for at least 6 weeks prior to randomization.

26. Has a history of idiopathic acute pancreatitis or chronic pancreatitis.

27. Has a history of severe hypoglycemia (hypoglycemia associated with altered sensorium, seizures, or loss of consciousness) while on insulin.

Other Exclusions

28. Has a known history of recreational or illicit drug use, or of alcohol abuse or dependence (within the past year).

29. Has donated blood products or has had phlebotomy of >10% of estimated total blood volume within 8 weeks of signing informed consent or intends to donate blood products or receive blood product within the projected duration of the study.

30. Is unlikely to adhere to the study procedures and appointment schedule, is planning to relocate outside of the geographic area during the study (including attending school at a remote location), or has poor mental function, or legally acceptable representative is in the opinion of the investigator, mentally or legally incapacitated preventing informed consent from being obtained.

31. Has a history or current evidence of any condition, therapy, lab abnormality or other circumstance which, in the opinion of the investigator, might pose a risk to the participant, make participation not in the participant's best interest, might confound the results of the study, or interfere with the participant's involvement for the full duration of the study.

At Visit 2/Week -1

32. Has symptomatic hyperglycemia or ketonuria.

33. Has a clinically significant ECG abnormality that requires further diagnostic evaluation or intervention (eg, new, clinically significant arrhythmia or a conduction disturbance) which, in the opinion of the investigator, exposes the participant to risk by enrolling in the study. Or participant has a prolonged QTc interval for age. Note: The same criterion will apply if the ECG is performed at Visit 3/ Day 1/Randomization instead of Visit 2/Week -1.

34. Requires initiation of concomitant medications listed in Section 6.5. The current Visit should be changed to an Unscheduled Visit and the participant should be rescheduled for a Visit 2/Week -1 (and Visit 3/Day 1/Randomization) to occur in accordance with the guidance in Section 6.5.

    Note: If the duration between Visit 1/Screening and Visit 3/Day 1/Randomization is greater than 28 days, participants must have all screening laboratory measurements repeated as described at the beginning of Section 5.2.

At Visit 3/Day 1/Randomization

35. Has symptomatic hyperglycemia, and/or ketonuria, requiring immediate change to his/her antihyperglycemic therapy.

36. Has developed a new medical condition, suffered a change in status of an established medical condition, developed a laboratory abnormality, or required a new treatment or medication during the run-in which meets any previously described study exclusion criterion.

    Note: If a participant requires initiation of a new medication (with the exception of medications prohibited in the exclusion criteria) at **Visit 3/Day 1/Randomization**, the current visit should be changed to an "**Unscheduled Visit**" and the participant should be rescheduled for a **Visit 3/Day 1/Randomization** to occur 1 to 2 weeks later. Additional single-blind placebo run-in treatment should be dispensed at this **Unscheduled Visit**.

37. Is female with a positive pregnancy test.

38. Has a site fasting fingerstick glucose (FFSG) >240 mg/dL (13.3 mmol/L).

    Note: If the investigator believes that the value does not reflect the participant's recent glycemic control, then the participant should not be excluded at this time. The current visit should be changed to an **Unscheduled Visit** and the participant should be rescheduled for **Visit 3/Day 1/Randomization**. If at the rescheduled visit, the participant meets this exclusion criterion, the participant MUST be excluded.

39. Has a FFSG <130 mg/dL (7.2 mmol/L) if on insulin

    Note: If the investigator believes that the value does not reflect the participant's recent glycemic control, then the participant should not be excluded at this time. The current visit should be changed to an **Unscheduled Visit** and the participant should be rescheduled for **Visit 3/Day 1/Randomization**. If at the rescheduled visit, the participant meets this exclusion criterion, the participant MUST be excluded.

5.3 Lifestyle Considerations

Participants will be advised to adhere to the recommended dietary and activity regimen for the duration of the study, with the objective of maintaining consistency.

5.3.1 Meals and Dietary Restrictions

The participant and legally acceptable representative will receive individualized diet counseling for weight maintenance consistent with the standard guidelines of the country of the investigational site (or other similar guidelines such as those from the ADA) for youths with T2DM from a dietitian or other qualified health care professional. Detailed dietary information will not be captured in the study database.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

Participants should not have any caffeine or tobacco within 30 minutes of blood pressure measurements.

5.3.3 Activity Restrictions

Participants must not engage in physically strenuous exercise (eg, heavy lifting, weight training, calisthenics, and aerobics) within 48 hours before each blood sample collection for clinical laboratory tests for the duration of participation in the study.

5.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

Participants who discontinue from study medication or withdraw from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies of blinded study medications provided by the Sponsor will be packaged to support enrollment in the study. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study medications to be used in this study are outlined in Table 1.

First Randomization at **Visit 3/Day 1/Randomization:**

All qualified participants will be randomized to receive 2 tablets per day of either:

- Ertugliflozin 5 mg and placebo matching ertugliflozin 15 mg –OR-
- Placebo matching ertugliflozin 5 mg and placebo matching ertugliflozin 15 mg

Second Randomization at **Visit 5/Week 12:**

Eligible participants in the ertugliflozin 5 mg group

- Treated with ertugliflozin 5 mg: FS A1C ≥7.0% (53 mmol/mol)
- Treated with ertugliflozin 5 mg and insulin: FS A1C ≥7.0% (53 mmol/mol) **and** FFSG ≥110 mg/dL (6.1 mmol/L)

will have a second randomization to receive 2 tablets per day of either:

- Ertugliflozin 5 mg and placebo matching ertugliflozin 15 mg OR-
- Ertugliflozin 15 mg and placebo matching ertugliflozin 5 mg.

Eligible participants in the placebo group

- Treated with placebo alone: FS A1C ≥7.0% (53 mmol/mol)
- Treated with placebo and insulin: FS A1C ≥7.0% (53 mmol/mol) and a FFSG ≥110 mg/dL (6.1 mmol/L)

will undergo a mock second randomization to maintain blinding, with no change in study medication. Participants who do not meet the threshold(s) for a second randomization will continue on ertugliflozin 5 mg/placebo.

If a participant discontinues study medication before **Visit 5/Week 12**, the second randomization should not be performed.

Table 1 Study Medications

Arm Name	Arm Type	Medication Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Placebo Run-in	Other	Placebo matching ertugliflozin 5 mg	Other	Tablet	0 mg	1 Tablet qd	Oral	Visit 2 to Visit 3 (Placebo Run-in Period)	Placebo	IMP	Provided centrally by Sponsor
Placebo Run-in	Other	Placebo matching ertugliflozin 15 mg	Other	Tablet	0 mg	1 Tablet qd	Oral	Visit 2 to Visit 3 (Placebo Run-in Period)	Placebo	IMP	Provided centrally by Sponsor
Ertugliflozin 5 mg	Experimental	Ertugliflozin 5 mg	Drug	Tablet	5 mg	1 Tablet qd	Oral	Visit 3 to Visit 5/8 (Double-blind Treatment Period)	Test Product	IMP	Provided centrally by Sponsor
Ertugliflozin 5 mg	Experimental	Placebo matching ertugliflozin 15 mg	Other	Tablet	0 mg	1 Tablet qd	Oral	Visit 3 to Visit 5/8 (Double-blind Treatment Period)	Placebo	IMP	Provided centrally by Sponsor
Placebo	Placebo Comparator	Placebo matching ertugliflozin 5 mg	Other	Tablet	0 mg	1 Tablet qd	Oral	Visit 3 to Visit 8 (Double-blind Treatment Period)	Placebo	IMP	Provided centrally by Sponsor
Placebo	Placebo Comparator	Placebo matching ertugliflozin 15 mg	Other	Tablet	0 mg	1 Tablet qd	Oral	Visit 3 to Visit 8 (Double-blind Treatment Period)	Placebo	IMP	Provided centrally by Sponsor
Ertugliflozin 15 mg (a)	Experimental	Ertugliflozin 15 mg	Drug	Tablet	15 mg	1 Tablet qd	Oral	Visit 5 to Visit 8 (Double-blind Treatment Period)	Test Product	IMP	Provided centrally by Sponsor

Arm Name	Arm Type	Medication Name	Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Ertugliflozin 15 mg (a)	Experimental	Placebo matching ertugliflozin 5 mg	Other	Tablet	0 mg	1 Tablet qd	Oral	Visit 5 to Visit 8 (Double-blind Treatment Period)	Placebo	IMP	Provided centrally by Sponsor

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Note: Standard of care medication to be sourced locally and to follow local guidelines and regulations. Rescue/intensification medication to be sourced locally and administration to be consistent with those specified in the protocol. Drug handling, storage, and accountability of blinded study medication, metformin, and insulin will be conducted per Section 6.2.2, as applicable.

(a) The ertugliflozin 15 mg dose will be administered to a portion of the participants who qualify for the second randomization (Section 8.1.14).

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending upon local country operational requirements. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation/randomization will occur centrally using an interactive response technology (IRT) system. At **Visit 3/Day 1/Randomization**, there will be 2 study intervention arms. Participants will be assigned randomly in a 2:1 ratio to ertugliflozin 5 mg or placebo.

At **Visit 5/Week 12**, all eligible participants (Section 6.1) will undergo a second randomization. Eligible participants in the ertugliflozin 5 mg group will be randomized in a 1:1 ratio to either stay on ertugliflozin 5 mg or up-titrate to ertugliflozin 15 mg (Section 8.1.14). Eligible participants in the placebo group will participate in the second randomization, but all will remain on placebo and be mock-titrated to preserve blinding.

If the PK IA (Section 9.7) results in a decision to drop the 15 mg dose, then:

1. The second randomization at **Visit 5/Week 12** will be discontinued and the corresponding FS A1C and FFSG should not be performed (the central laboratory A1C will still be performed).

2. Ongoing participants who have reached **Visit 5/Week 12** or beyond on study medication will return to the site to have blinded study medication redispensed through IRT to maintain blinding. Participants receiving placebo or ertugliflozin 5 mg will continue to receive the same medication. Participants who are receiving ertugliflozin 15 mg will be down-titrated to the ertugliflozin 5 mg dose for the remainder of the study.

If the ertugliflozin 15 mg dose is continued, the second randomization at **Visit 5/Week 12** will be monitored by the unblinded DMC statistician so that ~30 participants are up-titrated to ertugliflozin 15 mg/day.

6.3.2 Stratification

Treatment allocation/randomization at **Visit 3/Day 1/Randomization** will be stratified according to the following factors collected at **Screening Visit/Visit 1**:

1. Age: 10 to 14 years of age OR 15 to 17 years of age

2. Insulin use: Yes OR No

Treatment allocation/randomization at **Visit 5/Week 12** will be stratified according to the following factor collected at **Visit 5/Week 12**:

3. Insulin use: Yes OR No

6.3.3 Blinding

For the double-blind phase of the study, double-blinding technique with in-house blinding will be used. Ertugliflozin 5 mg and ertugliflozin 15 mg will be packaged identically relative to their matching placebos so that blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

At **Visit 5/Week 12**, eligible participants in the ertugliflozin 5 mg treatment group (Section 6.1) will undergo a second randomization in a 1:1 ratio to either continue on ertugliflozin 5 mg or up-titrate to ertugliflozin 15 mg. Similarly, eligible participants in the placebo group will be mock-titrated (Section 6.1) to maintain the blind. Participants who do not meet the threshold(s) for a second randomization will continue on ertugliflozin 5 mg/placebo.

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.4 Study Intervention Compliance

Every effort will be made to maintain 100% medication adherence. If a participant is found to have compliance <85%, site personnel should begin frequent contacts (at least once a week, until the next site visit) with the participant and the legally acceptable representative to reinforce compliance with study medication.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study if the participant is on double-blind study medication. If the participant is being followed up in the study off-study medication, these prohibited medications may be used at the discretion of the investigator.

Note: It is the responsibility of the investigator to ensure that participants with concomitant medical conditions (such as hypothyroidism, hypertension, and dyslipidemia) are treated according to local guidelines.

Antihyperglycemic Medications

Double-blind study treatment and metformin (as background) and insulin (as background or rescue/intensification therapy when appropriate), are the only AHAs permitted in the study. Participants who discontinue study medication may be treated with antihyperglycemic medication as considered clinically appropriate.

Lipid, Blood Pressure, and Thyroid Hormone Medications

Concurrent lipid-lowering, antihypertensive, and thyroid hormone replacement medications are permitted. However, it is the responsibility of the investigator to ensure that participants are on a stable dose of thyroid medication regimen for at least 6 weeks and/or a stable dose

of lipid-lowering and antihypertensive medications for at least 4 weeks prior to **Visit 3/Day 1/Randomization**.

Note: Medications to treat hyperthyroidism are prohibited.

Birth Control Medications

These medications are allowed, but participants should be on a stable regimen during placebo run-in and are expected to remain on a stable regimen during the double-blind treatment period (refer to Appendix 5 for further detail regarding contraceptive agents).

Note: Participants who initiate heterosexual activity during the study may begin hormonal contraception as detailed in Appendix 5.

Corticosteroids

Treatment for ≥14 consecutive days of pharmacologic doses of corticosteroids (oral, injectable/parenteral) is not permitted during the study. Oral corticosteroids used for physiologic replacement therapy (ie, in participants with adrenal insufficiency) and inhaled, nasal, and topical corticosteroids are allowed.

Note: Use or need for use of excluded medications will require consultation with the study investigator and the Sponsor.

Supplements

The use of herbal supplements and other so-called "natural products" should be discouraged for the duration of the study. Participants who do not discontinue the use of such supplements prior to the **Screening Visit** should be instructed not to change the use or dose of the supplement for the duration of the study. Participants should be instructed not to initiate new supplements for the duration of the study.

Imaging with contrast

Metformin should be temporarily discontinued at the time of, or prior to, iodinated contrast imaging procedures, and restarted if renal function is normal 48 hours after the imaging procedure.

6.5.1 Rescue Medications and Supportive Care

After randomization (**Visit 3/Day 1/Randomization**), participants who have ≥80% compliance with study medication (and diet/exercise recommendations) and meet protocol-specified glycemic thresholds will be eligible for glycemic rescue therapy during Phase A (Table 3) or glycemic intensification during Phase B (Table 4). Participants, who, in the investigator's judgment, are not compliant (<80%) with study medication and/or diet/exercise recommendation, should be retrained by site personnel on compliance with medication and diet/exercise (Section 6.4). The participant should be contacted a week later to assess if FFSG values still meet rescue/intensification criteria.

The participant and legally acceptable representatives will be (1) instructed on FFSG values that meet the threshold corresponding to the participant's duration in the study (eg, a participant has 3 consecutive days of FFSG values >240 mg/dL [13.3 mmol/L] between **Visit 3/Day 1/Randomization** and **Visit 4/Week 6**) and (2) instructed to call the site if the participant has 3 consecutive days of FFSG values that exceed the specified thresholds. For reference, site personnel will instruct the legally acceptable representative/participant of the threshold level for rescue for the specific time period in the study.

Participants and legally acceptable representatives will be counseled that if 1 FFSG value is above the threshold for rescue/intensification, the FFSG value must be checked the following morning. If the FFSG value is above the threshold for rescue/intensification on 2 consecutive days, the FFSG has to be checked on the third day as well, and the site called if all 3 values are above the threshold for rescue/intensification.

The participant will attend an **Unscheduled Visit** if the FFSG value exceed thresholds for 3 consecutive days and has been compliant with study medication, diet, and exercise recommendations.

During Phase A:

At the **Unscheduled Visit**, an FPG will be drawn for local and central laboratory evaluation. The FPG value reported from the local laboratory should be used to assess rescue criteria and must be recorded on the relevant electronic case report form (eCRF). If the local lab FPG value is less than the rescue threshold, but the central laboratory FPG value is greater than the rescue threshold, the participant will have to return to the site to complete a **Rescue Visit** (Section 8.10.7) and initiate rescue therapy.

Participants should also initiate glycemic rescue therapy if a central laboratory FPG alone meets rescue criteria during a routine site visit, even if the participant does not report 3 consecutive FFSG values above the threshold. In this situation, the participant will need to come to the site for an **Unscheduled Visit** to initiate glycemic rescue.

Participants on metformin alone who meet glycemic rescue criteria should initiate insulin glargine (dose at the investigator's discretion based on accepted local, national or international guidelines). If the participant is on metformin + insulin, the insulin dose should be increased by ≥15% (Table 2).

No participant should undergo glycemic rescue at an **Unscheduled Visit** between **Week 10** and **Visit 5/Week 12**.

Additionally, at **Visit 5/Week 12,** participants who are eligible for the second randomization should **NOT** undergo glycemic rescue even if they meet the specified criteria. Instead, these participants should be advised to check FFSG measurements every day for the next 2 weeks and glycemic rescue therapy should be initiated 2 weeks after **Visit 5/Week 12** if they continue to meet the prespecified thresholds (Table 3).

During Phase B (for participants not rescued in Phase A):

Starting from **Visit 6/Week 24**, FFSG and FS A1C will be measured at scheduled and unscheduled site visits, and glycemic intensification will be initiated if the participant meets criteria (Table 4). Between site visits, participants with FFSG >130 mg/dL (7.2 mmol/L) at home for 3 consecutive days will come to the site for an **Unscheduled Visit** if, in the investigator's judgment, the participant has been compliant with study medication and diet/exercise recommendations. At the unscheduled site visit, the participant's FFSG and FS A1C will be measured, and the participant will initiate glycemic intensification if both values meet criteria (Table 4). If the participant is on metformin alone, insulin glargine will be initiated (dose at the investigator's discretion based on accepted local, national or international guidelines). If the participant is on metformin + insulin the total daily insulin dose will be increased by ≥15% (Table 2).

Table 2 Glycemic Rescue/Intensification Strategy

Participant's Background Therapy	Phase A Rescue Therapy OR Phase B Intensification Therapy (for participants not rescued in Phase A)
Metformin alone	Insulin glargine
Metformin + Insulin	Increase insulin dose ≥15%

Note: In Phase A and Phase B, participants requiring transient (ie, <14 days) initiation of insulin or an increase in insulin (≥15% of the dose at baseline), for participants on background insulin therapy (eg, an intercurrent illness) will not be considered as having initiated rescue/intensification. Down-titration or weaning of insulin after a temporary initiation or increase in dose should occur at the investigator's discretion.

Note that participants rescued or intensified with basal insulin for 6 weeks or more, can have prandial insulin added at the investigator's discretion. The choice, dose, and titration of prandial insulin will be the investigator's responsibility.

Participants <18 years of age, who refuse to initiate insulin or up-titrate their background insulin (or for whom it is considered inappropriate) when glycemic thresholds for rescue/intensification are met will be discontinued from study medication (see Section 7.1). Participants ≥18 years of age can be rescued or undergo glycemic intensification using any of the antihyperglycemic agents approved for use with ertugliflozin.

Insulin (background, rescue, and intensification) will be sourced locally and administered subcutaneously based on instructions provided by the investigator (based on accepted, local, national or international guidelines for the indication and use of insulin or alternate medication).

Table 3 Glycemic Rescue Criteria (Phase A)

Time in Study	FFSG Thresholds for Rescue[1]	FPG Thresholds[1,2]
Day 1 through **Week 6**	>240 mg/dL (13.33 mmol/L)	>240 mg/dL (13.33 mmol/L)
After **Week 6** through **Week 12**	>225 mg/dL (12.50 mmol/L)	>225 mg/dL (12.50 mmol/L)
After **Week 12** through **Week 18**	>200 mg/dL (11.11 mmol/L)	>200 mg/dL (11.11 mmol/L)
After **Week 18** through **Week 24**	>180 mg/dL (10.00 mmol/L)	>180 mg/dL (10.00 mmol/L)

FFSG = fasting fingerstick glucose; FPG = fasting plasma glucose.

[1] The initial FFSG value will trigger a repeat FFSG measurement(s). An FPG measurement will be triggered when FFSG values meet rescue criteria for 3 consecutive days, and rescue will be initiated if the FPG is above threshold.

[2] Perform confirmatory FPG (central and local lab) if FFSG value is greater than the defined threshold on 3 consecutive days (after assessing for study medication compliance).

Table 4 Glycemic Intensification Criteria (Phase B)

Time in Study	FFSG Threshold for Intensification	FS A1C threshold for Intensification
From **Week 24** through **Week 54**	>130 mg/dL (7.2 mmol/L)	>7.5% (58 mmol/mol)

A1C = glycosylated hemoglobin; FFSG = fasting fingerstick glucose; FS = fingerstick.

Note: If at any time a participant has

1. FSG value >400 mg/dL (22.2 mmol/L) with or without ketonuria/ketonemia, OR
2. Moderate to large ketonuria, positive test for ketonemia, or a flag from the Central Laboratory for ketonuria, regardless of blood glucose levels after a workup of ketoacidosis,
   Note: Participants will be instructed to check for ketones if they meet the following criteria:
   a. Fever
   b. Nausea or vomiting
   c. Abdominal pain (unrelated to menstrual cramps in females)
   d. Fasting
   e. Unusual calorie restriction (eg, during an intercurrent illness or in preparation for surgery/procedure)

the investigator should consider initiating insulin for participants not on insulin treatment at **Screening Visit/Visit 1** OR should consider up-titrating insulin therapy for those participants on insulin treatment at **Screening Visit/Visit 1**. If after 14 days, the dose of insulin cannot be reduced (to the participant's previous dose) or weaned off, the participant should be considered as having initiated glycemic rescue or glycemic intensification. In addition, if the participant has ketonuria or ketonemia, study intervention should be interrupted, and guidelines in Section 7.1 for a suspected event of ketoacidosis should be followed.

6.6 Dose Modification (Escalation/Titration/Other)

Participants with A1C ≥7.0% (53 mmol/mol) at **Visit 5/Week 12** will be eligible for a second randomization at **Visit 5/Week 12**. Eligible participants in the ertugliflozin 5 mg treatment group will be re-randomized in a 1:1 ratio to up-titrate to ertugliflozin 15 mg or remain with ertugliflozin 5 mg. Similarly, eligible participants in the placebo group will undergo a mock-titration to maintain the blind (Section 6.1).

If the ertugliflozin 15 mg group is dropped after the PK IA, participants in the ertugliflozin 15 mg group will be down-titrated to ertugliflozin 5 mg (Section 6.3.1) and participants in the placebo group who have been mock up-titrated will also be mock down-titrated.

6.7 Intervention After the End of the Study

There is no study-specified medication following the end of the study.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9 and Section 8.10.8. Participants who discontinue study medication without withdrawing consent will have their diabetes managed as considered clinically appropriate by their primary doctor. Initiation of other AHAs will not be considered as prohibited medication in these participants. Participants who discontinue study medication before **Visit 5/Week 12** will not have the second randomization performed.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

The participant or participant's legally acceptable representative requests to discontinue study intervention.

Hyperglycemia: The participant meets the criteria for rescue/intensification and rescue/intensification therapy is refused by the participant or deemed clinically inappropriate by the investigator.

- Hypoglycemia:
    - Repeated (2 or more episodes since the prior study visit)
        - FSG <54 mg/dL (3.0 mmol/L) with or without symptoms of hypoglycemia, OR
        - FSG 54 to 70 mg/dL (3.0 to 3.9 mmol/L) with symptoms of hypoglycemia, and without a reasonable explanation (such as increased physical activity and/or skipped meal).

    Note: Participants who are on insulin (background, rescue, or intensification therapy) and who meet either of the hypoglycemia discontinuation criteria may have their insulin dose reduced or interrupted at the investigator's discretion and may continue in the study on study medication.

    Note: The investigator or site personnel should make sure the participant's glucose meter and test strips are functioning accurately and that the test procedure is being correctly performed by the participant prior to discontinuation from study medication.

- Abnormal liver function tests meeting criteria (see Appendix 10 for additional details on management and discontinuation of blinded investigational product for participants with elevated liver enzymes):
    - ALT or AST ≥3X ULN with total bilirubin ≥2X ULN and alkaline phosphatase (ALP) <2X ULN, and without established etiology; OR
    - ALT or AST ≥8X ULN or ≥3X ULN with symptoms consistent with liver injury and without an established etiology; OR
    - ALT or AST ≥5X ULN for 2 weeks or longer; OR
    - ALT or AST ≥3X ULN and participant is unwilling or unable to undergo repeat ALT and AST testing at the frequency defined in Appendix 10
- eGFR is consistently <45 mL/min/1.73 m^2 with no other explanation.

  Note 1: The eGFR cutoff for discontinuing study medication should be consistent with the local label for ertugliflozin if it is different from above.

  Note 2: A consistent value is defined as a repeat measurement within 14 days of notification from the central laboratory.
- Requirement for 1 of the excluded medications listed in Section 6.5.
- Pregnancy

  Note: A positive urine pregnancy test requires immediate interruption of study medication until serum hCG can be performed and found to be negative. Participant must be permanently discontinued from study medication and followed per Section 8.4.5, if pregnancy is confirmed by a positive serum pregnancy test. If the serum pregnancy test is negative, blinded study medication should be resumed and the participant should be counseled about appropriate contraceptive measures.
- Participant develops any condition for which ertugliflozin, metformin, or insulin is contraindicated according to the approved labels in the country in which the study site is located.
- Participant has a clinically confirmed event of ketoacidosis

  Note: If the participant has a suspected event of ketoacidosis, study medication should be interrupted.
- Consider interrupting blinded study medication in clinical situations known to predispose to ketoacidosis (refer to the IB).

- If study medication is interrupted, it should be re-initiated if the clinical situation resolves in ≤14 days. If resolution takes more than 14 days, consultation with the Sponsor is required prior to re-initiating study medication.

- Participant develops a hypersensitivity reaction to study medication.

- Participant develops any medical condition or personal circumstance which, in the opinion of the investigator, exposes the participant to risk by continuing on study medication or does not allow the participant to adhere to the requirements of the protocol.

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study intervention is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent, and assent if applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

8.1 Administrative and General Procedures

8.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent, and assent if applicable, from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent/assent is in place.

8.1.1.1 General Informed Consent/Assent

Consent/assent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent/assent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent/assent form should be given to the participant before participation in the study.

The initial informed consent/assent form, any subsequent revised written informed consent/assent form, and any written information provided to the participant must receive the

Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent/assent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent/assent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The assent, as applicable will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

If the participant's legally acceptable representative is illiterate, an impartial witness will be present when the entire ICF and other written information are read and explained. The impartial witness will sign and date the ICF indicating that the explanation of the written information was accurate, consent by the participant's legally acceptable representative was given freely and the participant's legally acceptable representative verbally acknowledged that they understood the information. Assent must be documented by the dated signature of the participant along with the dated signature of the person conducting the assent discussion.

When the study population includes non-English speaking people, the information in the consent and assent forms will be translated and communicated to the participant in language understandable to the participant and participant's legally acceptable representative. Either the investigator or Sponsor may take the responsibility for the translation; however, documentation must exist to demonstrate who performed the translation and the translation was verified by an individual other than the person who performed the translation. Accurately translated consent and assent forms will be provided with a written statement by the translator (whether the translator is the investigator or a professional translator), indicating that the consent and assent forms are an accurate translation of the accompanying English version.

8.1.1.2 Consent/Assent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent/assent to the participant, answer all of his/her questions, and obtain written informed consent/assent before performing any procedure related to future biomedical research. A copy of the informed consent/assent will be given to the participant.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent/assent. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The use of tobacco will be collected as part of medical history. Additionally, for male participants, sites must indicate if the participant is circumcised or uncircumcised.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use. The site may rely on the participant's report for this information. Please refer to the data entry guidelines for details on entering prior medications.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication taken by the participant during the study.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the **Screening Visit/Visit 1** requirements are provided in Section 8.10.2.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the

participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

8.1.8 Study Intervention Administration

Study medication will begin on the day of treatment randomization or as close as possible to the date on which the participant is assigned.

8.1.8.1 Timing of Dose Administration

Participants will be instructed to take study medication orally at approximately the same time of the morning with or without food from **Visit 3/Day 1/Randomization** through **Visit 8/Week 54** or discontinuation of study medication. Participants will be instructed **NOT** to take study medication the morning of each site visit.

If a participant misses a dose of study medication, he/she will be instructed to take it as soon as he/she remembers unless it is time for the next dose. Participants will be instructed **NOT** to 'make up' for the missed dose by taking 2 doses at the same time.

8.1.8.2 Witnessed Dose

Administration of study medication will be witnessed and documented at select study visits (including time of administration – see Section 1.3) by the investigator and/or study staff ***after*** completion of all study procedures including collection of all fasting blood samples.

8.1.8.3 Dispense Single-Blind Placebo Treatment

Eligible participants will be dispensed single-blind placebo and instructed to take 1 tablet orally per day from each row (total of 2 tablets) at approximately the same time of day in the morning with or without food. The last dose of single-blind placebo will be taken on the day prior to Randomization. Refer to Section 8.10.3 for further details.

8.1.8.4 Dispense Double-Blind Study Treatment

Participants will be dispensed double-blind study treatment (ertugliflozin or matching placebo) at study visits outlined in the SoA and instructed to take the double-blind study treatment once a day, orally, at approximately the same time of the morning with or without food (refer to Section 8.1.8.1).

8.1.8.5 Evaluation of Study Treatment Compliance

Participants will be directed to bring any unused study medication to the **Visit 3/Day 1/Randomization Visit**. The investigator must maintain a complete and current accountability record for the blinded study treatment.

Compliance with the single-blind placebo treatment will be monitored by study personnel at the site at the end of the single-blind placebo run-in period by comparing the returned

product with the amount dispensed and the information reported by the participant. The number of tablets issued minus the number of tablets returned will be used to calculate tablets taken according to the formula below.

$$\text{Compliance (\%)} = \frac{100 \times (\text{tablets dispensed} - \text{tablets returned})}{\text{No. of days between visits} \times \text{No. of tablets taken per day}}$$

Participants who are <80% compliant based on pill count with the single-blind placebo treatment are ineligible for randomization (**Visit 3/Day 1/Randomization**).

During the remainder of the study, compliance with ertugliflozin and matching placebo will be assessed by site review of the blister cards and participant report. Every effort should be made to maintain adherence as close to 100% as possible.

The investigator or designee will counsel participants who report taking <85% of the blinded study treatment following randomization. The investigator or designee will determine factors that resulted in <85% compliance with the blinded study treatment and will take steps to improve compliance (Section 6.4). Participants will be counseled on the importance of taking their medication as prescribed. Participants counseling will be documented in the source documents.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period will complete all applicable activities scheduled for the Discontinuation Visit (Section 8.10.8) and should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.10.8.

When a participant withdraws from participation in the study, all applicable activities scheduled for the **Discontinuation Visit** (Section 8.10.8) should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

Discontinuation Visit procedures need not be performed if the participant has had Visit 6 or a Discontinuation Visit (due to discontinuation of study intervention) within the last 4 weeks.

8.1.9.1 Withdrawal From Future Biomedical Research

A participant’s consent for Future Biomedical Research may be withdrawn by the participant or the participant’s legally acceptable representative (as appropriate) and their specimens and all derivatives destroyed. A participant’s consent may be withdrawn at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request

for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that this is required for participant safety.

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.1.12 Dispense Glucose Meters, Blood Glucose Assessment Tools, and SMBG Instructions

Glucose meters will be supplied to all participants (if needed) and both the participant and legally acceptable representative will be instructed on the procedure for performing FSG measurements. At a minimum, the participant and legally acceptable representative will be instructed to monitor and document FSG values (1) once daily with at least 2 fasting (before breakfast) measurements each week, (2) whenever the participant has symptoms of hypoglycemia (Section 6.5.1), and (3) during intercurrent illnesses. For participants on insulin (as background therapy or as rescue/intensification during the study), the investigator will counsel the participant and legally acceptable representative on the recommended frequency of home glucose monitoring based on locally accepted clinical practice guidelines. The Blood Glucose Assessment Tools should also be completed when the participant is away from home.

Note: The Blood Glucose Assessment Tools do not need to be dispensed during Discontinuation/Withdrawal from the Study Visit.

8.1.13 Instruct on Hypoglycemia Symptoms and Management

The site will review the symptoms and management of hypoglycemia with the participant and legally acceptable representative. The site will counsel the participant and legally acceptable representative to immediately perform an FSG measurement if any symptoms occur that may be related to hypoglycemia (eg, weakness, dizziness, shakiness, increased sweating, palpitations, or confusion), but also to avoid delay in treating these symptoms.

The participant and legally acceptable representative will be instructed to complete the provided blood glucose assessment tools provided for any symptomatic episodes he or she believes may represent hypoglycemia. If an FSG has been obtained before or shortly (ie, within a few minutes) after treating, the value will be recorded in the blood glucose assessment tools. In addition, participants and legally acceptable representatives will be instructed to record any FSG values ≤70 mg/dL (3.9 mmol/L) on the blood glucose assessment tools regardless of the presence of clinical symptoms.

Participant and legally acceptable representatives will be instructed to contact the investigational site to report:

- Any episode of possible hypoglycemia resulting in symptoms
- Any episode of hypoglycemia for which assistance was required (ie, severe hypoglycemia, details provided on the blood glucose assessment tools)
- Any episode of FSG ≤70 mg/dL (3.9 mmol/L) with or without symptoms

Note: As indicated, the participants will record symptoms and/or FSG measurements that they believe are related to hypoglycemia on the blood glucose assessment tools with the assistance of the legally acceptable representative. Each episode will be evaluated by the investigator and recorded on the appropriate eCRF. For episodes determined to be hypoglycemia (symptomatic or asymptomatic), and for all glucose values ≤70 mg/dL (3.9 mmol/L), regardless of whether they are considered an AE, the HA eCRF must also be completed. Each event of symptomatic hypoglycemia must be reported as an AE on the AE eCRF. Each episode of asymptomatic hypoglycemia considered by the investigator to be an AE will also be reported on the AE eCRF (refer to Appendix 3 for guidance on reporting).

Participants on Background Insulin Therapy

The dose of insulin will be down-titrated or interrupted if, in the opinion of the investigator, the hypoglycemia occurred in the absence of a readily apparent cause or precipitating factor. Further management of insulin doses will be at the investigator's discretion.

8.1.14 Second Randomization

At **Visit 5/Week 12**, all participants will have an FS A1C measured at the site (Section 8.3.8.1). Participants will undergo a second randomization as outlined in the SoA ***if*** their FS A1C is ≥7.0% (53 mmol/mol). At this second randomization, eligible participants on ertugliflozin 5 mg will be assigned to continue on the 5 mg dose or up-titrate to the ertugliflozin 15 mg dose in a 1:1 ratio. Eligible participants in the placebo group will participate in the second randomization, but all will remain on placebo and be mock-titrated to preserve blinding. Note: The up-titration criteria for participants on insulin will include a FFSG ≥110 mg/dL (6.1 mmol/L) in addition to A1C ≥7.0% (53 mmol/mol) at **Visit 5/Week 12**. Participants who do not meet the threshold(s) for a second randomization will continue on ertugliflozin 5 mg/placebo. If a participant discontinues study medication before **Visit 5/Week 12**, the second randomization (and related assessments) should not be performed.

At **Visit 5/Week 12**, a second allocation number will be randomly assigned by the IRT system for participants on ertugliflozin 5 mg who meet up-titration criteria. During the study, only the unblinded statistician will have access to this allocation number and its associated treatment assignment. Participants who undergo the second randomization will retain their initial randomization number assigned at **Visit 3/Day 1/Randomization** to uniquely identify them by blinded personnel during the study.

The unblinded statistician who supports the DMC described in Section 9.7 will review the number of participants randomized to the ertugliflozin 5 mg and ertugliflozin 15 mg group at the **Visit 5/Week 12** second randomization and throughout the study. Based on the distribution of participants within the ertugliflozin 5 mg and 15 mg arms, the randomization ratio for the second randomization at **Visit 5/Week 12** may be adjusted in order to achieve approximately 30 participants in the ertugliflozin 15 mg arm.

8.2 Efficacy Assessments

8.2.1 Body Weight

Body weight will be measured using a standardized digital scale. Details on measuring body weight are below.

- Weight will be measured ***in duplicate*** throughout the study, after voiding (ie, forced void), and while wearing only a gown and underwear (no street clothes, no shoes or socks). Investigator sites without access to gowns will weigh participants in light clothing.

- Participants will be instructed to step gently onto the scale, place both feet together in the center of the scale and stand straight with eyes directed ahead. Participants will be instructed to stand still and not sway. Measurements will be recorded after the weight has stabilized.

- The 2 measurements will be recorded in the source documents. If the 2 measurements differ by more than 0.2 kg or by 0.4 lb, (1) check the participant to ensure proper positioning as indicated above (2) a different set of duplicate measurements must be obtained, and the 2 new measurements will be recorded in the source documents. The average of the 2 measurements will be recorded in the eCRF.

Follow the manufacturer's manual for accuracy checks of the scale as required. Contact the Sponsor if supplies are required to perform accuracy checks, or if calibration is required, or for a replacement if the scale is malfunctioning.

8.2.2 Waist Circumference

Tension-controlled measuring tapes will be used to measure waist circumference. The tape measure will be a non-stretching, non-metallic retractable tape.

The tape is placed around the participant's trunk at the appropriate level for waist measurement. The tape's "zero line" is aligned alongside of the tape graduations on the Metric side of the tape. The zero end of the tape is held in the left hand above the remaining part of the tape held by the right hand. The measurement is read next to the tape's "zero line" and recorded in centimeters to the nearest millimeter.

Waist circumference will be measured according to the National Health and Nutrition Examination Survey (NHANES) III protocol. Measuring tapes may be provided by the

Sponsor. **It is advisable that the participant's waist be measured by the same study personnel at each visit to maintain consistency.** Waist circumference will be measured after voiding, in gown, underwear and socks but without shoes.

To define the level at which waist circumference is measured, a bony landmark is located and marked. The participant stands and the examiner, positioned at the right of the participant, palpates the upper hip bone to locate the right iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn using a black pen, and then crossed with a vertical mark on the midaxillary line. The measuring tape is placed in a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor and the tape is snug but does not compress the skin. The measurement is made at the end of normal minimal respiration (in duplicate). **Measurements will be collected until 2 consecutive measurements do not differ by more than 1 cm.** The average of these 2 measurements will be reported.

8.2.3 Height

Height will be measured without shoes, using a stadiometer or other appropriate device.

Standing height will be assessed through maximum vertical stature for persons who can stand unassisted. Hair ornaments, barrettes, braids, jewelry, or cornrows will be moved or removed from the top of the head before the measurement is taken.

A fixed stadiometer with vertical backboard, fixed floorboard and movable headboard will be used. Participants will stand with the heels of their feet against the vertical backboard with feet pointing outward at approximately a 60-degree angle. Body weight will be distributed evenly with both feet flat on the floor. The examiner will check several contact points with the vertical backboard, including heels, buttocks, shoulder blades, and the back of the head. This may be difficult for participants with certain body shapes. However, the head should be in the Frankfort plane (an imaginary line from the ear canal to just below the lower orbit of the eye will be parallel to the floor). Participants will be looking straight ahead and be asked to take a deep breath and stand tall. Once the participant is positioned, the headboard or a flat ruler will be placed on top of the head, with sufficient pressure to compress the hair. The measurement is recorded in centimeters (cm), to the nearest millimeter (mm). Measurements will be collected until 2 consecutive measurements do not differ by more than 2.5 cm from each other. The final height measurement must be recorded. Some participants may have physical conditions that may limit the ability to measure height accurately (eg, kyphosis). In such cases, height will be measured to the best of the examiner's ability, and a note will be made of the condition.

8.2.4 BMI Percentile

The following equation will be used to calculate BMI:

$$\text{BMI} = \frac{\text{Body weight in kilograms}}{(\text{height in meters})^2}$$

Sites will follow their approved country-specific BMI-for–age percentile charts. If none are available, refer to Appendix 8.

8.2.5 Vital Signs

Vital sign measurements include a triplicate measurement of sitting blood pressure and pulse rate. Blood pressure and pulse rate will be measured using an automated, oscillometric blood pressure measuring device. Site personnel will use the same blood pressure measuring device throughout the study for each participant.

The following method will be used to record sitting blood pressure and pulse rate for participants in triplicate:

- Participants will refrain from nicotine-containing products and/or ingesting caffeine for at least 30 minutes preceding the measurements.
- Participants will be seated in a chair with their back supported, feet flat on the floor and arm bared (free of restrictions such as rolled up sleeves) and supported at heart level.
- The appropriate cuff size must be used to ensure accurate measurement. Each participant's cuff size will be noted in his/her source file to assure the same cuff size is used throughout the study.
- Measurements will be taken on the same arm at each visit (preferably the non-dominant arm).
- Measurements will begin after at least 5 minutes of rest.
- The 3 measurements of both the blood pressure and pulse rate must be taken approximately 2 minutes apart with the triplicate set recorded in the source document and the average of the 3 measurements recorded in the eCRFs.
- Assessment of pulse rate can be manual (rather than using an automated device); however, when done manually, pulse rate must be measured in the brachial/radial artery for at least 30 seconds.

Other procedures will not be performed during the time of the blood pressure and pulse rate measurements.

8.2.6 Laboratory Measurements for Efficacy

Efficacy measurements include laboratory assessment for A1C and FPG. See Appendix 2 for additional details.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical exam will be performed at the visits indicated in the SoA. Abnormalities considered clinically significant will be reported as AEs.

8.3.2 Diet and Exercise Counseling and Monitoring

Participants and legally acceptable representatives will be counseled to maintain a medically appropriate, routine exercise program; consistency and adherence to the recommended regimen of diet and exercise will be encouraged throughout the study, with monitoring of diet and exercise occurring at each scheduled study visit as outlined in Section 1.3. Detailed dietary and exercise information will not be captured in the study database.

8.3.3 Tanner Staging

Tanner Staging will be performed in order to assess the physical measurements of sexual development (testicular volume and pubic hair in males and breast and pubic hair in females). Refer to Appendix 13.

Note: If at any of the evaluations, the participant's sexual maturation (for testicular volume, pubic hair, or breast) is assessed as being Tanner Stage V, no further evaluations of that parameter are needed during the study.

8.3.4 Abdominal Ultrasound

Abdominal ultrasounds will be performed at the visits indicated in the SoA. The abdominal baseline ultrasound is to be performed at **Visit 2/Week -1** or between **Visit 2/Week -1** and **Visit 3/Day 1/Randomization**. The abdominal baseline ultrasound must be successfully submitted to and pass a quality check by the central imaging vendor ***before*** **Visit 3/Day 1/Randomization**. If necessary, the placebo run-in period can be extended by a week to ensure an acceptable abdominal ultrasound is on file before **Visit 3/Day 1/ Randomization**.

If the **Visit 8/Week 54** or **Discontinuation Visit** abdominal ultrasound does not pass quality check, an acceptable abdominal ultrasound must be submitted within 2 weeks.

An independent reviewer will assess all ultrasounds for nephrocalcinosis.

If Discontinuation Visit procedures are not performed for a participant due to a site visit within 4 weeks (Section 8.1.9), an abdominal ultrasound will be performed if it was not performed at the site visit.

All ultrasounds will also be read locally to assess for any clinically relevant abnormalities. If any clinically relevant abnormality is detected, the site will be informed, and the participant will be followed up by the physician; the abnormality may be reported as an AE.

Abdominal ultrasound will be performed on all participants and images will be submitted to a central imaging vendor. The central imaging vendor will conduct a blinded independent central review (BICR). The BICR will not be done in real time. Details will be provided in the site imaging manual.

8.3.5 Electrocardiograms

A single supine 12-lead ECG will be obtained for screening purposes at the timepoint noted in the SoA. The ECG ***must*** be evaluated for study eligibility ***before*** **Visit 3/Day 1/ Randomization**.

- Participants will refrain from nicotine-containing products and/or ingesting caffeine for at least 30 minutes preceding the procedure.

- 12-lead ECGs will be performed after the participant has rested quietly **for at least 10 minutes** in a supine position.

12-lead ECGs will be obtained prior to the nominal time assessment of blood pressure, and pulse rate as well as prior to blood collection.

The ECG will be read and interpreted at the investigative site. The investigator is responsible for retaining all copies of ECG reports. ECGs with abnormalities that do not preclude exclusion of the participant should be entered into the appropriate eCRF.

8.3.6 Review of SMBG Measurements and Blood Glucose Assessment Tools

SMBG measurements and the blood glucose assessment tools will be reviewed at the site visits and telephone contacts outlined in the SoA. They will be used to determine the need for an **Unscheduled Visit** to evaluate criteria for glycemic rescue/intensification (Section 6.5.1), to assess for events of hypoglycemia, and to determine need for discontinuation from blinded study medication due to hypoglycemia.

8.3.7 Review Rescue Criteria and Assess Need for Glycemic Intensification

The participant and legally acceptable representative will be informed of the FFSG rescue/intensification threshold that is applicable until the next visit (Table 3 and Table 4) and will be instructed to call the site if the FFSG value is greater than the threshold on 3 consecutive days (see Section 6.5.1).

Participants should not undergo glycemic rescue at an **Unscheduled Visit** between **Week 10** and **Visit 5/Week 12** (see Section 6.5.1).

Additionally, at **Visit 5/Week 12,** participants who are eligible for the second randomization should **NOT** undergo glycemic rescue even if they meet the specified criteria. Instead, these participants should be advised to check FFSG measurements every day for the next 2 weeks and glycemic rescue therapy should be initiated 2 weeks after **Visit 5/Week 12** if they continue to meet the prespecified thresholds (Table 3).

Note: The participant will be telephoned weekly in-between visits if insulin is initiated/up-titrated until blood glucose and insulin doses are stable.

8.3.8 Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

All laboratory testing will be performed after an overnight fast ≥10 hours in duration, with the exception of **Visit 4/Week 6**. All laboratory tests outlined in the SoA will be performed by the central laboratory with the exception of the site FS A1C, site and participant FFSG, urine ketones (at **Visits 1**, **2**, and **3** only), and urine pregnancy tests. At **Visit 1**, fasting C-peptide will be collected in participants with diabetes for <2 years and all participants on insulin regardless of the duration of T2DM. At **Visits 3**, **6**, and **8**, fasting C-peptide will be collected in all participants.

Glycemic measurements will be masked during the double-blind treatment period for A1C and FPG. However, in order for the investigator to perform an evaluation for possible glycemic rescue/intensification and/or discontinuation, the central laboratory will report to

the investigator in an unmasked manner any FPG laboratory value meeting rescue/intensification and/or discontinuation criteria (Section 6.5.1 and Section 7.1).

Laboratory test results for chemistry (eg, ALT, AST, creatinine, eGFR) will not be masked, but will be flagged by the central laboratory if they meet protocol-specified exclusion and discontinuation criteria (Section 5.2 and Section 7.1).

At or after **Visit 3/ Day 1/Randomization**, ALT and AST elevations greater than or equal to 3x ULN will be flagged by the central laboratory and participants will be retested, according to Appendix 10.

8.3.8.1 Site FFSG and FS A1C Measurements

FFSG values performed at the study site will be used to assess exclusion criteria prior to randomization (**Visit 3/Day 1/Randomization**). The central laboratory A1C ***must*** be used to assess inclusion criteria.

FS A1C will be measured at **Visit 5/Week 12, Visit 6/Week 24, and Visit 7/Week 38**.

Site FFSG ***and*** FS A1C will be used at **Visit 5/Week 12,** on participants on insulin, to determine eligibility for the second randomization.

During the double-blind treatment periods, FFSG values performed at home and/or at the site will be used to determine the need for glycemic rescue/intensification (Section 6.5.1).

8.3.8.2 Site Measured Urine Ketones

Ketones will be checked by the site as outlined in the SoA and during intercurrent illnesses or if the participant's fingerstick blood glucose is >400 mg/dL (22.2 mmol/L) at any time during the study. If urine ketones are "moderate" or "large," or if ketonemia is positive at any time during the study, further assessment is required.

8.3.8.3 Urine Pregnancy Test

All females participating in the study will have a urine pregnancy test at visits indicated in the SoA. If local regulations or guidelines for testing exist, they should be followed in addition to the protocol requirements (for exceptions, see Section 10.7, Appendix 7). If required by an investigational site's Institutional Review Board/Ethics Review Committee (IRB/ERC), a serum pregnancy test can also be obtained in addition to the urine pregnancy test. A positive urine pregnancy test requires immediate interruption of study medication until serum beta-hCG is performed and found to be negative. Participants must be discontinued from study medication and followed (Section 7.1) if pregnancy is confirmed by a positive serum pregnancy test. Contraception assessments and counseling will be performed and documented at every visit as outlined in the SoA (see Appendix 5).

Note: For **Visits 2/Week -1** or **Rescue**, the urine pregnancy test should only be performed if the prior visit is more than 4 weeks apart or if pregnancy is suspected.

8.3.8.4 Archive Urine Sample

A urine sample to be archived will be collected at visits indicated in the SoA. Urine samples will be stored at the Sponsor-designated biorepository.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 5.

Table 5 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in)	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

  *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

- An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

8.4.8 Other Safety Topics of Interest

The following have been identified as other safety topics of interest. Participants with events related to these safety topics of interest will be identified based on prespecified criteria. Narratives will be written for events related to the terms listed below:

1. Renal-related events
2. Hypersensitivity reactions
3. Pancreatitis
4. Bone fractures
5. Ketoacidosis
6. Volume depletion
7. Amputations
8. Diabetic foot syndrome
9. Nephrolithiasis
10. Fournier's gangrene.

8.4.9 Monitor for Adverse Events

The investigator will evaluate all AEs with respect to the elements outlined in Appendix 3. Additionally, all potential ketoacidosis events will be assessed by the Internal Case Review Committee (Appendix 1).

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than 100 mg/day of ertugliflozin or matching placebo or any dose higher than 25 mg/day of ertugliflozin or matching placebo for more than 14 days.

In the event of an overdose, employ the usual supportive measures (eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the participant's clinical status. Removal of ertugliflozin by hemodialysis has not been studied.

Investigators/site personnel are to consult the local, approved metformin product label for guidance on the definition of an overdose and treatment for an overdose of metformin.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

Note: Any overdose (ertugliflozin or metformin) meeting above criteria whether or not associated with an AE must be reported to Sponsor's personnel within 5 calendar days of learning of the event.

8.6 Pharmacokinetics

To evaluate exposure of ertugliflozin 5 mg and 15 mg qd doses in pediatric T2DM participants, blood samples for PK analysis of ertugliflozin concentrations will be collected as shown in the SoA. The ertugliflozin plasma steady state exposure levels will be assessed using the predose PK samples collected at planned visits and times.

8.6.1 Blood Collection for Plasma Ertugliflozin

Blood samples (approximately 1 mL) to provide approximately 0.5 mL of plasma for PK analysis will be collected at visits specified in the SoA. The exact date and time of the blood draw and the date and time of the last dose of investigational product (based on participant's report) relative to that PK sample prior to the blood draw will be captured on the eCRF. The time of the observed dose taken after collection of the PK sample will also be captured on the eCRF. It is important to record the exact actual time of dose and PK sample draw. Site personnel will be trained to remind participants that the accuracy of the actual dose time is critical. Site personnel will also be asked to call on the evening 2 days prior to **Visit 4/Week 6**, **Visit 5/Week 12**, and **Visit 6/Week 24** and again text or call the morning prior to these visits to remind participants to take the morning dose 1 day prior to the visit and record the actual time of the dose.

Detailed instructions for the sample collection, processing, storage and shipment of plasma samples will be provided in the laboratory manual (supplied by the central laboratory).

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Serum for future research
- Plasma for future research
- DNA for future research

8.9 Health Economics

Not applicable.

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.10.1 General Information for Study Visits

Fasting Prior to Screening Visit/Visit 1, Visit 3/Day 1/Randomization, Visit 5/Week 12*, Visit 6/Week 24, Visit 7/Week 38, Visit 8/Week 54, Rescue and Discontinuation Visits

Participants will be counseled to fast (ie, no study medication, no food, no drink except water), for at least 10 hours prior to scheduled study visits that require fasting. Blinded study medication and background study medications (metformin and insulin) should **not** be taken the morning of the clinic visit; other medication(s) may be taken as directed by the prescribing physician.

*Fasting required only for participants on insulin.

Scheduling Visits, Visit Windows, and Study Duration

At the end of each study visit, the next study visit should be scheduled. Every effort should be made to adhere to the visit schedule in the SoA, and generally, visits may be scheduled ±1 week of the designated timepoint (**Visit 7/Week 38** and **Visit 8/Week 54** may be ± 2 weeks). If unavoidable, a visit may be scheduled at a time outside of this recommended range, but the schedule for subsequent visits must be adjusted so that the total duration of the double-blind study period is as close as possible to 54 weeks. The minimum interval between **Visit 2/ Week -1** and **Visit 3/Day 1/Randomization** should be 6 days. In this case, 100% compliance with single-blind placebo treatment will be required for randomization. The maximum interval between **Visit 2/ Week -1** and **Visit 3/ Day 1/ Randomization** should be 14 days, with ≥80% compliance with single-blind placebo treatment required for randomization. If a visit is scheduled at a time other than the protocol designated time, **careful consideration must be given to the amount of study treatment the participant has available.**

Visit Reminders – Telephone Contacts

Prior to each visit, participants will be contacted and reminded of:

- The date and time of appointment.
- The requirement to fast for at least 10 hours prior to **Screening Visit/Visit 1**, **Visit 3/ Day 1/Randomization**, **Visit 5/Week 12**, **Visit 6/Week 24**, **Visit 7/ Week 38**, **Visit 8/Week 54**, **Rescue/Intensification** and **Discontinuation Visits.**

- The requirement to record the time investigational product was taken the day prior to **Visit 4/Week 6**, **Visit 5/Week 12**, and **Visit 6/Week 24**.

- The requirement **not** to take any blinded study medication or background study medications (metformin and insulin) at home the morning of all site visits (except at **Visit 2/Week -1**). Other medication(s) may be taken as directed by the prescribing physician.

- The requirement to bring study medication (ie, double-blind treatment, background, and glycemic rescue/intensification medication), blood glucose meters, blood glucose assessment tools, and any collected SMBG information to the site visit.

- Lifestyle restrictions outlined in Section 5.3.2 and Section 5.3.3.

8.10.2 Screening Visit / Visit 1

At **Screening Visit/Visit 1**, written informed consent from the participant's legally acceptable representative and written assent from the participant must be obtained. Potential participants must be evaluated to determine that they fulfill the entry requirements as specified in protocol Section 5.1 and Section 5.2 and will receive a screening number. All procedures outlined in the SoA must be completed.

At the site, the investigator may choose to prescreen participants with FS A1C measurements (prior to drawing blood samples for central laboratory screening measurements) to evaluate the likelihood of the participants subsequently meeting study glycemic inclusion criteria.

Note: Investigators should be aware that although FS A1C is generally predictive of values measured in the central laboratory, modest differences can occur in individual participants. **Therefore, a FS A1C cannot substitute for a central laboratory measured A1C to determine if a participant meets study A1C inclusion criteria.**

Screening procedures may be repeated (ie, rescreening) **after** consultation with the Sponsor.

8.10.3 Single-Blind Placebo Run-in - Visit 2/Week -1

Participants who are on a stable dose of metformin ± insulin who meet all other enrollment criteria will be eligible to enter the single-blind placebo run-in period.

At **Visit 2/Week -1** the site must perform all procedures for this visit as detailed in the SoA. **The first doses of single-blind placebo (ertugliflozin placebo) will be taken as witnessed doses at the site *after* completion of all Visit 2/Week -1 study procedures.** It is essential that all procedures be performed *before* the participant takes the witnessed dose. Participants will then take single-blind placebo as directed for 1 week prior to Randomization and will continue to take their background medication as before.

8.10.4 Double-Blind Treatment Period – Phase A - Visit 3/Day 1/ Randomization to Visit 6/Week 24

At **Visit 3/Day 1/Randomization**, participants who meet all study enrollment criteria will have all baseline laboratory tests and study procedures performed (refer to the SoA). Assignment of a randomization number occurs at **Visit 3/Day 1/ Randomization**.

The first dose of double-blind study treatment will be taken as a witnessed dose at the site *after* completion of all procedures for the study visit. It is essential that all procedures be performed *before* the participant takes the witnessed dose.

Participants will remain on a stable dose of double-blind study treatment for the duration of the study and will remain on the background medication of metformin ± insulin without changes in the doses (except for reductions in insulin dose if the participant experiences hypoglycemia, see Section 6.5.1). The double-blind study treatment must be taken orally in the morning with or without food at approximately the same time each day. For missed doses see Section 8.1.8.1.

During Phase A, at **Visit 5/Week 12**, eligible participants will undergo a second randomization (see Section 8.1.14).

Note: For **Visit 4/Week 6**, **Visit 5/Week 12**, and **Visit 6/Week 24**, collect the time at which study medication was taken the day **before** the site visit **and** the time the dose was taken the day of the site visit and report on the appropriate eCRF.

If a participant discontinues study medication in Phase A but agrees to continue in the study, the participant's diabetic care will be handled by the participant's primary diabetes doctor or the investigator outside of this protocol. The study-site personnel will only collect assessments specified in the SoA.

Telephone Call Week 18

The **Week 18 Visit** is a telephone call visit. The site will call the participant/participant's legally acceptable representative and will complete all procedures indicated in the SoA. All AEs, changes in concomitant medication, and any hypoglycemia events will be documented in the appropriate eCRFs.

8.10.5 Double-Blind Treatment Period – Phase B - Visit 6/Week 24 Through Visit 8/Week 54

The first dose of Phase B double-blind study treatment will be taken as a witnessed dose at the site *after* completion of all procedures for the Visit 6/Week 24 study visit. It is essential that all procedures be performed *before* the participant takes the witnessed dose.

Participants Who Have *Not* Been Rescued During Phase A will continue on their double – blind study treatment and will initiate glycemic intensification as outlined in Table 2 if their

FFSG is >130 mg/dL (7.2 mmol/L) and their FS A1C is >7.5% (58 mmol/mol) (Table 4, Section 6.5.1).

Participants Who Have Been Rescued During Phase A will continue on their double – blind study treatment and background medication of metformin + insulin (for rescue). Insulin doses will be titrated based on glycemic responses at the investigator's discretion.

If a participant discontinues study medication in Phase B but agrees to continue in the study, the participant's diabetic care will be handled by the participant's primary diabetes doctor or the investigator outside of this protocol. The study site will only collect the assessments specified in the SoA.

Telephone Call Week 30 and Week 44

Week 30 and **Week 44** are telephone call visits. The site will call the participant/participant's legally acceptable representative and will complete all procedures indicated in the SoA. All AEs, changes in concomitant medication, and any hypoglycemia events will be documented in the appropriate eCRFs.

8.10.6 Study Visits Performed at Home

Visit 4/Week 6 and **Visit 7/Week 38** may be performed, if approved by the country and local IRB/IEC, by a qualified health professional at the participant's home or location other than the site. These visits may be performed according to the guidelines that may exist at the participating institution and will be consistent with the investigator's usual clinical practice.

8.10.7 Rescue/ Intensification Visit

Participants who require rescue therapy or intensification therapy per Section 6.5.1 must have glycemic rescue/intensification therapy initiated at either a scheduled or unscheduled site visit and not by a telephone call. At the **Rescue Visit**, all laboratory testing will be performed after an overnight fast ≥10 hours in duration and all procedures outlined in the SoA are to be completed.

Participants should not undergo glycemic rescue at an **Unscheduled Visit** between **Week 10** and the site visit at **Visit 5/Week 12** (Section 6.5.1).

8.10.8 Discontinuation Visit

The Sponsor should be contacted when a participant discontinues study medication, withdraws from the study, or interrupts study medication because of an AE or a laboratory safety test abnormality. All participants will be followed up until resolution (ie, return to normal or participant's baseline, diagnosis determined, or course of abnormalities established) for any laboratory safety test abnormality resulting in discontinuation.

All participants who discontinue study medication prior to completion of the protocol-specified treatment period will be encouraged to continue their participation in the study off study medication and be followed for all remaining study visits as outlined in the SoA.

At a **Discontinuation Visit**, all laboratory testing will be performed after an overnight fast ≥10 hours in duration and all procedures outlined in the SoA are to be completed. **Discontinuation Visit** procedures will be performed on participants who discontinue study medication or discontinue the study as soon as possible after discontinuing study medication (within 4 weeks).

If a participant discontinues study medication before **Visit 5/Week 12**, the second randomization (and related assessments) should *not* be performed.

8.10.9 Mandatory Poststudy Telephone Follow-up

For all participants (except for those who withdraw consent), a poststudy telephone follow-up call will be performed 14 days after the last dose of study medication (whether due to study completion or premature discontinuation from the study) to assess and collect information on AEs, SAEs, and any other reportable safety events that occurred after the administration of the last dose of study medication. The date of the telephone contact will be recorded and any events that have occurred will be recorded in the AE eCRF.

If any event requires supplemental procedures, they will be performed as medically necessary and recorded in the applicable eCRF.

8.10.10 Follow Up of Participants Who Have Discontinued Study Medication Prior to Study Completion

After the 14-day post-study medication discontinuation telephone contact is made, activities scheduled in the SoA will be performed for participants who discontinued study medication, but agreed to remain in the study. No follow-up telephone call is needed after Week 54.

Note: Study-site personnel should make all reasonable efforts to counsel the participant to stay in the study even if they discontinued the study medication.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 to 9.12.

Statistical Analysis Plan Summary

Study Design Overview	Ertugliflozin T2DM Pediatric Study
Treatment Assignment	Participants will be randomized in a 2:1 ratio to the ertugliflozin 5 mg group or placebo group. Randomization will be stratified by age (10 to 14 years of age, 15 to 17 years of age) and insulin use (No, Yes). A second randomization at Visit 5/Week 12 will randomize eligible participants (Section 6.1) in the ertugliflozin 5 mg group in a 1:1 ratio to continue on ertugliflozin 5 mg or up-titrate to ertugliflozin 15 mg. The second randomization will be stratified by insulin use (No, Yes). An IA to assess PK may result in dropping the 15 mg dose group. If this occurs, the second randomization will be discontinued and the participants in the 15 mg group will be down-titrated to the 5 mg dose for the remainder of the study.
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Participants as Treated (APaT)
Primary Endpoint	A1C: Change from baseline at Week 24
Secondary Endpoints	A1C: Change from baseline at Week 54 FPG: Change from baseline at Week 24 and at Week 54
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The primary hypothesis will be evaluated by comparing ertugliflozin (combined 5 mg and 15 mg doses) to placebo with respect to A1C change from baseline at Week 24. The treatment policy (TP) estimand is expected to be considered primary in some regions. In all other regions, the Treatment Effect (TE) estimand will be primary. The TP estimand will estimate the difference in change from baseline means comparing the effect of being randomized to ertugliflozin versus placebo whereas the TE estimand will estimate the effect of being treated with ertugliflozin versus placebo. The primary analysis approach for the TP estimand will evaluate the treatment difference via a Bayesian borrowing approach using an informative prior distribution derived from a completed adult study of ertugliflozin (MK-8835 P007) and with missing Week 24 A1C data imputed using a Retrieved Dropout (RD) or Washout Imputation (WI) approach. The weight given to the adult prior distribution for the primary hypothesis test will be 0.134. The primary analysis approach for the TE estimand will evaluate the treatment difference via a frequentist analysis using a constrained longitudinal analysis model (cLDA). The key secondary hypotheses will be assessed using an ANCOVA model after imputing missing data using RD or WI. These hypotheses will be tested under only the TP estimand and will apply weights to the treatments as follows: • Participants on placebo have a weight of 1 • Participants on ertugliflozin 5 mg who were not re-randomized at Visit 5/Week 12 have a weight of 1 For the hypothesis comparing the addition of ertugliflozin, with dosing optimized according to A1C response, to the addition of placebo, the weights for the re-randomized participants will be defined as follows: • Participants who were re-randomized to 15 mg at Visit 5/Week 12 have a weight of 2

	• Participants who were re-randomized to 5 mg at Visit 5/Week 12 have a weight of 0. For the hypothesis comparing ertugliflozin 5 mg with placebo the weights for the re-randomized participants will be defined as follows: • Participants who were re-randomized to 5 mg at Visit 5/Week 12 have a weight of 2. • Participants who were re-randomized to 15 mg at Visit 5/Week 12 have a weight of 0.
Statistical Methods for Key Safety Analyses	P-values (Tier 1 AEs) and 95% confidence intervals (CI) (Tier 1 and Tier 2 AEs) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen (M&N) method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	When ~30 participants on study medication (~20 participants on ertugliflozin) complete Visit 4/Week 6, the PK IA will be conducted to confirm ertugliflozin exposure. Details are provided in Section 9.7.
Multiplicity	The type 1 error rate for the Bayesian methodology addressing the primary hypothesis under the TP estimand was estimated via simulation to be 0.10. If the success criterion for the primary hypothesis (H1) is met under the TP estimand, then hypotheses H2 will be tested at alpha = 0.05. If H2 is successful then H3 will be tested at alpha = 0.05. The overall study wise type 1 error rate will be greater than 0.05 [Maurer, W. and Bretz, F. 2013].
Sample Size and Power	The planned sample size is approximately 165 participants with 55 participants in the placebo group and 110 participants in the ertugliflozin group (ertugliflozin 5 mg and 15 mg groups combined). Assuming that approximately 96.1% of participants will have data at Week 24 on study medication, this sample size will provide approximately 80% power (percent of posterior credible intervals <0) to detect a between-group difference in A1C change from baseline at Week 24 of -0.6% given a standard deviation of 1.5% under the TP estimand with RD imputation. Under the TE estimand using the cLDA method, the planned sample size provides 80% power assuming the difference in A1C change from baseline at Week 24 is -0.75% using a standard deviation of 1.5% and missing data due to discontinuation from study medication or censoring due to initiation of glycemic rescue or intensification is at most 14%. The power for each secondary hypothesis is approximately 74% for the TP estimand.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented by the IRT vendor.

Blinding issues related to the planned IA are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypotheses are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

The baseline value will be defined as the **Visit 3/Day 1/Randomization** measurement. If this measurement is not available, the last available pre-treatment value will be used. If no pre-treatment measurement is available, the baseline value will be treated as missing.

9.4.1 Efficacy Endpoints

The descriptions of the efficacy measurements and timepoints at which they are measured are described in Section 8.2 and Section 1.3. The efficacy endpoints to be analyzed are listed in Table 6.

The mapping of relative day ranges to Week is provided in Appendix 11.

Table 6 Efficacy Variables/Endpoints

Primary
Change from Baseline in A1C at Week 24 (pooled ertugliflozin 5 mg and 15 mg versus placebo)
Key Secondary
Change from Baseline in A1C at Week 24 (dose-optimized ertugliflozin versus placebo, and ertugliflozin 5 mg versus placebo)
Secondary
Change from Baseline in A1C at Week 54 Change from Baseline in FPG at Week 24 and at Week 54
Exploratory
Change from Baseline in A1C at Week 12 Proportion of participants initiating glycemic rescue therapy by Week 24 Proportion of participants initiating glycemic rescue or intensification therapy by Week 54 Proportion of participants with A1C <7.0% (53 mmol/mol) at Week 54 among those who up-titrated from ertugliflozin 5 mg/day to 15 mg/day At Week 24 and Week 54: Proportion of participants with A1C <7.0% (53 mmol/mol) Proportion of participants with A1C <6.5% (48 mmol/mol) Proportion of participants with A1C <7.0% (53 mmol/mol) among those with a baseline A1C ≥7.0% (53 mmol/mol) Change from Baseline in: • Body weight • BMI percentile • A1C among participants who up-titrated from ertugliflozin 5 mg/day to 15 mg/day • Systolic blood pressure • Diastolic blood pressure • Waist circumference • Waist circumference to height ratio
A1C = glycosylated hemoglobin; BMI = body mass index; FPG = fasting plasma glucose.

9.4.2 Safety Endpoints

The descriptions of the safety measurements and timepoints at which they are measured are described in Section 8.3 and Section 1.3. The safety endpoints to be analyzed are listed in Table 9. Safety analyses will be conducted across Week 0 to Week 54 (Phase A+B) with selected analyses also done across Week 0 to Week 24 (Phase A).

Events of symptomatic hypoglycemia, AEs associated with genital mycotic infection (gender specific), hypovolemia, and UTI are considered Tier 1 events.

Hypoglycemia will be described using the following definitions:

- Symptomatic hypoglycemia: Episodes with clinical symptoms reported by the investigator as hypoglycemia (biochemical documentation not required).
- Severe hypoglycemia: Episodes that required assistance, either medical or non-medical. Episodes with a markedly depressed level of consciousness, a loss of consciousness, or seizure will be classified as having required medical assistance, whether or not medical assistance was obtained.
- Documented symptomatic hypoglycemia: Episodes with clinical symptoms attributed to hypoglycemia with a glucose level ≤70 mg/dL (3.9 mmol/L) or <54 mg/dL (3.0 mmol/L).
- Asymptomatic hypoglycemia: Episodes without symptoms attributed to hypoglycemia, but with a documented glucose level ≤70 mg/dL (3.9 mmol/L) or <54 mg/dL (3.0 mmol/L).
- Documented hypoglycemia (symptomatic and asymptomatic): Episodes with a glucose level ≤70 mg/dL (3.9 mmol/L) or <54 mg/dL (3.0 mmol/L), with or without symptoms.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The FAS population will serve as the primary population for efficacy analyses. The FAS population will include all randomized participants who took at least one dose of study treatment.

For exploratory analyses in those who up-titrated from ertugliflozin 5 mg/day to 15 mg/day, participants will be counted only if they received at least one tablet of ertugliflozin 15 mg/day after the second randomization at Visit 5/Week 12.

For analyses that require a baseline value, participants with a missing baseline value will be excluded. All participants randomized within the incorrect stratum for insulin use will be classified according to their intended stratum (ie, the stratum to which they should have been randomized) in all analyses that include the stratification factor. The intended stratum will be

derived based on insulin use at Visit 1/Screening. An accounting of incorrectly stratified patients will be provided in the CSR.

9.5.2 Safety Analysis Populations

Safety analyses will be performed in the APaT population consisting of all randomized participants who received at least one dose of study treatment and will include participants in the ertugliflozin 15 mg dose group, regardless of the outcome of the PK IA.

At least 1 laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Safety analysis will be based on observed data only. No imputation will be performed for missing data.

9.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. Nominal p-values (ie, unadjusted for multiplicity) may be computed for other efficacy analyses for descriptive purposes rather than for assessing statistical significance.

The primary approach for all efficacy and safety analyses will pool participants from both ertugliflozin dose groups (5 mg and 15 mg) for comparison with placebo. In addition, A1C change from Baseline at Week 24 will be compared for 2 treatment strategies, (1) dose-optimized ertugliflozin versus placebo and (2) ertugliflozin 5 mg versus placebo. Dose-optimized ertugliflozin consists of participants who were randomized to ertugliflozin and either did not meet the re-randomization criterion at Week 12 or who met the re-randomization criterion and were re-randomized to ertugliflozin 15 mg. Descriptive statistics will be used for efficacy and safety endpoints to summarize ertugliflozin data by dose group and by combined doses. Descriptive statistics will also be used to summarize the individual ertugliflozin dose arms in the subset of participants who were re-randomized at Visit 5/Week 12.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

There will be 2 estimands for the analysis of continuous efficacy endpoints, TP and TE. The primary hypothesis will be tested using both estimands. Based on local regulatory requirements, one of the estimands will be considered primary and the other supplementary. The key secondary endpoints and hypotheses associated with them (H2 and H3) will be analyzed under only the TP estimand.

The TP estimand consists of the following elements:

- Target population: Pediatric patients (age 10 to 17 years, inclusive) with T2DM who meet the glycemic criteria defined in this protocol
- Variable: Change from baseline in A1C at Week 24
- Intercurrent events: Regardless of whether study treatment or rescue medication was taken
- Population level-summary: Difference in means at Week 24
- Treatment Comparison of Interest: The effect of being randomized to ertugliflozin (combined doses) versus placebo.

Analyses corresponding to the TP estimand will include all available data at the Week 24 timepoint, including data after rescue or after the last dose of study treatment in any participants who remain in the study after discontinuing study treatment.

Analyses corresponding to the TP estimand will include all available data at the Week 24 timepoint, including data after rescue or after the last dose of study treatment in any participants who remain in the study after discontinuing study treatment.

The TE estimand consists of the following elements:

- Target population: Pediatric patients (age 10 to 17 years, inclusive) with T2DM who meet the glycemic criteria defined in this protocol
- Variable: Change from baseline in A1C at Week 24 as if all participants remained on treatment
- Intercurrent events: Data obtained after discontinuation of treatment or after taking rescue treatment are not relevant to this estimand
- Population level-summary: Difference in means at Week 24
- Treatment comparison of interest: The effect of taking the randomized treatments (ertugliflozin [combined doses] versus placebo).

The TE estimand will exclude measurements collected more than 5 days after the last dose of study treatment or after other AHA treatments, such as rescue/intensification treatment, are added.

For all efficacy analyses with the exception of exploratory analyses for participants who up-titrated from ertugliflozin 5 mg/day to 15 mg/day, participants will be classified as belonging to the ertugliflozin or placebo group according to their randomized treatment assignment at

Visit 3/Day 1/Randomization regardless of the treatment received during the course of the study.

Any participant randomized at the first or second randomization within the incorrect stratum will be classified according to the intended stratum in all analyses that include stratum. The intended stratum will be derived based on the participant's age and insulin use at Screening Visit/Visit 1 or insulin use at Visit 5/Week 12 as captured in the study database. An accounting of any incorrectly stratified participants will be provided in the CSR.

Week 24

For the primary analysis using the TP estimand, treatment group comparisons for the A1C mean change from baseline at Week 24 will be done using a Bayesian borrowing approach. The Bayesian borrowing approach will be done using an ANCOVA model with treatment, the age and insulin use strata as fixed effects, and the baseline A1C measurement as a covariate with normal priors on the model parameters and a mixture prior distribution on the treatment model effect, δ_p:

$Y_{Week24} \sim N(\beta_0 + \beta_1 * \text{Age} + \beta_2 * \text{Insulin Use} + \beta_3 * \text{Baseline A1C} + \delta_p * \text{Treatment}, \sigma^2)$.

The model parameters for intercept, age, insulin use and baseline A1C will have wide normal prior distributions as follows:

$$\beta_i \sim N(0, 100^2), i = 0,1,2,3$$

The treatment effect parameter will have a mixture normal prior with 2 components: an informative prior mean and variance based on the full ITT population from the 8835-007 study and a general skeptical prior. The prior distribution of δ_p is as follows:

$$\delta_p \,|z = 0 \sim N_{general}\,(0, (1.5*1.5^2))$$

$$\delta_p \,|z = 1 \sim N_{adult}\,(-0.598, 0.066^2)$$

where the weight z has a prior Bernoulli distribution with a parameter, p.

For the primary analysis, a Bernoulli parameter of 0.134 will be used. The skeptical prior variance as well as the mixture prior parameter of 0.134 were selected based on the Effective Sample Size (ESS) metric as defined in Neuenschwander et al. [Neuenschwander, B., et al 2020]. For the variance of the general normal distribution in the mixture prior, an ESS of 3 pediatric participants (2 in ertugliflozin arm and 1 in placebo arm) will be used to ensure the prior is skeptical without being non-informative. A prior parameter with a value of 0.134 was selected to ensure the mixture distribution has an ESS equal to a total of 165 pediatric participants (110 in ertugliflozin arm and 55 in placebo arm). This will ensure that the information borrowed from the mixture prior does not exceed the planned sample size of 165 pediatric participants in the P059 study.

The success criterion for declaring that ertugliflozin (pooled doses) is superior to placebo in reducing A1C at Week 24 is having the upper bound of the posterior 95% credible interval for $\delta_p < 0$.

As a sensitivity analysis, a tipping point-like approach will be used in which the prior weight parameter, p, will be varied from 0 to 1 in increments of 0.05. The point at which the analysis shifts from not significant to significant will be noted.

Data permitting (discussed below), missing data will be imputed using an RD approach which assumes that all missing Week 24 data can be represented by the observed Week 24 data for participants in the same group who discontinued study treatment but remained in the study.

A "retrieved dropout" value is defined as an observed Week 24 value in a participant who discontinued study medication prior to Week 24 but remained in the study. For the RD approach, missing Week 24 values will be imputed as follows:

RD imputation will be done within each treatment arm (placebo or combined ertugliflozin for H1, placebo or dose-optimized ertugliflozin for H2, or placebo or ertugliflozin 5 mg for H3). All Week 24 RD values will be used for imputation, regardless of when a participant discontinued from study medication. CCI

CCI

The RD analysis may not be feasible due to insufficient observed Week 24 data post discontinuation of study medication. If the number of RD participants per group is at least 50% of participants who discontinue from study medication per arm, then RD will be the primary approach to impute missing data for the TP estimand. If at least one group has either less than 50% RD participants or fewer than 5 total RD participants, then RD will not be performed, and WI will become the primary analysis method. If the minimum data requirement for the RD method is met, then WI will be implemented as a sensitivity approach for the TP estimand. The WI analysis assumes participants who prematurely discontinued from the study or who have an intermittent missing Week 24 value would have a 'washout' of any potential effect of the assigned study medication.

CCI

For all analyses involving simulated data, a seed of 8835059 will be used for random number generation.

A constrained longitudinal data analysis (cLDA) model, based on Liang and Zeger [Liang, K.-Y. and Zeger, S. L. 2000], will be used for analyses addressing the TE estimand for A1C mean change from baseline and FPG mean change from baseline. Time will be treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The cLDA model will also adjust for treatment, the age stratum, the insulin use stratum, and the interaction of time by treatment. The cLDA model assumes a common mean across treatment groups at baseline within each age and insulin use category (due to randomization) but different means between categories, and a different mean for each treatment at each of the post-baseline timepoints. In the cLDA model, the response vector consists of baseline and the values observed at each post-baseline timepoint. The treatment difference in terms of mean change from baseline to a given timepoint will be estimated and tested from this model. An unstructured covariance matrix will be used to model the correlation among repeated measurements.

For the cLDA model, the Kenward-Roger adjustment will be used with restricted (or residual) maximum likelihood (REML) to make proper statistical inference. An unstructured covariance matrix will be used to model the correlation among repeated measurements and hence avoids the potential bias that could result from the use of specific structured covariance models. If the unstructured covariance model fails to converge with the default Newton-Raphson algorithm, the Fisher scoring algorithm or other appropriate methods can be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yield convergence, a structured covariance such as Toeplitz can be used to model the correlation among repeated measurements. In this case, the empirical option will be used because the sandwich variance estimator is asymptotically unbiased while the model-based variance estimator can substantially overestimate or underestimate the true variance. The cLDA model uses the maximum likelihood principle to estimate the parameters and account for missing data in an implicit fashion.

Although the baseline measurement is included in the response vector, it is independent of treatment, and hence, the baseline means are constrained to be the same for different treatment groups within the same age and insulin use categories. Of note, in the event that there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal ANCOVA model, which uses the baseline value as a covariate. However, unlike longitudinal ANCOVA, the cLDA model accounts for variability in the baseline values, thus providing more accurate standard errors and CIs for individual treatment effects. Moreover, this model allows the inclusion of participants who are missing either the baseline or post-baseline measurements, thereby increasing efficiency.

The cLDA method assumes that the mechanism for missing data is missing at random (MAR).

<u>Assessment of the Key Secondary Endpoints</u>

The key secondary endpoints will be evaluated under only the TP estimand analysis approach.

All elements of the TP estimands below are the same as the primary TP estimand except for the treatment comparisons:

Treatment comparison of interest:

For H2 - The effect of being randomized to dose-optimized ertugliflozin versus placebo.

For H3 - The effect of being randomized to ertugliflozin 5 mg versus placebo.

Specific weighting schemes will be used to test H2 and H3. The weighting schemes are defined as follows:

- All participants on placebo have a weight of 1
- All participants on ertugliflozin who were not re-randomized at Visit 5/Week 12 have a weight of 1
- For H2 - the hypothesis comparing dose-optimized ertugliflozin to placebo (weighting scheme A):
    - All participants on ertugliflozin who were re-randomized to 5 mg at Visit 5/Week 12 have a weight of 0
    - All participants on ertugliflozin who were re-randomized to 15 mg at Visit 5/Week 12 have a weight of 2
- For H3 - the hypothesis comparing ertugliflozin 5 mg with placebo (weighting scheme B):
    - Participants who were re-randomized to 5 mg at Visit 5/Week 12 have a weight of 2
    - Participants who were re-randomized to 15 mg at Visit 5/Week 12 have a weight of 0

For the key secondary endpoints, treatment group comparisons for the A1C mean change from baseline at Week 24 will be done using an ANCOVA model with treatment, the age and insulin use strata as fixed effects, and baseline measurement as a covariate. Hypotheses H2 and H3 analyses for RD and WI are shown below.

The RD imputation and analysis steps are as follows for H2 and H3 using Rubin's rule for 100 total imputed datasets:

1. Within each imputation sample, do the following:
   a. Impute missing Week 24 values using a normal distribution where the expected change from baseline value is set to the estimated mean change from baseline value from the RD participants in the same treatment group. The standard deviation will be the RMSE derived from the ANCOVA model described above and estimated based on all participants with Week 24 data.
   b. After step a, each of the 100 resulting datasets will contain the original non-missing data and the imputed data for those with missing Week 24 values.

2. The 100 datasets will be analyzed using a weighted ANCOVA model with Baseline A1C and the two stratification factors as covariates. The weights will be defined as listed above and included in the model using the weight option from SAS PROC MIXED. The 100 weighted ANCOVA-based estimates of the treatment difference will be combined using PROC MIANALYZE based on Rubin's rule, which accounts for between and within imputation variability.

The WI imputation and analysis steps are as follows for H2 and H3:

For participants in the ertugliflozin group:

1) Fit a regression model as $Y_{24} = \beta_0 + \beta_1 * Y_0 + \gamma * X + \text{error}$, where Y_0 and Y_{24} are the placebo group A1C values at Baseline and Week 24, respectively, and X is a matrix for the age and insulin stratum fixed covariates.
2) Impute missing Week 24 A1C values for ertugliflozin using the estimated mean from the above model and standard deviation equal to the RMSE from the model.

For participants in the placebo group:

1) Fit models according to the intermittent missing data pattern with A1C values from the placebo group only:
   a. For participants with only Baseline data: $Y_{24} = \beta_0 + \beta_1 * Y_0 + \gamma * X + \text{error}$
   b. For participants with only Baseline and Week 6 data: $Y_{24} = \beta_0 + \beta_1 * Y_0 + \beta_2 * Y_6 + \gamma * X + \text{error}$
   c. For participants with only Baseline, Week 6 and Week 12 data: $Y_{24} = \beta_0 + \beta_1 * Y_0 + \beta_2 * Y_6 + \beta_2 * Y_{12} + \gamma * X + \text{error}$
2) Impute missing Week 24 A1C values for placebo using one of the 3 models above based on the missing data pattern with a mean equal to the mean from the regression model and a standard deviation equal to the RMSE from the model.

Descriptive statistics will be used to summarize the A1C mean change from baseline at Week 24 for the individual ertugliflozin dose arms in the subset of participants who were re-randomized at Visit 5/Week 12. All other continuous efficacy endpoints with the exception

of the 2 key secondary endpoints associated with hypotheses H2 and H3, including the Week 12 A1C change from baseline, will be analyzed following the same cLDA method used for the A1C TE estimand under H1 (combined ertugliflozin doses vs. placebo) and will not be analyzed under the TP estimand.

Week 54

The Week 54 analyses will be based on the same FAS population used for the Week 24 analyses. The statistical models for the analyses at Week 54 will be analogous to those at Week 24, except that no between-group comparisons will be provided for **Week 54**. The efficacy endpoints will be summarized for within-group mean change from baseline with estimates and 95% CIs calculated from the analysis model.

Table 7 summarizes the analysis strategy for primary and secondary efficacy endpoints at Week 24 and at Week 54.

Table 7 Analysis Strategy for Efficacy Variables at Week 24 and at Week 54

Variable	Estimand/Approach	Statistical Method	Missing Data Approach
Primary			
Change from baseline in A1C - pooled ertugliflozin vs placebo	TP/Primary TE/Primary	Bayesian Borrowing cLDA	RD† Model-based
Key Secondary			
Change from baseline in A1C - dose-optimized ertugliflozin vs placebo	TP/Primary	ANCOVA (weighting scheme A)	RD†
Change from baseline in A1C - ertugliflozin 5 mg vs placebo	TP/Primary	ANCOVA (weighting scheme B)	RD†
Secondary			
Change from baseline in FPG	TE/Primary	cLDA	Model-based

A1C = glycosylated hemoglobin; ANCOVA = analysis of covariance; cLDA = constrained longitudinal data analysis; FPG = fasting plasma glucose; RD = Retrieved Dropout; TE = Treatment Effect; TP = Treatment Policy; WI = Washout Imputation.

† The primary analysis for the TP estimand will use RD to impute missing data if RD is feasible. If RD is not feasible, WI will be used.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs measurements. Safety analyses will be conducted across Week 0 to Week 54 (Phase A+B) with selected analyses also done across Week 0 to

Week 24 (Phase A). For safety and tolerability analyses, the pooled ertugliflozin group (5 mg and 15 mg) will be compared with the placebo group.

Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized, except for any participants who take incorrect study treatment for the entire treatment period. Such participants will be included in the treatment group corresponding to the study treatment actually received.

The following analysis approaches will be used:

All safety endpoints except hypoglycemia will be summarized regardless of the initiation of rescue or intensification therapy. This approach is referred to as the "including rescue" approach (IR). The Treatment Period will include all data from randomization up to 14 days after the last dose of study treatment for AEs, Tanner Staging and abdominal ultrasounds, up to 2 days after the last dose of study treatment for laboratory endpoints, and up to 5 days after the last dose for growth velocity and vital signs with the exception of analyses of Phase A alone, for which the additional follow-up days will not be included for participants who continue into Phase B (ie, Phase B data will be excluded from analyses of Phase A only).

SAEs and deaths will also be summarized inclusive of all post-randomization follow-up (APRFU), regardless of study treatment adherence and without an upper day limit.

AE summary measures will be tabulated by ertugliflozin dose in the subset of participants who were re-randomized at Visit 5/Week 12.

Hypoglycemia endpoints will be summarized excluding data collected following the initiation of rescue therapy or intensification therapy. This approach is referred to as the "excluding rescue" approach (ER).

Table 8 summarizes the analysis strategy by study phase and analysis approach.

Table 8 Analysis Strategy for Safety Endpoints by Study Phase

Phase	Analysis Approach	Endpoints
Phase A	Treatment period, IR	all AE endpoints and PDLCs
	Treatment period, ER	hypoglycemia endpoints
A + B	Treatment period, IR	all safety endpoints except for hypoglycemia endpoints
	Treatment period, ER	hypoglycemia endpoints
	Treatment period + APRFU, IR	SAEs and deaths
AE = adverse event; APRFU = all post-randomization follow-up; ER = excluding data after initiation of glycemic rescue/intensification therapy; IR = including data after initiation of glycemic rescue/intensification therapy; PDLC = predefined limits of change; SAE = serious adverse event(s).		

The analysis of safety results will follow a tiered approach (Table 9). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) are either prespecified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be tested for statistical significance with p-values and 95% CIs to be provided for between-treatment differences in the proportion of participants with events; these analyses will be performed using the M&N method [Miettinen, O. and Nurminen, M. 1985], an unconditional, asymptotic method. For this protocol, events of symptomatic hypoglycemia, and AEs associated with genital mycotic infection (gender specific), hypovolemia, and UTI are considered Tier 1 events. AEs associated with UTI, hypovolemia, and genital mycotic infection will be identified by Custom MedDRA queries (CMQ), which will be defined in the sSAP.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events (also via the M&N method [Miettinen, O. and Nurminen, M. 1985]).

Membership in Tier 2 requires that at least 8 participants in the combined ertugliflozin group or 2 participants in the placebo group exhibit the event; all other adverse events and predefined limits of change will belong to Tier 3.

The thresholds of events were chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when fewer participants per group, respectively, experience events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and safety parameters that meet predefined limits of change.

In addition to individual events that occur in at least 8 participants in the combined ertugliflozin group or 2 participants in the placebo group, the summary measures of AEs consisting of the proportion of participants with any AE, a drug-related AE, an SAE, an AE that is both drug-related and serious, and discontinuation due to an AE, will be considered Tier 2 endpoints.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory and vital signs, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format. In addition, for continuous Tier 3 safety endpoints, graphical representations of mean ± SE values over time may be provided for selected endpoints.

For safety endpoints, all analyses will be based on the observed data (ie, with no imputation of missing data). Table 9 summarizes the analysis strategy for safety endpoints.

Table 9 Analysis Strategy for Safety

Tier	Safety Variable/Endpoint	p-Value	95% CI for Treatment Comparisons	Descriptive Statistics
Tier 1	AEs of genital mycotic infection (gender specific)	X	X	X
	AEs of hypovolemia	X	X	X
	Events of symptomatic hypoglycemia	X	X	X
	AEs of UTI	X	X	X
Tier 2[†]	Episodes of severe hypoglycemia		X	X
	Any		X	X
	Requiring medical assistance		X	X
	Not requiring medical assistance		X	X
	Episodes of documented hypoglycemia		X	X
	AE summary measures		X	X
	Specific AEs[‡] or PDLCs (incidence ≥8 participants in the combined ertugliflozin group or ≥2 participants in the placebo group)		X	X
Tier 3	Specific AEs[‡] or PDLCs (incidence <8 participants in combined ertugliflozin group or <2 participants in the placebo group)			X
	Additional hypoglycemia endpoints			X
	Change from baseline results (labs [including bone biomarkers], vital signs, and abdominal ultrasounds)			X
	Growth velocity and Tanner Staging			X

AE = adverse event; CI = confidence interval; PDLC = predefined limits of change; UTI = urinary tract infection; X = results will be provided.

[†] Endpoints listed here will qualify for Tier 2 only if the incidence is ≥8 participants in the combined ertugliflozin group or ≥2 participants in the placebo group.

[‡] Includes only those endpoints not prespecified as Tier 1 or not already prespecified as Tier 2 endpoints.

Analysis of Hypoglycemia

For the hypoglycemia endpoints described in Section 9.4.2, the analyses of hypoglycemia will be performed separately for participants on a background of insulin and for participants not on a background of insulin at screening. Analyses of hypoglycemia combining participants on and not on a background of insulin are not planned.

Tier 1 endpoints for hypoglycemia are the percentages of participants experiencing 1 or more episodes of symptomatic hypoglycemia.

Tier 2 endpoints for hypoglycemia are the percentages of participants experiencing 1 or more episodes of documented or severe hypoglycemia defined above. Summaries will be provided for all episodes.

Tier 3 endpoints for hypoglycemia are the percentages of participants with documented hypoglycemia as defined above:

- by lowest reported glucose category (<54 mg/dL [3.0 mmol/L], ≤70 mg/dL [3.9 mmol/L]); and
- by number of episodes.

Glucose categorization will be performed based on the units (mg/dL or mmol/L) in which the glucose measurements were reported. A participant's lowest glucose category will be classified as unknown only if no glucose measurements are available for that participant.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

Periodic review of data to include safety and study conduct will be performed by an external Data Monitoring Committee (DMC). An internal unblinded statistician and unblinded programmer who otherwise have no other responsibilities associated with the study or the ertugliflozin program will support the DMC.

Additionally, one PK IA will be performed to estimate ertugliflozin exposure in pediatric T2DM participants. The PK IA will be conducted when ~30 participants on study medication have completed **Visit 4/Week 6** (with the expectation that ~20 of those participants would be on ertugliflozin). An unblinded PK analyst, external to the Sponsor, will perform the PK IA and present the results to the DMC. The unblinded PK analyst will have no other responsibilities associated with the study or the ertugliflozin program.

The DMC will serve as the primary reviewer of the results of the PK IA and will make recommendations regarding the continuation of the second randomization to the Executive Oversight Committee (EOC). The PK IA will compare the median dose-normalized trough concentration to a 2.0 ng/mL/mg cutoff. This cutoff was determined by simulations based on

adult PK data with details provided in Appendix 12. If the median dose-normalized trough concentration at the time of the IA is >2.0 ng/mL/mg, the DMC may recommend the 15 mg dose be down-titrated to 5 mg, and the second randomization discontinued. If the median trough concentration is ≤2.0 ng/mL/mg, then the study will continue with the second randomization, and up-titrate to ertugliflozin 15 mg if they meet eligibility criteria. With a sample of ~20 ertugliflozin participants, the PK IA is expected to result in a decision to down-titrate the 15 mg dose and discontinue the second randomization 90.9% of the time if the mean pediatric clearance is ≤60% of the adult clearance.

If the second randomization is discontinued, ongoing participants who have up-titrated to ertugliflozin 15 mg/day will have an Unscheduled Visit as soon as possible to be down-titrated to ertugliflozin 5 mg/day in a blinded manner, participants in the placebo group who have been mock up-titrated will also be mock down-titrated. If the 15 mg arm is dropped then hypotheses H2 and H3 will not be tested.

Study enrollment will be ongoing at the time of the PK IA. Blinding to treatment assignment will be maintained at all investigational sites. Results of the PK IA will not be shared with the investigators prior to the completion of the study. Study monitors will remain blinded. The EOC may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of the PK IA will be documented by the internal unblinded statistician, who will be different from the unblinded PK analyst.

Additional details such as DMC meeting frequency and conduct, governance, and communication with the EOC will be provided in the DMC Charter.

9.8 Multiplicity

The type 1 error rate for the Bayesian methodology addressing the primary hypothesis under the TP estimand was estimated via simulation to be 0.10. If the success criterion for the primary hypothesis (H1) is met under the TP estimand, then hypotheses H2 will be tested at alpha = 0.05. If H2 is successful then H3 will be tested at alpha = 0.05. The overall study wise type 1 error rate will be greater than 0.05.

If the 15 mg arm is dropped then hypotheses H2 and H3 will not be tested.

9.9 Sample Size and Power Calculations

This study will randomize approximately 165 participants using a 2:1 randomization ratio at Visit 3/Day 1/Randomization for ertugliflozin and placebo resulting in approximately 110 participants in the ertugliflozin group (combined doses) and 55 participants in the placebo group.

TP Estimand Power

The type 1 error and power (percent of 95% posterior credible intervals <0) were simulated (10,000 simulations) using the rjags and coda packages in R and the credible intervals were

computed using the HDInterval package. With an informative prior, the type 1 error will exceed 0.05. Using the adult data from 8835-007 and a weight parameter of 0.134, a sample size of 165 will provide approximately 80% power to detect a true difference of -0.6% in the mean change from baseline in A1C between ertugliflozin and placebo, given the SD=1.5% and discontinuations from study medication as of the primary timepoint are approximately 3.9%. The type 1 error and power were estimated based on the WI approach instead of the RD approach given all randomized participants have either completed on or off study medication or have discontinued from the study in Phase A.

Regarding the secondary hypotheses, the assumptions for the efficacy of the dose-optimized ertugliflozin regimen and of the 5 mg ertugliflozin dose are the same as for the pooled ertugliflozin doses. However, the power for the secondary hypotheses will be lower than that of the primary hypothesis on account of the weighting scheme. Based on simulations, the percent reduction in power is 13% of the primary hypothesis power. Thus, the estimated power for each secondary hypothesis is 70%.

TE Estimand Power

Assuming 86% of the participants will have data at Week 24 (14% with missing data due to discontinuation from study medication or censoring after initiation of rescue), 95 participants in the combined ertugliflozin arm and 47 in the placebo arm will provide at least 80% power for the primary hypothesis test assuming that the between-group difference in A1C change from baseline at Week 24 is -0.75% and using a SD of 1.5%. Assumptions of cumulative attrition rates and covariance matrix at Week 6, Week 12 and Week 24 are listed below:

1. The cumulative attrition rates (due to dropout and/or censoring due to discontinuation of study medication or initiation of rescue) at Week 6, Week 12, and Week 24 are 4%, 8% and 14%.

2. The conditional covariance matrix is

1.11	0.8	0.6
0.8	1.17	0.8
0.6	0.8	2.25

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect for the primary variable will be summarized and plotted within each category of each subgroup. Treatment groups will be consistent with the primary analysis: ertugliflozin (combined doses) and placebo. Subgroups analyses will be performed only for the primary analysis and treatment comparison. The following subgroups will be analyzed:

- Baseline A1C by categories: ≥ or <median A1C

- Sex (Male, Female)
- Race (White, Black, Asian, American Indian or Alaska Native)
  Participants who report belonging to more than one racial group will each be assigned to the racial group that has the highest risk for Type 2 diabetes in the order of American Indian or Alaska Native, Asian, Black, White [Copeland, K. C., et al 2011].
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Age at Screening (10 to 14 years of age, 15 to 17 years of age)
- Insulin use at Screening (No, Yes)
- Geographic region (EU, North America, Other)

Under the TP estimand, summary statistics will be provided for each subgroup analysis to include sample sizes, means, medians, standard deviations, and 95% confidence intervals on the differences in means based on a normal distribution.

Under the TE estimand, the subgroup analyses will be based on a repeated measures ANCOVA model including terms for treatment, insulin use, the subgroup, time as a categorical factor, baseline A1C, and the treatment-by-subgroup interaction. Treatment effects and nominal 95% CIs by category for the classification variables listed above will be reported. Formal statistical testing of treatment-by-subgroup interactions will not be performed. Forest plots will be produced for each estimand, which provide the point estimates and 95% CIs for the estimated treatment effect across the categories of subgroups listed above.

Results from the subgroup analyses should be reviewed cautiously. Because sample sizes within subgroups will be smaller than the overall study sample size, estimation may not be precise, and 95% CIs will usually be wide in the subgroup analyses.

9.11 Compliance (Medication Adherence)

A day within the Double-blind Treatment Period will be considered a compliant day if the participant takes 1 tablet of ertugliflozin 5 mg/placebo and 1 tablet of ertugliflozin 15 mg/placebo.

If the study treatment eCRF indicates general compliance problems with any double-blinded therapy, the participant will be considered non-compliant for that day regardless of the number of tablets for the assigned treatment(s) and any matching placebo reported.

For each participant, the compliance rate, based on time until study treatment discontinuation, and the adherence rate, based on time until study discontinuation, will be calculated, using the following formulas:

$$\text{Compliance rate (\%)} = \frac{\text{Number of Compliant Days}}{\text{Number of Days in the Double-blind Treatment Period}} \times 100\%.$$

$$\text{Adherence rate (\%)} = \frac{\text{Number of Compliant Days}}{\text{Number of Days in the Study}} \times 100\%.$$

For each participant the "Number of Days in Double-blind Treatment Period" is the total number of days from the first dose of double-blind study treatment to the date of the last dose of study treatment. The "Number of Days in the Study" is the total number of days from Day 1 to the day of study completion or withdrawal from the study.

9.12 Extent of Exposure

The extent of exposure to study treatment will be evaluated by summary statistics and frequencies for the "Number of Days on Therapy" by treatment group (ertugliflozin and placebo).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, the International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease-related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned,

according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Pursuant to Union law (Clinical Trials Directive 2001/20/EC and Clinical Trials Regulation 536/2014), the Investigator is responsible for pseudonymizing and assigning a key-code/patient ID to each study subject. In addition, the Investigator is required by Union law to store the Key (linking the Patient ID to the full name of the study subject) at the site in the

EU/EEA throughout the course of the study and for a designated period of time thereafter. Finally, the study site is only permitted to share pseudonymized study subject personal data with the Sponsor.

The European Data protection Board, in its Recommendations 01/2020 on measures that supplement transfer tools to ensure compliance with the EU level of protection of personal data ("Recommendations"), states in Paragraph 85 that pseudonymization (of study subject) personal data under the conditions described above constitutes effective supplemental measure.

Organizational measures are contractually imposed on third party vendors whenever possible, to ensure that Personal Data are protected by industry-best practices against accidental destruction or loss (physical/logical) which include regular backup procedures, Firewalls, and disaster recovery plans.

In support of Corporate Policy 1 Information Risk Management, on a Sponsor-wide basis all supplier relationships, both IT and non-IT related, are strongly encouraged to meet the Sponsor's Supplier Information Risk Management Standard. To protect the confidentiality, availability and integrity of Sponsor information, conformity to information risk requirements by supplier personnel, hardware and software may be measured, analyzed and appropriate corrective/preventative actions taken as necessary. Based on the supplier criticality, additional activities (e.g., on-site reviews, integrated business continuity exercises) may be required to ensure the cyber-resiliency of the supplier on an ongoing basis.

The Sponsor has implemented (Corporate Policy 13.1 Information Security Standards Handbook) an organization-wide process to assign user access rights based on the whether the employee/contractor has a legitimate need to utilize a database in order to carry out his/her job; manager approval is required when granting user access rights (beyond those sites or databases intended for all employees/contractors); and a process is in place for an annual review by each manager of the user access rights currently in place. Organizational measures, also contractually imposed on third party vendors, to prevent data processing systems from being used by unauthorized persons include i) user identification and authentication procedures (e.g., special characters, minimum length, regular change of password), and ii) automatic blocking (e.g., password or timeout).

The Sponsor utilizes a database called "InForm", operated by Oracle, for the storage of its study subject clinical trial data. InForm is a role-based system and only authorized users can see the data. Sites may only see the data they have entered. Access by Sponsor users is restricted to only those associated with a specific clinical trial.

Study sites are provided with a password to access the database. Access to InForm requires https (Secure Socket Layer) with a FIPS 140-2 compliant algorithm to connect to the application via the study site's web browser. Once logged into the system, the connection between the database, located in Ashburn, Virginia, USA, and the site, is encrypted. The Sponsor also stores the name and access credentials of the Investigators and other site staff (Study Coordinators) who record patient data into InForm. Such study staff personal data is not pseudonymized. Note, such encryption during transmission may not meet all conditions

imposed by the EDPB in its Recommendations for this encryption, on its own, to constitute an effective supplemental measure.

Data, whether concerning a study subject or site staff, stored in the InForm database is encrypted. Note, such encryption may not meet all conditions imposed by the EDPB in its Recommendations for this encryption, on its own, to constitute an effective supplemental measure.

Whenever possible, organization-wide measures are imposed on third party vendors to prevent unauthorized persons from gaining access to the data processing systems available on premises and in facilities (including databases, application servers and related hardware), where Personal Data are processed, include i) Access control system (ID reader, chip), ii) key management, card-keys procedures, and iii) on-site security personnel and alarm system.

InForm is a HIPAA Part 11 capable system. Any data entered/changed or deleted will be associated with a viewable audit trail.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20). Pursuant to organization-wide requirements, the Sponsor periodically conducts audits of the vendors providing IT services, including Oracle, the vendor supporting the InForm database. The most recent audit of Oracle and its operations of InForm occurred in May 2020. Finally, Oracle has obtained ISO 27001 certification for the various databases it offers to third parties as a service, including the InForm database.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Scientific Advisory Committee

This study was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.4.2 Executive Oversight Committee

The Executive Oversight Committee (EOC) is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the DMC regarding the study.

10.1.4.3 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.4 Internal Case Review Committee for Ketoacidosis

An internal case review committee will be set-up to review potential ketoacidosis events identified in the ertugliflozin pediatric study. The committee will assess whether the cases meet a prespecified case definition of ketoacidosis. Further details will be provided in the

charter for clinical case review of ketoacidosis. All personnel involved in the Internal Case Review Committee will remain blinded to study treatment allocation throughout the study.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are

requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participant's documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Participants should not engage in physically strenuous exercise (eg, heavy lifting, weight training, calisthenics, and aerobics) within 48 hours before each blood sample collection for clinical laboratory tests for the duration of participation in the study.

Laboratory safety tests will be performed after at least a 10-hour fast (ie, no food, no study treatment, no AHA medication, and no drink except for water and non-AHA prescribed medication), **except at Visit 4/Week 6**.

List of Laboratory Evaluations:

- FPG test
- Whole blood A1C test
  Do not collect A1C at **Rescue/Intensification** or **Discontinuation Visits** if the visit occurs before Week 8.
  The **Visit 5/Week 12, Visit 6/Week 24, and Visit 7/Week 38** samples must be measured both at the site and by the Central lab.
- Fasting serum C-peptide test
  Fasting C-peptide will be collected at **Visit 1/Screening** only in participants with diabetes for <2 years and in all participants on background insulin regardless of the duration of T2DM. At **Visits 3**, **6**, and **8**, it will be collected in all participants.
- Lipid analyses: total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol-calculated, non-HDL cholesterol – calculated.
- Hematology (CBC differential): hemoglobin, hematocrit, red blood cell count, mean corpuscular hemoglobin concentration and mean corpuscular volume, white blood cell count and differential, platelet count, absolute neutrophil count, eosinophils, monocytes, basophils, lymphocytes.
- Serum blood chemistry: sodium, potassium, chloride, bicarbonate, calcium, phosphate, albumin, ALP, uric acid, total serum protein, ALT, AST, creatine phosphokinase, total bilirubin (direct conjugated bilirubin and indirect unconjugated bilirubin will be measured when total bilirubin is greater than ULN), BUN, creatinine, magnesium.

- Urine pregnancy test performed for all females at the investigator's site (for exceptions, see Section 10.7).
  Serum beta-human chorionic gonadotropin (hCG) test in all randomized participants with a positive urine pregnancy test.

- Eligibility serum hCG test performed for female participants from countries where it is required by Health Authorities and/or IRBs/ECs (see Section 10.7.2).

- Urine collection for dipstick urinalysis (pH, protein, blood, ketones, leukocyte, esterase, nitrites) and urine albumin/creatinine ratio should be performed on a mid-stream sample collected after adequately cleaning the genital area using appropriate wipes ("clean catch").
  Notes:
  (1) If dipstick urinalysis is positive for blood, leukocyte esterase, nitrites, or protein, then microscopy will be done.
  (2) Participants found to have microscopic hematuria (defined as the presence of 3 or more red blood cells per high powered field on microscopic examination) from a properly collected, non-contaminated urinalysis with no evidence of infection, will be referred to an urologist for appropriate work-up.
  (3) Urine collection should not be performed if participant is menstruating, has vigorously exercised within 24 hours, or had fever or an active infection within 2 days of the visit. Under such circumstances, the participant should provide a urine sample at an **Unscheduled Visit**.

- Thyroid function test: serum TSH test

- Biomarkers of bone turnover:
  -urine (second AM void) N-terminal cross-linking telopeptide of bone collagen (NTX) and creatinine
  -serum bone-specific alkaline phosphatase (Ostace assay).

- Cystatin C

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Note: At the indicated times in the SoA, samples for ertugliflozin PK will be collected and sent to the Central Lab prior to transfer to the vendor for analyses.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**
- **Is life-threatening**
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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 prolongation of existing hospitalization**

  - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

- **Results in persistent or significant disability/incapacity**

  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.

  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

  - In offspring of participant taking the product regardless of time to diagnosis.

- **Other important medical events**

  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer

- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product intervention cause the AE?
- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the Sponsor's product in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability; (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
    - Yes, there is a reasonable possibility of Sponsor's product relationship:
        - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
    - No, there is not a reasonable possibility of Sponsor's product relationship:
        - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.

  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.

  - Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collections, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

10.5.2 Contraception Requirements

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in Table 10 consistently and correctly during the protocol-defined time frame.

Table 10 Contraceptive Methods

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c,d] • IUS[c,e] • Non-hormonal IUD
• Bilateral tubal occlusion • Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. • Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progestogen-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Penile/external or vaginal/internal condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of penile/external condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b) Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). c) Male condoms must be used in addition to hormonal contraception. d) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. e) IUS is a progestin releasing IUD Note: The following are not acceptable methods of contraception: -Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. -Male condom with cap, diaphragm, or sponge with spermicide. -Male and female condom should not be used together (due to risk of failure with friction).

10.5.3 Pregnancy Testing

All females participating in the study will have a urine pregnancy test at visits indicated in the SoA (for exceptions, see Section 10.7) (if required by an investigational site's IRB/ERC, a serum pregnancy test can also be obtained in addition to the urine pregnancy test). A positive urine pregnancy test requires immediate interruption of study treatment until serum beta-hCG is performed and found to be negative. Participants must be discontinued from study treatment and followed (Section 7.1) if pregnancy is confirmed by a positive serum pregnancy test.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3,4]

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3,4]

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3,4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant's clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3,4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3,4]

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the study investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3,4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3,4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3,4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3,4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3,4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council for Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

10.7.1 Saudi Arabia and United Arab Emirates Requirements

The protocol change outlined in this section is being made to align with legal and cultural mores in Saudi Arabia and United Arab Emirates:

Pregnancy Testing

All married female participants (or female participants who in the clinical opinion of the investigator could be pregnant) will have a urine pregnancy test at the visits indicated in the SoA.

10.7.2 Serum Pregnancy Requirements

Pregnancy Testing

If required by the Health Authorities and/or IRBs/ECs, female participants from those countries/sites (eg, United Kingdom, Guatemala) will have a serum pregnancy test performed to determine eligibility instead of a urine pregnancy test.

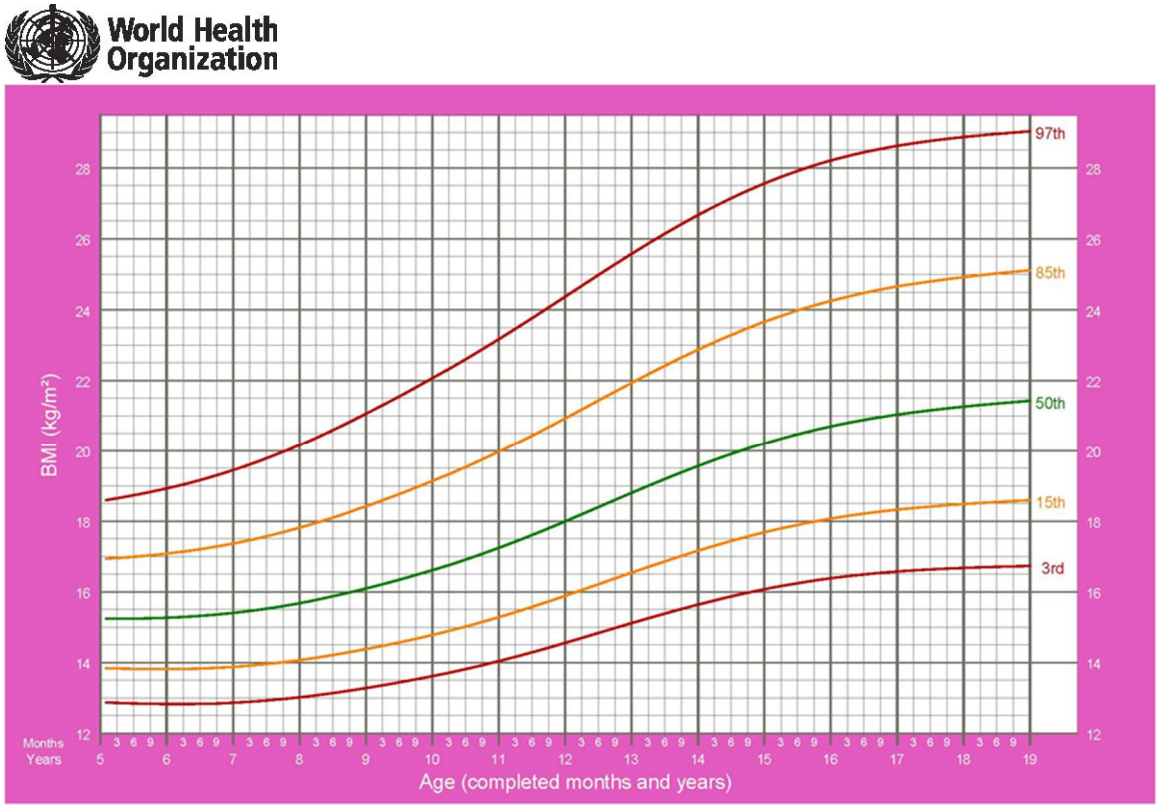
10.8 Appendix 8: BMI for Age Charts

Sites should follow their approved country-specific BMI-for-age percentile charts, if available (eg, sites within the US will refer to the Centers for Disease Control charts). If an approved country-specific BMI-for-age percentile chart is not available, refer to the WHO charts shown in Figure 2 and Figure 3.

Instructions for obtaining the body mass index-for-age percentile:

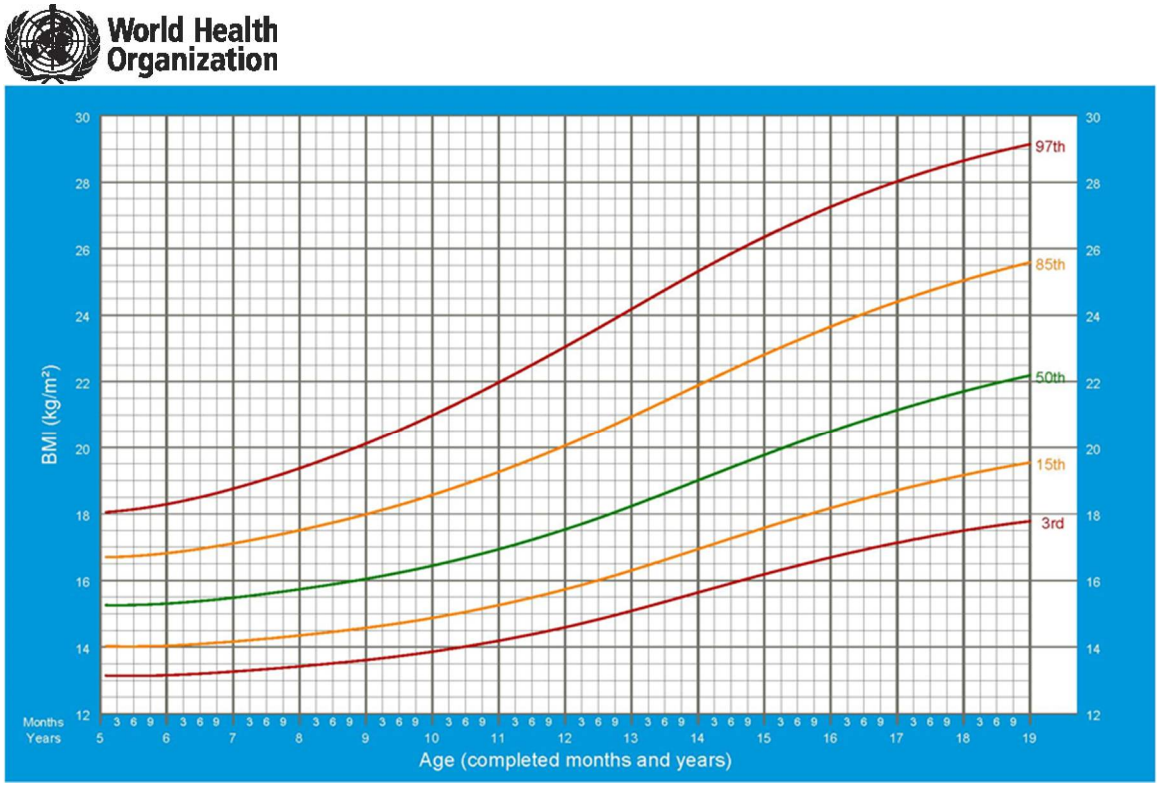
- Find the child's age on the horizontal axis
- Find the BMI measurement on the vertical axis (to determine BMI, refer to Section 8.2.4).
- The body mass index-for-age percentile will be at the intersection of the child's age and BMI measurement.

Figure 2 BMI for Age Girls, 5 to 19 Years (Percentiles)



Ref: [deOnis, M. 2007]

Figure 3 BMI for Age Boys, 5 to 19 Years (Percentiles)



Ref: [deOnis, M. 2007]

10.9 Appendix 9: Blood Pressure Tables

Table 11 Blood Pressure Table for Gender/Age/Height for Boys Age 10 to 17

Years of Age	Blood Pressure	Systolic Blood Pressure by Percentile of Height (mmHg)							Diastolic Blood Pressure by Percentile of Height (mmHg)						
(Years)	Percentile	5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
10	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97
Note: country-specific Blood Pressure norms may be used; otherwise, these guidelines should be used.															

Ref: [National High Blood Pressure Education Program Working Group on 2004]

Table 12 Blood Pressure Table for Gender/Age/Height for Girls Age 10 to 17

Years of Age (Years)	Blood Pressure Percentile	Systolic Blood Pressure by Percentile of Height (mmHg)							Diastolic Blood Pressure by Percentile of Height (mmHg)						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
10	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
+15	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

Note: country-specific Blood Pressure norms may be used; otherwise, these guidelines should be used.

Ref: [National High Blood Pressure Education Program Working Group on 2004]

10.10 Appendix 10: Management of Participants with Elevated Liver Enzymes (ALT or AST ≥3x ULN)

Section I: Identification and Management of Participants with ALT or AST Results ≥3X ULN

Increases in ALT or AST ≥3X the ULN are defined as clinically significant for this study. The central laboratory report will alert the investigator if a participant meets this threshold. When a randomized participant who is receiving blinded investigational product has an ALT or AST elevation beyond the clinical significant margin above, the investigator should monitor the participant according to the instructions below and discontinue the participant from blinded investigational product if a prespecified criterion is met.

The investigator should select the appropriate set of instructions (either A, B, or C below) for managing a participant with elevated liver enzymes based upon the following factors: (1) the magnitude of a participant's ALT or AST elevation, (2) the presence or absence of symptoms, (3) whether there is a corresponding increase in total bilirubin ≥2X ULN.

Investigator Instructions for Management of Participants with ALT or AST ≥3X ULN

A) Participant has:

- **ALT or AST ≥3X ULN with total bilirubin ≥2X ULN and ALP <2X ULN**

1. The participant should *interrupt* blinded investigational product.
2. Refer to the *"Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials"* (located in the Investigator Trial File Binder or equivalent) and perform procedures accordingly.
3. If an etiology for the elevated ALT or AST and total bilirubin levels is established and the abnormalities resolve, blinded investigational product may be restarted with approval by the Sponsor. Otherwise, the participant should discontinue treatment with blinded investigational product.

Note: Laboratory assessments prescribed in the *Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials* may be sent locally in emergent cases and to support participant compliance with the necessary evaluations. Participants unwilling or unable to undergo the prescribed testing should be discontinued from treatment with blinded investigational product.

B) Participant has:

- **ALT or AST ≥8X ULN OR**
- **ALT or AST ≥3X ULN and signs or symptoms of a drug reaction consistent with liver injury (eg, fever, eosinophilia, right upper quadrant pain, dark urine, fatigue, etc.)**

1. The participant should *interrupt* blinded investigational product.
2. Perform repeat ALT and AST within 3 days of receipt of the laboratory report.
3. Initiate evaluation for potential causes. See Section II below.
4. Repeat ALT and AST tests at appropriate intervals, initially approximately 2-times per week, until resolution or return to baseline.
5. If an etiology for the elevated liver enzymes is established (eg, active hepatitis with specific etiology demonstrated, cholecystitis, biliary obstruction), blinded investigational product may be restarted with approval by the Sponsor. Otherwise, the participant should discontinue treatment with blinded investigational product.

Note: Local laboratory assessments can be used to support compliance with the repeat testing procedure described above if required. Participants unwilling or unable to undergo repeat ALT and AST testing at the frequency recommended above should be discontinued from treatment with blinded investigational product.

C) Participant has:

- **ALT or AST ≥3X and <8X ULN**

1. For participants with:
   ALT or AST ≥3X and <5X ULN:
   - Perform repeat ALT and AST within 3-5 days of receipt of the laboratory report.

     OR

     ALT or AST ≥5X ULN and <8X ULN:
   - Perform repeat ALT and AST within 3 days of receipt of the laboratory report. Participants unable to undergo repeat measurements within 3 days *must interrupt* blinded investigational product.
2. Initiate evaluation for potential causes. See Section II below.
3. Actions based upon ***initial*** repeat testing:
   - If **ALT or AST ≥3X ULN with total bilirubin ≥2X ULN**, then interrupt blinded investigational product and monitor as described in the Section **A** Instructions above and also per the *"Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials"* (located in the Investigator Trial File Binder or equivalent) and perform procedures accordingly.

- If **ALT or AST ≥8X ULN or ALT or AST ≥3X ULN** with symptoms present (eg, fever, eosinophilia, right upper quadrant pain, dark urine, fatigue, etc.), then interrupt blinded investigational product and monitor as described in the Section **B** Instructions above.
- If **ALT or AST ≥3X ULN and <8X ULN** (without above criteria met), continue to measure ALT and AST 1- to 2-times per week (2-times per week if ALT or AST ≥5X ULN or if an increase >20% occurred since the first elevated value[s]).
- If **ALT and AST > ULN and <3X ULN**, perform repeat determination in 5-7 days, and then at appropriate intervals (eg, every other week) until the participant's ALT and AST levels are within normal limits or are similar to baseline.

4. Actions based upon ***follow-up*** repeat testing:
   - If **ALT or AST ≥5X ULN** after 2 weeks, *discontinue blinded investigational product.*
   - If **ALT or AST remain elevated** (≥3X and <5X ULN) but stable, the frequency of retesting can decrease (eg, every other week) with approval from the Sponsor.
   - If **ALT and AST >ULN and <3X ULN**, perform repeat determination in 5-7 days, and then at appropriate intervals (eg, every other week) until the participant's ALT and AST levels are within normal limits or are similar to baseline.

Note: Local laboratory assessments can be used to support compliance with the repeat testing procedures described above if required. Participants unwilling or unable to undergo repeat ALT and AST testing at the frequency defined above should be discontinued from treatment with blinded investigational product.

In summary, participants should be discontinued from blinded investigational product for any of the following reasons:

- ALT or AST ≥3X ULN with total bilirubin ≥2X ULN and ALP <2X ULN and without an established etiology
- ALT or AST ≥8X ULN or ≥3X ULN with symptoms consistent with liver injury and without an established etiology
- ALT or AST ≥5X ULN for 2 weeks or longer

Section II: Guidance for Assessment of Potential Etiology

Questions to Assess Etiology

Investigate potential causes for the participant's elevated liver enzymes using the questions below. Answers to the questions should be recorded in the participant's source documents and appropriate eCRFs.

1. Has the participant recently:
    - Had a change in his/her pattern of alcohol use? Investigate historic pattern of alcohol use as well.
    - Administered an illegal drug(s) (including intravenous drugs)?
    - Been exposed to a chemical agent or other environmental toxin?
    - Consumed any unusual foods (eg, mushrooms), seasonal foods, or initiated treatment with new herbal/nutritional supplements?
    - Initiated a new diet regimen, started a rigorous exercise program, or experienced any form of severe physical exertion?
    - Traveled to another country or region?
2. Does the participant have a relevant concomitant illness (eg, cholelithiasis, hepatitis, etc.) or has the participant had potential exposure to viral hepatitis (transfusion, tattoo, new sexual partner)?
3. Does the participant have a relevant medical history (eg, autoimmune disorder, cancer, Gilbert's syndrome, obesity, Wilson's disease, NASH, alcoholic or infectious hepatitis, biliary tract disease, hypoxic/ischemic hepatopathy, etc.)?
4. Has the participant recently been treated with a concomitant medication(s) with demonstrated or suspected effects on the liver (eg, acetaminophen; amiodarone; aspirin; chlorpromazine; dantrolene; erythromycin; halothane; isoniazid; methyldopa; nitrofurantoin; oxyphenisatin; perhexiline maleate; phenytoin; propylthiouracil; rifampin; sulfonamides; tetracyclines) or initiated treatment with another new medication(s)?

Additional Laboratory/Imaging Evaluations

In participants for whom an etiology for the abnormal liver enzymes is unknown or whose elevated liver enzymes persist for more than 1-week:

1. Consider performing serologic tests including: (a) Hepatitis A (IgM); (b) Hepatitis B (surface antigen and core IgM); (c) Hepatitis C (antibody); (d) Hepatitis E (IgG and IgM). Obtain consent prior to testing, if required locally. Additional evaluations may be performed at the discretion of the investigator.

2. Consider an ultrasound of the participant's right upper quadrant and additional scans (endoscopic retrograde cholangiopancreatography [ERCP] or magnetic resonance cholangiopancreatography [MRCP]) if needed.

Note: Participants may also be referred to a gastroenterologist or hepatologist for an additional work-up if considered necessary by the investigator.

10.11 Appendix 11: Mapping of Relative Day Ranges to Weeks

The rules outlined in Table 13 will be used to map the relative day ranges to weeks for A1C.

Table 13 Relative Day Ranges to Weeks for A1C

Week	Required Phase	Relative Day Range
		Day Relative to Start of Trial†
Min (Day/7, -1)	--	Visit < 2 and Day < 1
-1	Placebo Run-In	Visit ≥ 2 and Day <1
0	Placebo Run-In	Visit ≥ 3 and Day ≤1
6	A	2≤ Day ≤63
12	A	64≤ Day ≤126
24	A	Day ≥127
		Day Relative to Start of Phase B‡
38	B	1≤ Day ≤154
54	B	Day ≥155

A1C=glycosylated hemoglobin
†Start of Phase A is defined as first dose of Phase A study treatment for all treated participants and the randomization day for participants who did not take any dose of study treatment.
‡Start of Phase B is defined as first dose day of Phase B study treatment or Week 24 for participants who entered Phase B off study treatment.

The rules outlined in Table 14 will be used to map the relative day ranges for FPG, lab, and lipid endpoints.

Table 14 Relative Day Ranges to Weeks for FPG, Lab, and Lipid Endpoints

Week	Required Phase	Relative Day Range
		Day Relative to Start of Trial†
Min (Day/7, -1)	--	Visit < 2 and Day < 1
-1	Placebo Run-In	Visit ≥ 2 and Day <1
0	Placebo Run-In	Visit ≥ 3 and Day ≤1
24	A	Day ≥2
		Day Relative to Start of Phase B‡
54	B	Day ≥1

†Start of Phase A is defined as first dose of Phase A study treatment for all treated participants and the randomization day for participants who did not take any dose of study treatment.
‡Start of Phase B is defined as first dose day of Phase B study treatment or Week 24 for participants who entered Phase B off study treatment.

10.12 Appendix 12: Interim PK Analysis

Background

In Phase 1 dose-escalation studies, oral doses of ertugliflozin as high as 300 mg (single dose) and 100 mg qd (up to 14 days) were safe and well tolerated in healthy adult participants. The maximum dose given long term (12 weeks) to adult T2DM participants was 25 mg qd; this dose was generally safe and well tolerated. Based on the known linear PK of ertugliflozin, this provides a conservative 1.67-fold margin over the highest dose studied in the adult Phase 3 program (15 mg qd). The PK IA will be performed to confirm ertugliflozin exposure in pediatric T2DM participants in order to limit potentially exceeding the exposures observed with the highest dose used in adult Phase 2 clinical trials.

Due to challenges of collecting post-dose PK samples in the T2DM pediatric population, only trough samples will be collected to evaluate exposure in this population. With the sparse PK sampling, AUC_{24} can only be calculated using post hoc individual CL/F estimates from a population PK analysis. Shrinkage (a reduction in inter-individual variability) with estimating post hoc individual CL/F would be expected; this is an artifact of PK sampling that is too sparse. Therefore, the PK interim assessment will be based on observed trough concentrations collected in this study rather than model-based estimates of AUC_{24}.

Objective

Define criterion for the IA where:

1) If the mean AUC_{24} in the pediatric participants is 1.67 times higher than adults, the criterion would have >90% probability of leading to a recommendation to drop the 15 mg qd dose and discontinue the second randomization;

2) If the mean AUC_{24} in the pediatric participants is the same as adults, the criterion would have a <10% probability of incorrectly leading to a recommendation to drop the 15 mg qd dose and discontinue the second randomization.

Data

The adult population PK model and the input dataset for the final model were used for the simulation. Observed trough PK concentrations from 3 Phase 3 studies (P003/1022, P005/1019, and P007/1017) were included in the simulation. A PK sample was defined as “trough” if it was collected 20 to 28 hours post dose based on the actual PK sample collection time, and the time of the dose preceding PK sample collection. If a participant has multiple trough samples, only the first 3 were included to mimic the expected PK sampling in the pediatric study. A total of 3387 trough samples from 1335 adult participants were included in the dataset used for the simulation.

Methods

The PK IA will be conducted by comparing the median of the dose-normalized trough concentrations to a cutoff. The median value had the lowest variability among the various percentiles considered (eg, 90th or 95th percentiles) based on observed adult data in the Phase 3 studies and was therefore selected for IA decision-making. Dose normalization is appropriate given that the PK of ertugliflozin is linear from 0.5 mg to 300 mg. Dose normalization allows for the IA to be conducted with a smaller sample size for earlier decision-making because data from both the 5 mg and 15 mg doses can be combined. In this study, a PK sample will be defined as "trough" and included in the PK IA if it is collected 20 to 28 hours post dose based on the actual PK sample collection time, and the time of the dose preceding PK sample collection.

A population PK simulation was conducted to determine the sample size (number of participants) required for the IA and to select a cutoff value for the median of the dose normalized observed trough concentrations that would ensure: 1) if the model based mean AUC_{24} in the pediatric participants were 1.67 times higher than adult participants, the criterion would have >90% probability of leading to a recommendation to drop the 15 mg dose; 2) if the model based mean AUC_{24} in the pediatric participants is the same as adults participants, the criterion would have a <10% probability of incorrectly leading to a recommendation to drop the 15 mg qd dose. Three different samples sizes were simulated: N=15, N=20, and N=25.

Two different scenarios were simulated: 1) the pediatric PK (mean apparent CL/F) is the same as adults; and 2) the mean (typical value) CL/F in pediatrics is 7.2 L/hr, which is 60% of the typical value of adult CL/F (12.0 L/hr) and represents 1.67 times exposure (as if the 15 mg steady state AUC_{24} in pediatrics were the same as the 25 mg steady state AUC_{24} in adults). Under both scenarios, it was assumed 1 to 3 steady state trough samples per participant will be available for analysis.

<u>Scenario 1) Pediatric PK is the same as adult PK:</u>

The following assumptions were made: the PK in the pediatric population is the same as adults; the distribution of the trough concentrations is the same as the 3 adult Phase 3 studies where PK was collected (P003/1022, P005/1019, and P007/1017). Therefore, the observed trough concentrations from the 3 adult Phase 3 studies were used for this simulation.

The simulations were conducted by randomly sampling N=15, N=20, or N= 25 participants from the 1335 phase 3 participants. For each simulation, the observed trough concentrations from the sampled participants (N=15, N=20, or N=25) were dose normalized and the median was compared to a cutoff value. If the median was greater than the cutoff, this was counted as a decision to down-titrate the participants who were up-titrated to the 15 mg ertugliflozin dose and discontinue the second randomization; if median was less than or equal to the cutoff, this was counted as a decision to keep the 15 mg ertugliflozin dose and keep the second randomization. Given the linearity of ertugliflozin PK and Week 6, 12, and 24 troughs are at steady state regardless of the dose the participant is taking immediately prior to the PK draw, the random sampling of the dose-normalized trough concentrations does not

differentiate whether a participant is on the 5 mg ertugliflozin dose or the 15 mg ertugliflozin qd dose. A thousand simulations were run for each sample size, and the percentage of times that a decision to drop the 15 mg dose was made was calculated.

Scenario 2) The pediatric AUC_{24} is 1.67 times that of the adults given the same dose:

Trough concentrations were simulated using a modified ertugliflozin adult population PK model where the typical value of CL/F (7.2 L/hr) is 60% of the typical value of CL/F (12.0 L/hr) in the final adult population PK model. The input dataset for this simulation was a subset of the input dataset of the final adult population PK model with only participants from the 3 Phase 3 studies (P003/1022, P005/1019, and P007/1017). In this scenario, it was assumed that the mean (typical value) for all PK parameters, eg, the volume of distribution and rate of absorption, as well as intersubject variability of CL/F and intrasubject variability (residual error) were the same between the adult phase 3 population and the pediatric population, the only difference being the mean CL/F was set to 60% of the mean CL/F of the adults. Thus, in the population PK model used to simulate the pediatric trough concentrations, all parameters (fixed effects and random effects) were set to the same values as in adults, with the exception of typical value of the clearance changed from 12.0 L/hr to 7.2 L/hr.

To obtain the hypothetical trough levels, simulations were run to generate 200 sets of the 1335 Phase 3 participants using the observed Phase 3 dosing times and PK sampling times. For each participant, a maximum of 3 troughs were used. If a participant had more than 3 troughs, the first 3 were used.

Using the simulated trough concentrations from 1335x200=267,000 participants, random samples of N=15, N=20, or N=25 participants were drawn for each iteration. In each iteration to simulate N participants with **Week 6** PK sample collections, the following assumptions were used: 1) Assume a total enrollment rate of 2 participants (placebo+ertugliflozin) per month (based on sitagliptin pediatric T2DM recruitment rate). 2) In each iteration, for 2 participants (with only **Week 6** PK sample collection), if the participant had more than 1 trough, only the first 1 was used. 3) In each iteration, for 4 participants (with both **Week 6** and **Week 12** PK collections) if the participant had more than 2 troughs, only the first 2 were used. 4) In each iteration, for the remaining participants a maximum of 3 troughs (as discussed in previous paragraph) were used. These trough concentrations from the sampled participants were dose normalized and the median was compared to a cutoff value. If the median was greater than the cutoff, this was counted as a decision to down-titrate the participants who were up-titrated to the 15 mg dose and discontinue the second randomization; if median was less than or equal to the cutoff, this was counted as a decision to keep the 15 mg dose and the second randomization. Given the linearity of ertugliflozin PK and **Week 6**, **Week 12**, and **Week 24** troughs are at steady state regardless of the dose the participant is taking immediately prior to the PK draw, the random sampling of the dose-normalized trough concentrations does not differentiate whether a participant is on the 5 mg or the 15 mg qd ertugliflozin dose. One thousand iterations were run for each condition (sample size and cutoff), and the percentage of times that the 15 mg dose was dropped was calculated.

Nonlinear mixed effects modeling using NONMEM 7.3 was used to generate the population PK simulations for the trough concentrations. All other data processing and simulation were conducted using R 3.4.3.

Results

Simulation results showing the proportion of trials in which the 15 mg dose met the criteria for recommendation to be dropped under Scenario 1 and Scenario 2 are reported in Table 15. As a reference, the adult pop-PK model predicted median of the dose-normalized C_{trough} (including inter and intra participant variability) is 1.18 ng/mL/mg.

Table 15 Simulation Results: Estimated Probability that the 15 mg Dose Could be Discontinued Based on the PK IA

Cutoff (ng/mL/mg)	Scenario 1: CL/F is the same for adults and pediatrics			Scenario 2: CL/F of the pediatrics is 60% that of adults		
	N=15	N=20	N=25	N=15	N=20	N=25
2.0	<1%	<1%	<1%	90.0%	90.9%	94.8%
2.1	<1%	<1%	<1%	86.0%	86.6%	91.1%

CL/F=apparent clearance

The cutoff is compared to the median of the dose-normalized trough. N is the sample size (number of participants on ertugliflozin) assuming 1-3 trough PK samples per participant. 1000 simulations were conducted per Scenario, cutoff value, and sample number.

Based on the results presented in Table 15, given a cutoff of 2.0 ng/mL/mg, a sample size of 20 ertugliflozin participants would provide a <1% chance of incorrectly deciding to drop the 15 mg dose if the exposure in pediatrics and adults is the same and a 90.9% probability that a correct decision to drop the 15 mg dose would be made if the exposure in pediatrics is equivalent to 25 mg dose in adults. PK sample collection in Phase 3 may be less well controlled, and it is expected that not all planned troughs will be available for the IA due to missing samples or sample collection outside of the defined 20-28-hour window. With N=15 and a cutoff of 2.0 ng/mL/mg, it is expected that a correct decision to drop the 15 mg dose would be made 90.0% of the time under the condition that the pediatric exposure was 1.67 times that in adults.

10.13 Appendix 13: Tanner Staging

Tanner Stages of Maturation

In male participants, Tanner Staging will be assessed by testicular volume and pubic hair distribution as denoted in the listings below. An orchidometer (Prader) will be used to evaluate testicular volume. The testes will be palpated with a gloved hand and the wooden ball of the orchidometer that most closely matches the testicular size is determined. For each male participant, Tanner Staging will be recorded for both pubic hair and testicular volume. When both are Stage V, then no further exam is required.

In female participants, Tanner Staging will be evaluated by the stage of breast development and pubic hair distribution as denoted in the listings below. If breast development is asymmetrical, the development should be characterized using more advanced stage. Additionally, each female participant will be asked at each visit if menarche has occurred and this information will be captured at each visit. For each female participant, Tanner Staging will be recorded for both pubic hair and breast. When both are Stage V, then no further exam is required.

Pubic hair (both male and female)

- Tanner I – none (prepubertal state)
- Tanner II – small amount of long, downy hair with slight pigmentation at the base
- Tanner III – hair becomes more coarse and curly and begins to extend laterally
- Tanner IV – adult-like hair quality, extending across pubis but sparing medial thighs
- Tanner V—hair extends to medial surface of the thigh

Genitals (male)

- Tanner I – prepubertal (testicular volume less than 4.0 mL; small penis)
- Tanner II – testicular volume between 4.0 and 8 mL; skin on scrotum thins, reddens and enlarges; penis length unchanged
- Tanner III – testicular volume between 9 and 12 mL; scrotum enlarges further; penis begins to lengthen
- Tanner IV – testicular volume between 15 and 20 mL; scrotum enlarges further and darkens; penis increases in length and circumference
- Tanner V – testicular volume greater than 20 mL; adult scrotum and penis

Breast (female)

- Tanner I – no glandular tissue; areola follows the skin contours of the chest (prepubertal)
- Tanner II – breast bud forms, with small area of surrounding glandular tissue; breast but within area of areola; areola begins to widen
- Tanner III – breast begins to become more elevated, and extends beyond the borders of the areola which continues to widen but remains in contour with surrounding breast
- Tanner IV – increase breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast
- Tanner V – breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla

10.14 Appendix 14: Abbreviations

Abbreviation	Expanded Term
A1C	glycosylated hemoglobin
ADA	American diabetic association
AE	adverse event
AHA	antihyperglycemic agent
ALP	Alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
APaT	all participants as treated
APRFU	all post-randomization follow-up
AST	aspartate transaminase
AUC	area under the curve
BICR	blinded independent central review
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulation
CI	confidence interval
CL/F	apparent clearance
cLDA	constrained longitudinal data analysis
CMQ	custom MedDRA query
CONSORT	consolidated standards of reporting trials
CSR	clinical study report
CTFG	clinical trial facilitation group
DBP	diastolic blood pressure
DCCT	diabetes control and complications trial
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
ECI	events of clinical interest
eCRF	electronic case report form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ER	excluding data after initiation of glycemic rescue/intensification therapy
ERC	ethics review committee
ESS	Effective Sample Size
EU	European Union
FAS	full analysis set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFSG	fasting fingerstick glucose
FPG	fasting plasma glucose
FS	fingerstick
FSG	fingerstick glucose
FSH	follicle stimulating hormone
GCP	Good Clinical Practice

Abbreviation	Expanded Term
GLUT1-4	glucose transporters
HA	hypoglycemia assessment
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IR	including data after initiation of glycemic rescue/intensification therapy
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
J2R	jump to reference
LDL-C	low-density lipoprotein cholesterol
LS	least-squares
M&N	Miettinen and Nurminen
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputations
MNAR	missing not at random
N/A	not applicable
NGSP	National glycohemoglobin standardization program
NHANES	National Health and Nutrition Examination Survey
NSAE	non-serious adverse event
OGTT	oral glucose tolerance test
Pbo	placebo
PDLC	predefined limits of change
PE	physical exam
PK	pharmacokinetics
qd	once daily
RD	retrieved dropout
REML	restricted (or residual) maximum likelihood
RMSE	root mean squared error
RNA	ribonucleic acid
RTB	return-to-baseline
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SCR	screening
SE	standard error
SGLT1	sodium glucose co-transporter 1
SGLT2	sodium glucose co-transporter 2
SMBG	self-monitoring of blood glucose
SoA	schedule of activities
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reactions

Abbreviation	Expanded Term
T2DM	type 2 diabetes mellitus
TC	telephone call/telephone contact
TE	treatment effect
TP	treatment policy
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
USA / US	United States of America
UTI	urinary tract infection
WHO	World Health Organization
WI	washout imputation
Wk	week
WOCBP	woman of childbearing potential

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