Amsterdam, 29 January 2026
EMADOC-1700519818-2547236
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Steglatro

International non-proprietary name: Ertugliflozin

Procedure no.: EMA/PAM/0000307025

Marketing authorisation holder (MAH): Merck Sharp & Dohme B.V.

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	2025-12-01	2025-12-01	☐
☐	CHMP Rapporteur Assessment Report	2026-01-05	2026-01-05	☐
☐	CHMP members comments	2026-01-19	2026-01-19	☐
☐	Updated CHMP Rapporteur Assessment Report	2026-01-22	2026-01-22	☐
☒	CHMP adoption of conclusions:	2026-01-29	2026-01-29	☐

Administrative information

Procedure resources	
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1. Introduction

On 15 October 2025, the MAH submitted a completed paediatric study for Steglatro (MK-8835-P059/B1521066), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The MAH informed the EMA that, further to this Article 46 submission, a separate Type II variation application is planned to update the product information based on the results of study MK-8835-P059/B1521066 (also known as P059) to expand the indication of ertugliflozin to children 10 years of age and older.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the study MK-8835-P059/B1521066 (also known as P059): "A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled Clinical Study to Evaluate the Safety and Efficacy of Ertugliflozin (MK-8835/PF-04971729) in Paediatric Participants (ages 10 to 17 years, inclusive) with Type 2 Diabetes Mellitus" is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

No new study formulation was developed or used for P059. Paediatric participants received ertugliflozin for investigational use, which is identical in formulation to the commercially available ertugliflozin for adults.

2.3. Clinical aspects

2.3.1. Introduction

In accordance with Article 46 of Commission Regulation (EC) NO 1901/2006, the MAH is submitting herewith a final study report summarizing the results of paediatric study MK-8835-059 (also known as P059) for Steglatro (ertugliflozin) 5 mg and 15 mg, film-coated tablets.

In the EU, ertugliflozin is approved for adults for T2DM. Study P059 is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of ertugliflozin in paediatric participants with T2DM on a stable dose of metformin ≥1500 mg/day with or without stable insulin. Study P059 was performed to evaluate ertugliflozin as an alternative therapeutic treatment option for paediatric patients with T2DM and inadequate glycemic control on metformin with or without insulin. Study P059 was part of the Paediatric Investigational Plan (PIP) for Steglatro.

2.3.2. Clinical study

MK-8835-059 - A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled Clinical Study to Evaluate the Safety and Efficacy of Ertugliflozin (MK-8835/PF-04971729) in Paediatric Participants (ages 10 to 17 years, inclusive) with Type 2 Diabetes Mellitus

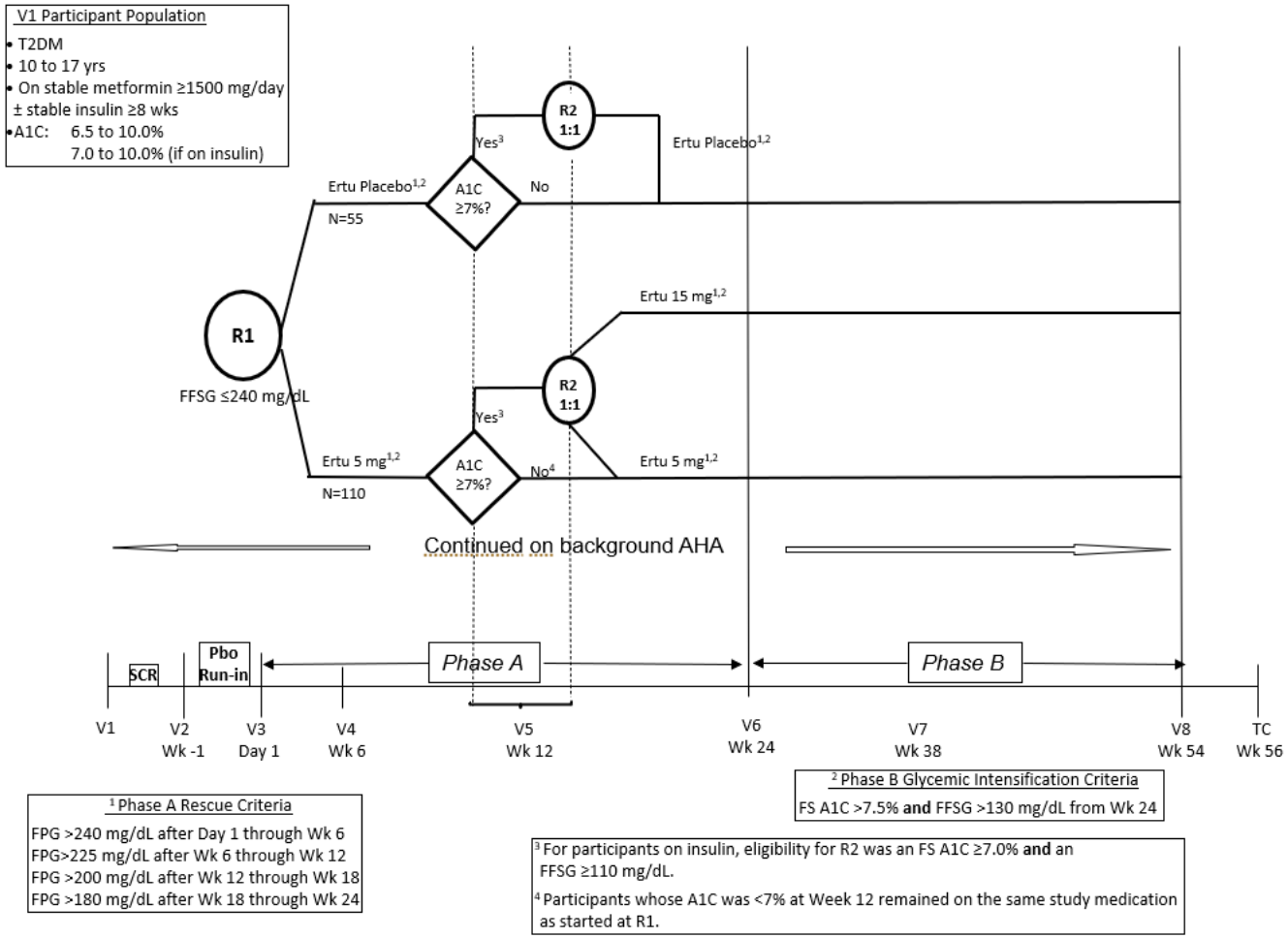
Description

Study MK-8835-P059/B1521066 (also known as P059) was a Phase 3, multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of ertugliflozin in pediatric participants from 10 years and above, with T2DM on a stable dose of metformin ≥1500 mg/day with or without stable insulin.

A total of 166 pediatric participants were randomized in a 2:1 ratio to either ertugliflozin 5 mg or placebo. At Week 12, participants in the ertugliflozin 5-mg group whose A1C was ≥7.0% (or A1C ≥7.0% and FFSG ≥110 mg/dL if on 5 mg ertugliflozin + insulin) were rerandomized 1:1 to either continue ertugliflozin 5 mg or uptitrate directly to ertugliflozin 15 mg. Participants in the placebo group were mock titrated maintain the blind. See Figure 1.

The primary efficacy objective was to compare the effect of ertugliflozin with placebo on the change from baseline in A1C at Week 24. The primary safety objective was to assess the safety and tolerability of ertugliflozin over 24 and 54 weeks. General safety and tolerability assessments were conducted including prespecified AEs of interest (e.g. symptomatic hypoglycemia, hypovolemia, genital mycotic infections (gender specific), and UTIs). Sparse sampling to assess PK of ertugliflozin and confirm exposure were also performed.

Figure 1 Study design



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

Rapporteur's comment:

The overall study design and the duration of the study are considered adequate.

Methods

Study participants

The study included pediatric participants 10 years and above, with a diagnosis of T2DM for ≥ 2 years or for <2 years with a fasting C-peptide value >0.6 ng/mL; A1C ≥6.5% and ≤10.0%; BMI ≥85th percentile; who were on a stable dose of metformin with or without insulin for ≥8 weeks.

Main inclusion criteria:

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

    i. Participant had diabetes diagnosed by 1 of the following 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 OGTT plasma glucose ≥200 mg/dL (11.1 mmol/L), OR

        d. A1C ≥6.5% (48 mmol/mol) test performed using a method that was NGSP certified and standardized to the DCCT assay.

    ii. Participant had BMI ≥85th percentile at screening OR participant had a history of being overweight or obese at time of diagnosis of T2DM.

2. Had:

    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.

3. Were:

    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).

4. Had 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.

Main exclusion criteria:

Participants were excluded from the study if any of the following key criteria were met:

1. Type 1 diabetes mellitus or documented evidence of positive diabetes auto-antibodies.

2. Had symptomatic hyperglycemia and/or moderate to large ketonuria requiring immediate initiation of another anti-hyperglycaemic agent (AHA), including insulin.

3. Had history of malignancy ≤5 years prior to signing informed consent.

4. Had a known hypersensitivity or intolerance to any SGLT2 inhibitor.

5. Participant was on other medications associated with weight changes and was not weight stable.

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

7. Had been previously diagnosed with disorders of growth or bone metabolism.

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

9. Had an eGFR <45 mL/min/1.73 m2 at Screening Visit/Visit 1.

10. Had a history of idiopathic acute pancreatitis or chronic pancreatitis.

Rapporteur's comment:

Inclusion and exclusion criteria are overall considered adequate for recruiting a study population representative for the patient population and for a possible future treatment population. It is noted that according to inclusion criteria, all participants had background medication. For adults, ertugliflozin is indicated for treatment as monotherapy and as addition to other diabetes medications. If a blood glucose lowering effect of treatment with ertugliflozin as monotherapy in the future can be assumed for children will be a matter of the indication which will be applied for in, and the assessment of, the future Type II variation envisaged to be submitted by the MAH.

Treatments

Investigational product

At Day 1/Randomisation, all qualified participants were 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

At week 12 a second randomisation took place. Eligible participants in the ertugliflozin 5-mg group treated with ertugliflozin 5 mg: FS A1C ≥7.0% (53 mmol/mol) or treated with ertugliflozin 5 mg and insulin: FS A1C ≥7.0% (53 mmol/mol) and FFSG ≥110 mg/dL (6.1 mmol/L) were randomised 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 underwent a mock second randomization to maintain blinding, with no change in study medication. Participants who did not meet the threshold(s) for a second randomisation continued ertugliflozin 5 mg/placebo.

If a participant discontinued study medication before Visit 5/Week 12, the second randomisation was not performed.

Prior and concomitant medication

Metformin (as background) and insulin (as background or rescue/intensification therapy when appropriate) are the only AHAs permitted in the study. Medications specifically prohibited in the exclusion criteria, such as medications for weight loss and hyperthyroidism or other SGLT2 inhibitors, were not allowed during the study.

Rescue medication and glycemic intensification during Phases A and B of the study

Criteria for initiation of rescue medication in Phase A is presented in Table 1. Insulin was used as 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). Participants already on insulin (i.e. on metformin + insulin) should increase the insulin dose by ≥15%.

Table 1 Criteria for initiation of rescue medication in 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).

For patients not rescued in Phase A, there is an option of intensifying glycemic control in Phase B if high blood glucose levels. Glycemic intensification criteria are shown in Table 2.

Table 2 Glycemic intensification criteria

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.		

Rapporteur's comment:

The rescue criteria, and the use of insulin as rescue medication are acknowledged.

Objectives

The **primary** efficacy **objective** of the study was to compare the addition of ertugliflozin with the addition of placebo on the change from baseline in A1C at 24 weeks. For safety investigation, the primary objective was to assess the safety and tolerability of ertugliflozin over 24 weeks and 54 weeks.

The **secondary objectives** included

- To compare the effect of the addition of:
    - ertugliflozin, with dosing optimised according to A1C response, to the addition of placebo on the change from baseline in A1C at 24 weeks
    - ertugliflozin 5 mg with the addition of placebo on the change from baseline in A1C at 24 weeks
    - ertugliflozin to the addition of placebo on the change from baseline in fasting plasma glucose (FPG) at 24 weeks.
- To assess the within-group (ertugliflozin and placebo) changes from baseline at 54 weeks for A1C and FPG.

Exploratory objectives included:

To assess the within-group (ertugliflozin and placebo) mean changes from baseline for A1C at week 12, 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)

and acceptability and palatability of ertugliflozin in terms of AEs.

To assess the within-group (ertugliflozin and placebo) mean ertugliflozin exposure at 24 weeks was another explorative objective.

A pharmacokinetic objective included to explore the exposure of ertugliflozin.

Outcomes/endpoints

Primary endpoints

Efficacy: Change from baseline in A1C at 24 weeks between ertugliflozin and placebo

Safety: Safety and tolerability of ertugliflozin over 24 weeks and 54 weeks measured as AEs and discontinuation of study medication due to AEs.

Secondary endpoints

The secondary endpoints included:

- The change from baseline on FPG at Week 24 for ertugliflozin versus placebo
- The changes from baseline within-group (ertugliflozin and placebo) on HbA1c and FPG at week 54.

For a list of efficacy variables/endpoints including explorative endpoints, see Table 3.

Table 3 Efficacy variables/endpoints

Primary
Change from Baseline in A1C at Week 24
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 • Homeostatis Model Assessment of β-cell function • Homeostatis Model Assessment of insulin resistance
A1C = glycosylated hemoglobin; BMI = body mass index; FPG = fasting plasma glucose.

Rapporteur's comment:

The primary efficacy endpoint was change from baseline in A1C at 24 weeks between ertugliflozin (5 mg or 15 mg, all doses combined) and placebo.

Primary safety endpoint consisted of Safety and tolerability of ertugliflozin over 24 weeks and 54 weeks measured as AEs and discontinuation of study medication due to AEs.

Secondary efficacy endpoints included change from baseline on FPG at Week 24 for ertugliflozin (5 mg or 15 mg, all doses combined) versus placebo and changes from baseline within-group (ertugliflozin and placebo) on HbA1c and FPG at week 54.

The endpoints are acknowledged as clinically relevant.

Sample size

The actual study size was 166 participants randomised, 111 for ertugliflozin and 55 for placebo. When planning the study, sample size was originally planned to be approximately 150 participants with 50 participants in the placebo group and 100 participants in the ertugliflozin group (ertugliflozin 5 mg and 15 mg groups combined). Assuming that 90% of participants will have data at Week 24 on study

medication, the sample size would provide at least 84% power to detect a between-group difference in A1C change from baseline at Week 24 of -0.6% given a standard deviation of 1.1% under the TP estimand with RD imputation given a 2-sided alpha=0.05. Under the TE estimand using the cLDA method, the planned sample size provides 82% power assuming the difference in A1C change from baseline at Week 24 is -0.6% using a standard deviation of 1.1% and missing data due to discontinuation from study medication or censoring due to initiation of glycemic rescue or intensification is at most 20%. According to the supplemental statistical analysis plan, the study size was revised to 165 participants, with 55 in the placebo group and 110 participants in the ertugliflozin group.

Randomisation and blinding (masking)

After screening at visit 1, a screening period between visits 1 and 2, and an approximately 1 w single-blind placebo run-in period between visits 2 and 3, the eligible participants were, at visit 3, randomised 2:1 to receive oral, double-blind 5 mg ertugliflozin or placebo. Randomisation was 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

At Visit 5/Week 12, eligible participants in the ertugliflozin 5 mg treatment group underwent a second randomisation 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 to maintain the blind.

Eligibility for the second randomization was defined as having a:

- finger-stick A1C ≥7.0% (53 mmol/mol) for participants treated with ertugliflozin 5 mg or
- finger-stick A1C ≥7.0% (53 mmol/mol) and FFSG ≥110 mg/dL (6.1 mmol/L) for participants treated with ertugliflozin 5 mg and insulin.

Randomisation at Visit 5/Week 12 was stratified according to Insulin use: Yes OR No.

Participants who do not meet the threshold(s) for a second randomization will continue on ertugliflozin 5 mg/placebo. Also, to maintain the blind, all participants were treated with a placebo matching the 15 mg ertugliflozin tablet from start, which at w 12 was changed for ertugliflozin 15 mg or kept, according to the second randomization.

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

Statistical Methods

For the primary hypothesis, analyses were made both using treatment policy (TP) estimand (estimating the difference in change from baseline comparing the effect of being randomized to ertugliflozin versus placebo) and Treatment Effect (TE) estimand (estimating the effect of being treated with ertugliflozin versus placebo).

Efficacy analyses were performed in the Full analysis set (FAS) population, defined as all randomized participants who received at least 1 dose of study medication. All 166 randomized participants received at least 1 dose of study medication and no participants were excluded from the FAS population. The primary analysis approach for the TP estimand evaluated the treatment difference via an analysis of covariance (ANCOVA) model with missing Week 24 A1C data imputed using a retrieved dropout (RD)

approach. The primary analysis approach for the TE estimand evaluated the treatment difference via a constrained longitudinal analysis model.

Tippning point sensitivity analysis and subgroup analyses were made of the primary endpoint change from baseline in A1C (%).

The key secondary hypotheses were assessed only under the TP estimand and tested in accordance with the multiplicity strategy. All other secondary and tertiary endpoints were assessed only under the TE estimand.

For multiplicity the following was stipulated: 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 type 1 error rate for the Bayesian methodology addressing the primary hypothesis under the TP estimand was estimated via simulation to be 0.10.

Safety analyses were based on the All patients as treated (APaT) population, which included all 166 randomised participants who received at least 1 dose of study medication.

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.

Pharmacokinetics

Sparse predose PK samples were collected at 3 protocol-specified visits (Visit 4/Week 6, Visit 5/Week 12, and Visit 6/Week 24) to assess ertugliflozin exposure. To support the second randomization at Visit 5/Week 12, which allowed eligible participants to increase their dose from 5 to 15 mg, a protocol specified interim analysis (IA) for PK data was conducted. The IA was performed by an unblinded PK analyst external to the Sponsor after 35 participants received study medication (23 on ertugliflozin and 12 on placebo) and results were provided to the eDMC. The median dose-normalized predose exposures observed in the PK population were evaluated against the predefined threshold of 2 ng/mL/mg. Based on this evaluation, the eDMC concluded that the second randomization was appropriate and supported dose escalation to 15 mg for eligible participants.

Results

Participant flow

A total of 273 participants were screened and 166 were randomised. The majority of non-randomized participants were screen failures, with non-eligible A1C values being the most common reason for screen failure For participant disposition, see Table 4. In brief:

• Ertugliflozin: 111 treated, 105 completed treatment, 6 discontinued treatment, 106 completed study, 5 discontinued study

• Placebo: 55 treated, 49 completed treatment, 6 discontinued treatment, 53 completed study, 2 discontinued study

Table 4 Disposition of Participants all participants randomised

	Combined Ertugliflozin		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Not Randomized					107	
Participants in population	111		55		166	
Trial Disposition						
Completed	106	(95.5)	53	(96.4)	159	(95.8)
Discontinued	5	(4.5)	2	(3.6)	7	(4.2)
Physician Decision	2	(1.8)	1	(1.8)	3	(1.8)
Withdrawal By Subject	3	(2.7)	1	(1.8)	4	(2.4)
Participant Study Medication Disposition						
Completed	105	(94.6)	49	(89.1)	154	(92.8)
Discontinued	6	(5.4)	6	(10.9)	12	(7.2)
Adverse Event	0	(0.0)	1	(1.8)	1	(0.6)
Hypoglycemia Discontinuation Criteria	1	(0.9)	0	(0.0)	1	(0.6)
Patient Decided To Stop The Study Medication And Agreed With Sub Investigator To Shift To Alternative Treatments.Patient Agreed To Continue Follow Up As Per The Protocol Scheduled Visit.	0	(0.0)	1	(1.8)	1	(0.6)
Patient's Parents Decided That Their Son Will Not Take The Study Medication And Agreed To Complete The Study Of Treatment	0	(0.0)	1	(1.8)	1	(0.6)
Physician Decision	2	(1.8)	1	(1.8)	3	(1.8)
Pregnancy	0	(0.0)	1	(1.8)	1	(0.6)
Withdrawal By Subject	3	(2.7)	1	(1.8)	4	(2.4)
Protocol Milestone						
Continued Into Phase B	108	(97.3)	55	(100.0)	163	(98.2)
Not Continuing Into Phase B	3	(2.7)	0	(0.0)	3	(1.8)
Each Participant is counted once for Trial Disposition, Participant Study Medication Disposition, Protocol Milestone based on the latest corresponding disposition record.						

At Week 12, the proportion of participants who met the FS A1C criterion for possible up-titration (≥7.0%) was lower in the ertugliflozin group (46.4%) compared with the placebo group (67.9%). See Table 5

Table 5 The proportion of participants who met the FS A1C criterion for possible up-titration

	Combined Ertugliflozin		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	111	(100.0)	55	(100.0)	166	(100.0)
with FS A1C data at Week 12	109	(98.2)	52	(94.5)	161	(97.0)
without an FS A1C at Week 12 but had Visit 5/Week 12	1[d]	(0.9)	1[e]	(1.8)	2	(1.2)
FS A1C[a] and Up-titration[b] at Week 12						
Week 12 FS A1C <7.0%	59[f]	(53.6)	17	(32.1)	76	(46.6)
Re-randomized to be up-titrated[c]	1	(0.9)	0	(0.0)	1	(0.6)
Week 12 FS A1C ≥7.0%	51	(46.4)	36	(67.9)	87	(53.4)
Re-randomized to be up-titrated	25	(22.7)	0	(0.0)	25	(15.3)
By Week 12 Insulin Status						
On insulin at Week 12	48	(43.6)	24	(45.3)	72	(44.2)
Week 12 FS A1C <7.0%	13	(11.8)	5	(9.4)	18	(11.0)
Re-randomized to be up-titrated[c]	1	(0.9)	0	(0.0)	1	(0.6)
Week 12 FS A1C ≥7.0%	35	(31.8)	19	(35.8)	54	(33.1)
Re-randomized to be up-titrated	16	(14.5)	0	(0.0)	16	(9.8)
Not On insulin at Week 12	62	(56.4)	29	(54.7)	91	(55.8)
Week 12 FS A1C <7.0%	46	(41.8)	12	(22.6)	58	(35.6)
Week 12 FS A1C ≥7.0%	16	(14.5)	17	(32.1)	33	(20.2)
Re-randomized to be up-titrated	9	(8.2)	0	(0.0)	9	(5.5)

[a] Participants with a missing FS A1C value at Week 12 were considered as having a FS A1C of <7.0%.
[b] Up-titration is applicable only to the ertugliflozin 5 mg group from the original randomization (participants randomized to placebo do not get re-randomized at Week 12, regardless of their FS A1C).
[c] Per the protocol, participants with FS A1C <7.0% at Week 12 were not eligible for re-randomization.
[d] This participant's FS A1C was collected 8 days prior to the re-randomization date, which was outside the window used for this table.
[e] This participant's FS A1C result was not captured in InForm.
[f] Includes one participant whose Week 12 FS A1C was incorrectly entered as mmol/mol instead of % with a numerical value meeting the A1C criterion for up-titration.

Source: [P059MK8835: adam-adsl]

Rapporetur's comment:

111 participants were randomised to the active treatment group. At week 12, 51 participants met the FS A1C criterion for possible up-titration (≥7.0%), of which 25 were re-randomised to up-titration and 26 were re-randomised to stay on the 5 mg treatment. In the placebo group 36 participants had A1C ≥7.0% but according to the protocol, they were mock-randomised to maintain the blind.

Recruitment

The study was conducted at 104 centers in 22 countries (Belgium, Canada, Colombia, Costa Rica, Dominican Republic, France, Guatemala, Hungary, Israel, Italy, Malaysia, Mauritius, Mexico, Philippines, Poland, Russia, Saudia Arabia, Turkey, Ukraine, United Arab Emirates, United Kingdom, and the US). The first participant´s first visit was on 08-OCT-2019 and last participant´s last visit on 11-APR-2025.

Baseline data

Demographic and patient and disease baseline characteristics were generally comparable between the ertugliflozin and placebo groups. See Table 6 and Table 7.

A total of 41% of participants were male, the most commonly reported race was white (59.6%), and 43.4% of participants were Hispanic or Latino. The mean age of participants was 14.8 years old; 41.4% were ≤14 years old. The population was obese (mean BMI 31.5 kg/m2, mean BMI percentile 95.6%) with central obesity. At screening, all participants were taking metformin with a mean dose of 1717.4 mg; 44.0% were on metformin + insulin. The mean A1C was 8.0% and mean FPG was ~144 mg/dL at baseline in both groups. The majority of participants in both groups had T2DM for ≥1 year. See Table 7.

Table 6 Participant Characteristics. All participants treated

	Combined Ertugliflozin		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	111		55		166	
Sex						
Male	43	(38.7)	25	(45.5)	68	(41.0)
Female	68	(61.3)	30	(54.5)	98	(59.0)
Age at Randomization (Years)						
≤14	44	(39.6)	23	(41.8)	67	(40.4)
>14	67	(60.4)	32	(58.2)	99	(59.6)
Mean	14.7		15.1		14.8	
SD	2.0		1.7		1.9	
Median	15.0		15.0		15.0	
Range	10 to 18		11 to 18		10 to 18	
Race						
American Indian Or Alaska Native	14	(12.6)	5	(9.1)	19	(11.4)
Asian	15	(13.5)	10	(18.2)	25	(15.1)
Black Or African American	4	(3.6)	1	(1.8)	5	(3.0)
Multiple	10	(9.0)	8	(14.5)	18	(10.8)
American Indian Or Alaska Native, White	5	(4.5)	4	(7.3)	9	(5.4)
Black Or African American, White	5	(4.5)	3	(5.5)	8	(4.8)
Native Hawaiian Or Other Pacific Islander, White	0	(0.0)	1	(1.8)	1	(0.6)
White	68	(61.3)	31	(56.4)	99	(59.6)
Ethnicity						
Hispanic Or Latino	50	(45.0)	22	(40.0)	72	(43.4)
Not Hispanic Or Latino	60	(54.1)	33	(60.0)	93	(56.0)
Unknown	1	(0.9)	0	(0.0)	1	(0.6)
Geographic Region						
EU	12	(10.8)	8	(14.5)	20	(12.0)

	Combined Ertugliflozin		Placebo		Total	
	n	(%)	n	(%)	n	(%)
United States	5	(4.5)	5	(9.1)	10	(6.0)
Latin America	48	(43.2)	21	(38.2)	69	(41.6)
Middle East	30	(27.0)	12	(21.8)	42	(25.3)
Asia Pacific	16	(14.4)	9	(16.4)	25	(15.1)
Body Weight (kg)						
Participants with data	111		55		166	
Mean	84.0		85.8		84.6	
SD	22.8		26.8		24.1	
Median	78.3		81.9		80.6	
Range	44.5 to 177.4		39.4 to 201.6		39.4 to 201.6	
Body Mass Index (kg/m2) at Screening						
Participants with data	111		55		166	
Mean	31.3		31.7		31.5	
SD	7.1		8.1		7.4	
Median	30.0		29.8		29.9	
Range	19.8 to 57.8		18.2 to 64.0		18.2 to 64.0	
BMI percentile at Screening						
<85%	9	(8.1)	4	(7.3)	13	(7.8)
≥85%	102	(91.9)	51	(92.7)	153	(92.2)
Participants with data	111		55		166	
Mean	95.6		95.6		95.6	
SD	8.9		9.0		8.9	
Median	99.3		98.9		99.2	
Range	50.8 to 100.0		57.1 to 100.0		50.8 to 100.0	
Waist Circumference (cm) Males						
Participants with data	43		25		68	
Mean	102.9		104.4		103.4	
SD	18.6		19.4		18.8	
Median	99.0		102.3		99.5	
Range	76.4 to 155.0		71.0 to 154.0		71.0 to 155.0	
Waist Circumference (cm) Females						
Participants with data	67		29		96	
Mean	98.8		98.1		98.6	
SD	18.4		16.6		17.8	
Median	97.1		98.5		97.4	
Range	63.1 to 160.0		70.0 to 134.5		63.1 to 160.0	
Waist Circumference to Height Ratio Males						
Participants with data	43		25		68	
Mean	0.61		0.62		0.61	
SD	0.10		0.10		0.10	
Median	0.60		0.58		0.59	
Range	0.44 to 0.91		0.48 to 0.87		0.44 to 0.91	
Waist Circumference to Height Ratio Females						
Participants with data	67		29		96	
Mean	0.62		0.61		0.62	
SD	0.11		0.10		0.11	
Median	0.60		0.61		0.60	
Range	0.40 to 0.99		0.46 to 0.81		0.40 to 0.99	
Diastolic Blood Pressure (mmHg)						
Participants with data	111		55		166	
Mean	71.4		71.4		71.4	
SD	7.6		8.7		8.0	
Median	71.0		72.0		71.0	
Range	53.0 to 89.0		56.0 to 100.0		53.0 to 100.0	
Systolic Blood Pressure (mmHg)						
Participants with data	111		55		166	
Mean	115.2		115.9		115.4	
SD	11.9		10.7		11.5	
Median	116.0		117.0		116.0	
Range	89.0 to 144.0		90.0 to 141.0		89.0 to 144.0	
Metformin Dose at Screening						
<1500 mg	13	(11.7)	3	(5.5)	16	(9.6)
≥1500 mg - ≤2000 mg	90	(81.1)	49	(89.1)	139	(83.7)
>2000 mg	8	(7.2)	3	(5.5)	11	(6.6)

	Combined Ertugliflozin		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants with data	111		55		166	
Mean	1692.8		1770.0		1718.4	
SD	380.5		358.4		374.1	
Median	1700.0		1700.0		1700.0	
Range	1000.0 to 3000.0		850.0 to 3000.0		850.0 to 3000.0	
Insulin Use at Screening						
No	62	(55.9)	31	(56.4)	93	(56.0)
Yes	49	(44.1)	24	(43.6)	73	(44.0)
Total Daily Dose Insulin at Screening						
Participants with data	49		24		73	
Mean	38.8		37.9		38.5	
SD	24.5		21.9		23.5	
Median	30.0		33.0		32.0	
Range	7.0 to 120.0		12.0 to 84.0		7.0 to 120.0	
Total Daily Dose Insulin/Body Weight (kg) at Screening						
Participants with data	49		24		73	
Mean	0.49		0.52		0.50	
SD	0.28		0.37		0.31	
Median	0.45		0.42		0.42	
Range	0.10 to 1.10		0.13 to 1.62		0.10 to 1.62	

SD=Standard deviation.
Hungary, Italy, Russian Federation, Turkey, Ukraine are classified as EU countries, EU-like countries, or countries in Europe not in the EU.
Colombia, Costa Rica, Dominican Republic, Guatemala, Mexico are classified as Latin American countries. Israel, Saudi Arabia, United Arab Emirates are classified as Middle Eastern countries.
Malaysia, Mauritius, Philippines are classified as Asian Pacific countries.

Source: [P059MK8835: adam-adsl]

Table 7 Summary of Baseline Efficacy Endpoints and Diabetes History

	Combined Ertugliflozin		Placebo	
	n	(%)	n	(%)
Participants in population	111		55	
A1C (%, mmol/mol)				
<8% (64 mmol/mol)	53	(47.7)	29	(52.7)
≥8% (64 mmol/mol) and <9% (75 mmol/mol)	36	(32.4)	15	(27.3)
≥9% (75 mmol/mol)	22	(19.8)	11	(20.0)
Participants with data	111		55	
Mean	8.0		8.0	
SD	1.2		1.0	
Median	8.1		7.9	
Range	6.1 to 11.2		6.3 to 10.6	
A1C (mmol/mol)				
Participants with data	111		55	
Mean	64.4		64.1	
SD	12.7		10.6	
Median	65.0		62.8	
Range	43.2 to 98.9		45.4 to 92.4	
FPG (mg/dL)				
Participants with data	111		55	
Mean	143.8		144.0	
SD	46.2		44.8	
Median	133.0		133.0	
Range	60.0 to 304.0		84.0 to 318.0	
FPG (mmol/L)				
Participants with data	111		55	
Mean	8.0		8.0	
SD	2.6		2.5	
Median	7.4		7.4	
Range	3.3 to 16.9		4.7 to 17.6	
Duration of Type 2 Diabetes Mellitus (years)				
<1 year	29	(26.1)	15	(27.3)
≥1 year	82	(73.9)	40	(72.7)
Participants with data	111		55	
Mean	2.5		2.8	
SD	2.0		2.5	
Median	1.9		2.4	
Range	0.3 to 9.1		0.1 to 14.0	

SD=Standard deviation.

Source: [P059MK8835: adam-adsl; adbase]

Rapporteur's comment:

Subjects in the active treatment (ertugliflozin) group and the placebo group had a median age of 14,7 years and 15,1 years, respectively (10-17 years). Mean BMI at screening was 31,3 and 31,7, respectively (18,2 – 64,0) kg/m^2 in the active treatment group and the placebo group, respectively. The groups are considered well balanced with respect to age and BMI. The percentage of females were slightly higher in the active treatment (ertugliflozin) group (61,3) than in the placebo group (54,5). This is not considered to have an impact on study results.

The active treatment group had a mean duration of disease (T2DM) of 2,5 (0,3-9,1) years and a median duration of 1,9 years. The placebo group had slightly higher mean duration of 2,8 (0,1-14,0) years and median duration 2,4 years. The mean A1c at screening was well balanced between the groups: the ertugliflozin group, 8,0 (6,1 to 11,2) %, compared to the placebo group 8,0 (6,3 to 10,6) %. In both groups, 44 % of the participants had insulin treatment in addition to metformin at screening.

Overall, the ertugliflozin and placebo groups were comparable with respect to demographic and disease characteristics, reflecting a possible future intended population.

Number analysed

A total of 273 participants were screened and 166 were randomized: 111 for ertugliflozin and 55 for placebo. See Table 2. All randomised participants received at least one dose of study drug. The Full analysis set (FAS) population, defined as all randomized participants who received at least 1 dose of study medication, therefore consisted of all randomised participants. The All patients as treated (APaT) population also included all 166 randomised participants who received at least 1 dose of study medication.

PK results

Sparse predose PK samples were collected to assess ertugliflozin exposure and to support the study design of uptitrating eligible participants to 15 mg during the second randomization at Week 12. An interim PK analysis was performed after 35 participants received study medication (23 on ertugliflozin and 12 on placebo). The median dose-normalized predose ertugliflozin concentration was 0.92 ng/mL/mg across all visits, which was below the predefined threshold of ≤2 ng/mL/mg. Consequently, the decision was made by eDMC to proceed with the second randomization and increase the ertugliflozin dose to 15 mg for eligible participants.
Across treatment groups, predose ertugliflozin plasma concentrations showed dose- dependent increases and remained stable over visits, indicating steady-state was reached by Week 6. Median concentrations for the 5-mg group were 5.11, 5.23, and 7.09 ng/mL at Weeks 6, 12, and 24, respectively, while the 15-mg group had a median concentration of 17.49 ng/mL at Week 24, approximately 3-fold higher than the 5-mg group at the same time, see Table 8.

Table 8. concentrations at Weeks 6, 12, and 24.

Table 11-10
Descriptive Statistical Summary of Ertugliflozin Predose Concentration (ng/mL) Values Across Visits Following Multiple-Dose Administration of 5 mg or 15 mg Ertugliflozin Once-Daily in Pediatric Participants

Nominal Time Point	Dosage/Treatment	n	Mean (SD)	GM (% GCV)	Median (Min[a] - Max[b])
Week 6	5 mg	94	11.974 (20.252)	6.085 (149.1)	5.110 (0.510 - 143.070)
Week 12	5 mg	88	9.329 (13.406)	5.666 (125.1)	5.230 (0.630 - 111.540)
Week 24	5 mg	67	14.107 (22.617)	7.915 (128.1)	7.090 (1.230 - 141.220)
	15 mg	17	31.134 (46.998)	17.339 (138.7)	17.490 (3.020 - 197.720)

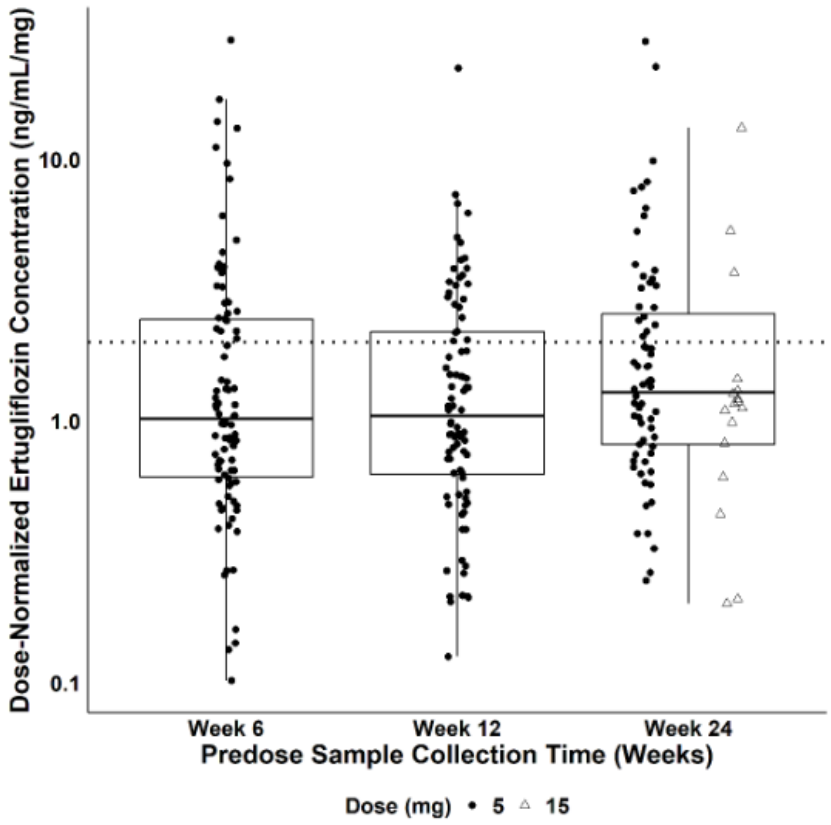
[a] Minimum concentration value.
[b] Maximum concentration value.
GCV = geometric coefficient of variation; GM = geometric mean.
% GCV = 100*sqrt[exp(s^2)-1], where s^2 is the observed between-subject variance on the natural log-scale.
n represents the number of participants with measurable ertugliflozin concentration

Source: [P059MK8835: adam-adpc]

The median dose-normalized plasma concentrations were consistent across Weeks 6, 12, and 24 for the 5-mg group (1.02, 1.05, and 1.42 ng/mL/mg, respectively) and were largely similar at Week 24 for the 15-mg group (1.17 ng/mL/mg). The dose-normalized median predose values at each visit are shown in Figure 2. Taken together, these results indicate linear PK in pediatric participants with T2DM.

Figure 2. Box-plot, dose normalized Ertuglifozin predose concentration at week 6, 12 and 24.

Figure 11-6
Dose-Normalized Steady-State Individual Ertugliflozin Predose Concentration Values Across Visits Following Multiple-Dose Administration of 5 mg or 15 mg Ertugliflozin Once-Daily in Pediatric Participants



Boxes represent median (central horizontal line), first quartile, and third quartile of the dose-normalized data. Vertical solid line through the middle of the boxes (whiskers) represents 1.5*IQR. Closed round circle represents the dose normalized 5 mg exposures and open triangle represents the dose normalized 15 mg exposures. Dotted line representing 2 ng/mL/mg reference threshold line.
Source: [P059MK8835: adam-adpc]

Efficacy results

Primary efficacy endpoint

Success criteria for the primary hypothesis tests were achieved for both the TP and TE estimands at Week 24. Under the TE estimand: The LS mean reduction from baseline A1C at Week 24 was significantly greater in the combined ertugliflozin group than in the placebo group (-0.68%, p=0.007). See Table 9.

For summary descriptions of change from baseline in A1C at Week 24, see Table 10 and Table 11, and Week 54, see Table 12, and over time see Figure 3.

Table 9 Constrained Longitudinal Data Analysis of Change from Baseline in A1C (%) at Week 24. Treatment effect, FAS population

	Baseline		Week 24		Change from Baseline		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[a]
Combined Ertugliflozin	111	8.05 (1.16)	102	7.41 (1.54)	111	-0.61 (1.45)	-0.58 (-0.87, -0.30)
Placebo	55	8.01 (0.97)	47	7.97 (1.82)	55	-0.04 (1.62)	0.10 (-0.31, 0.51)
Pairwise Comparison						Difference in LS Means (95% CI)[a]	p-Value[a]
Combined Ertugliflozin vs. Placebo						-0.68 (-1.18, -0.19)	0.007
Root Mean Squared Error of Change = 1.44							

Treatment Effect Full Analysis Set excludes data following initiation of rescue therapy as well as data collected more than 5 days after the discontinuation of study medication.

For baseline and Week 24, N is the number of subjects with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of subjects in the population.

[a] Based on a cLDA model including terms for treatment, time, age (10 to 14 years/15 to 17 years), insulin use (yes/no), interaction of time by treatment with the constraint that the mean baseline is the same for all treatment groups.

CI = Confidence Interval, LS = Least Square, SE = Standard Error, cLDA = Constrained Longitudinal Data Analysis.

Source: [P059MK8835: adam-adeff]

Table 10 Summary of Change from Baseline in A1C (%) by Week 24. Treatment Effect Full Analysis Set

Treatment	N	Baseline Mean (SD)	Timepoint Mean (SD)	Change from Baseline Mean (SD)	Median	[Min, Max]
Baseline						
Combined Ertugliflozin	111	8.05 (1.16)	8.05 (1.16)			
Placebo	55	8.01 (0.97)	8.01 (0.97)			
Week 6						
Combined Ertugliflozin	107	7.99 (1.12)	7.13 (1.00)	-0.86 (0.70)	-0.80	[-2.90, 2.00]
Placebo	51	8.02 (0.99)	7.73 (1.19)	-0.29 (0.89)	-0.30	[-2.10, 2.80]
Week 12						
Combined Ertugliflozin	105	7.98 (1.12)	7.12 (1.15)	-0.85 (1.11)	-0.80	[-3.80, 3.60]
Placebo	50	8.01 (0.98)	7.87 (1.63)	-0.14 (1.45)	-0.10	[-2.70, 5.60]
Week 24						
Combined Ertugliflozin	102	8.01 (1.12)	7.41 (1.54)	-0.61 (1.45)	-0.70	[-3.60, 5.10]
Placebo	47	8.01 (0.97)	7.97 (1.82)	-0.04 (1.62)	0.10	[-4.20, 4.60]

N = Number of participants with both baseline and timepoint measurements.
Treatment Effect Full Analysis Set excludes data following initiation of rescue therapy as well as data collected more than 5 days after the discontinuation of study medication.
SD = Standard deviation.

Source: [P059MK8835: adam-adeff]

Table 11 Summary of Change from Baseline in A1C (%) by Week 24. Treatment Policy Full Analysis Set

Treatment	N	Baseline Mean (SD)	Timepoint Mean (SD)	Change from Baseline Mean (SD)	Median	[Min, Max]
Baseline						
Combined Ertugliflozin	111	8.05 (1.16)	8.05 (1.16)			
Placebo	55	8.01 (0.97)	8.01 (0.97)			
Week 6						
Combined Ertugliflozin	109	8.04 (1.17)	7.15 (1.01)	-0.89 (0.72)	-0.80	[-2.90, 2.00]
Placebo	52	8.00 (1.00)	7.70 (1.20)	-0.29 (0.88)	-0.30	[-2.10, 2.80]
Week 12						
Combined Ertugliflozin	107	8.03 (1.17)	7.13 (1.14)	-0.90 (1.14)	-0.80	[-3.80, 3.60]
Placebo	53	8.01 (0.99)	7.92 (1.63)	-0.09 (1.45)	-0.10	[-2.70, 5.60]
Week 24						
Combined Ertugliflozin	106	8.06 (1.16)	7.44 (1.55)	-0.62 (1.49)	-0.70	[-4.50, 5.10]
Placebo	53	7.99 (0.99)	8.13 (1.92)	0.14 (1.90)	0.10	[-4.20, 7.30]

N = Number of participants with both baseline and timepoint measurements.
Treatment Policy Full Analysis Set includes all the available data, including data following initiation of rescue therapy as well as data collected after the last dose of study treatment in any participants who remain in the study after discontinuing study treatment.
SD = Standard deviation.

Source: [P059MK8835: adam-adeff]

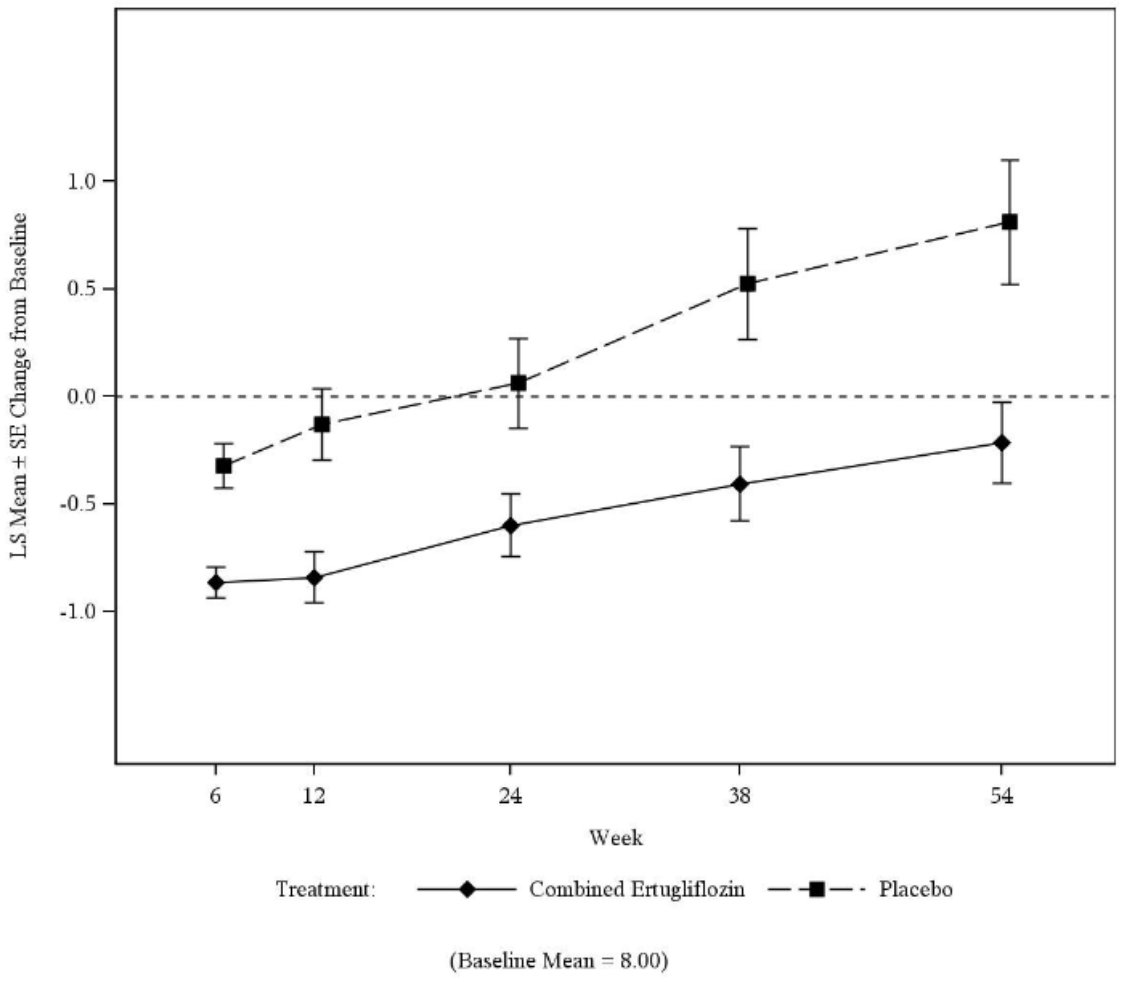
Table 12 Summary of Change from Baseline in A1C (%) by Week 54. Treatment Effect Full Analysis Set

Treatment	N	Baseline Mean (SD)	Timepoint Mean (SD)	Change from Baseline Mean (SD)	Median	[Min, Max]
Baseline						
Combined Ertugliflozin	111	8.05 (1.16)	8.05 (1.16)			
Placebo	55	8.01 (0.97)	8.01 (0.97)			
Week 6						
Combined Ertugliflozin	107	7.99 (1.12)	7.13 (1.00)	-0.86 (0.70)	-0.80	[-2.90, 2.00]
Placebo	51	8.02 (0.99)	7.73 (1.19)	-0.29 (0.89)	-0.30	[-2.10, 2.80]
Week 12						
Combined Ertugliflozin	105	7.98 (1.12)	7.12 (1.15)	-0.85 (1.11)	-0.80	[-3.80, 3.60]
Placebo	50	8.01 (0.98)	7.87 (1.63)	-0.14 (1.45)	-0.10	[-2.70, 5.60]
Week 24						
Combined Ertugliflozin	102	8.01 (1.12)	7.41 (1.54)	-0.61 (1.45)	-0.70	[-3.60, 5.10]
Placebo	47	8.01 (0.97)	7.97 (1.82)	-0.04 (1.62)	0.10	[-4.20, 4.60]
Week 38						
Combined Ertugliflozin	98	7.95 (1.11)	7.44 (1.58)	-0.51 (1.49)	-0.70	[-3.50, 4.20]
Placebo	40	7.97 (1.00)	8.16 (2.24)	0.19 (1.98)	0.05	[-2.80, 6.70]
Week 54						
Combined Ertugliflozin	84	7.80 (1.01)	7.40 (1.51)	-0.40 (1.57)	-0.50	[-3.50, 5.70]
Placebo	30	7.68 (0.85)	7.89 (2.21)	0.21 (2.16)	-0.05	[-3.70, 5.60]

N = Number of participants with both baseline and timepoint measurements.
Treatment Effect Full Analysis Set excludes data following initiation of rescue therapy as well as data collected more than 5 days after the discontinuation of study medication.
SD = Standard deviation.

Source: [P059MK8835: adam-adeff]

Figure 3 Constrained Longitudinal Data Analysis of Change from Baseline in A1C (%) Over Time. Weeks 0 to 54. (LS Mean ± SE) by Treatment Group. Treatment Effect Full Analysis Set



Results from the tipping point sensitivity analysis of the change from baseline in A1C (%) support the results of the primary analysis based on the TP estimand. The results of the post hoc frequentist sensitivity analysis of LS mean change from baseline in A1C using only the data from this study showed a similar treatment effect mean estimate and interval bounds as the tipping point approach (-0.76%, p=0.003). See Table 13.

Table 13 ANCOVA of Change from Baseline in A1C (%) at Week 24. Treatment Policy Full Analysis Set, Washout Imputation

Treatment	Baseline		Week 24		Change from Baseline		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[a]
Combined Ertugliflozin	111	8.05 (1.16)	106	7.44 (1.55)	111	-0.62 (1.49)	-0.55 (-0.85 , -0.25)
Placebo	55	8.01 (0.97)	53	8.13 (1.92)	55	0.14 (1.90)	0.21 (-0.21 , 0.63)
Pairwise Comparison					Difference in LS Mean (95% CI)[a]		p-Value[a]
Combined Ertugliflozin vs Placebo					-0.76 (-1.26 , -0.25)		0.003
Root Mean Squared Error of Change = 1.540							

Treatment Policy FAS includes all data following initiation of rescue therapy as well as data collected after the discontinuation of study medication.

For Baseline and Week 24, N is the number of subjects with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of subjects in the population.

[a] Based on an ANCOVA model including terms for Baseline A1C, treatment, age (10 to 14 years/15 to 17 years), and insulin use (yes/no) at Screening and calculated by Rubin's Rule.

ANCOVA = Analysis of Covariance, CI = Confidence Interval, LS = Least Squares, SD = Standard Deviation.

Source: [P059MK8835: adam-adefl]

Results from sub-group analyses (baseline A1C, gender, race, ethnicity, age, insulin use, and geographic region) of A1C change from baseline at Week 24 for TP and TE were generally consistent with those from the primary analyses by estimand. See Figure 4. A summary of the sub-group analysis results at Week 54 is provided in Table 14.

Figure 4 Forest Plot for A1C (%): Change from Baseline at Week 24. Subgroup Summaries. Treatment Policy Full Analysis Set

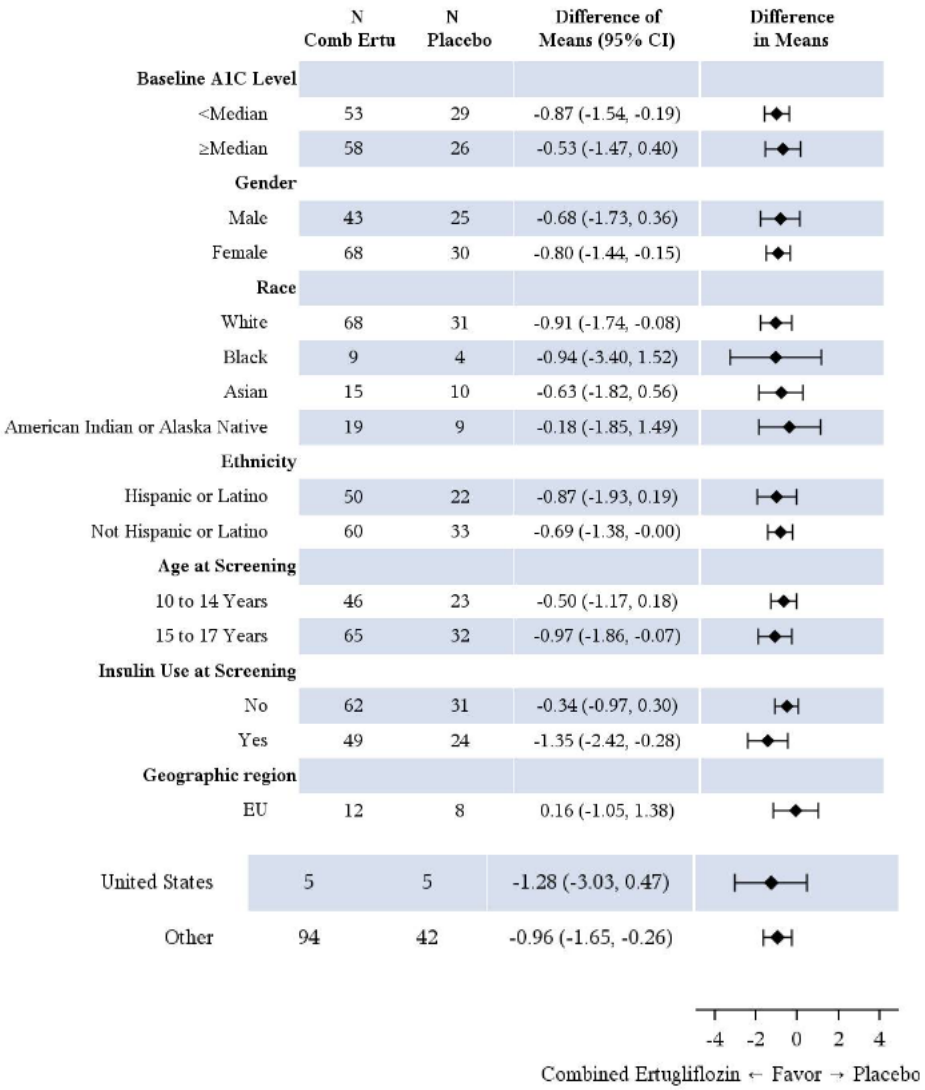


Table 14 A1C (%): Change from Baseline at Week 54. Subgroup Summaries. Treatment Policy Full Analysis Set

	Baseline		Week 54		Change From Baseline in A1C at Week 54	
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean[a] (95% CI)
Baseline A1C Level						
<Median						
Combined Ertugliflozin	53	7.02 (0.38)	52	7.07 (1.40)	52	0.05 (-0.32, 0.42)
Placebo	29	7.26 (0.46)	27	8.31 (2.13)	27	1.04 (0.26, 1.81)
≥Median						
Combined Ertugliflozin	58	8.98 (0.76)	53	8.11 (1.70)	53	-0.93 (-1.43, -0.43)
Placebo	26	8.85 (0.64)	25	8.43 (2.30)	25	-0.40 (-1.20, 0.39)
Gender						
Male						
Combined Ertugliflozin	43	7.79 (1.10)	41	7.64 (1.64)	41	-0.15 (-0.67, 0.37)
Placebo	25	8.02 (0.91)	22	8.49 (2.12)	22	0.43 (-0.50, 1.37)
Female						
Combined Ertugliflozin	68	8.21 (1.17)	64	7.56 (1.65)	64	-0.63 (-1.05, -0.22)
Placebo	30	8.00 (1.04)	30	8.28 (2.28)	30	0.28 (-0.48, 1.04)
Race						
White						
Combined Ertugliflozin	68	8.00 (1.19)	66	7.58 (1.79)	66	-0.44 (-0.84, -0.04)
Placebo	31	8.01 (1.07)	29	8.33 (2.27)	29	0.32 (-0.52, 1.16)
Black						
Combined Ertugliflozin	9	8.42 (1.32)	7	7.00 (1.83)	7	-1.41 (-3.45, 0.63)
Placebo	4	8.58 (1.02)	4	10.28 (3.15)	4	1.70 (-1.39, 4.79)
Asian						
Combined Ertugliflozin	15	8.09 (1.14)	15	7.97 (1.34)	15	-0.12 (-0.97, 0.73)
Placebo	10	7.73 (0.89)	10	8.28 (1.98)	10	0.55 (-0.46, 1.56)

Treatment	Baseline		Week 54		Change From Baseline in A1C at Week 54	
	N	Mean (SD)	N	Mean (SD)	N	Mean[a] (95% CI)
American Indian or Alaska Native						
Combined Ertugliflozin	19	7.99 (1.04)	17	7.57 (1.16)	17	-0.35 (-0.95, 0.25)
Placebo	9	8.14 (0.70)	8	7.76 (1.57)	8	-0.49 (-1.65, 0.68)
Ethnicity						
Hispanic or Latino						
Combined Ertugliflozin	50	7.95 (1.15)	47	7.60 (1.63)	47	-0.32 (-0.73, 0.08)
Placebo	22	8.11 (1.11)	20	8.51 (2.29)	20	0.28 (-0.60, 1.17)
Not Hispanic or Latino						
Combined Ertugliflozin	60	8.12 (1.17)	57	7.61 (1.66)	57	-0.52 (-1.02, -0.03)
Placebo	33	7.94 (0.88)	32	8.28 (2.16)	32	0.38 (-0.40, 1.16)
Age at Screening						
10 to 14 Years						
Combined Ertugliflozin	46	7.95 (1.08)	42	7.63 (1.66)	42	-0.28 (-0.80, 0.25)
Placebo	23	8.03 (0.95)	22	8.28 (1.92)	22	0.22 (-0.52, 0.95)
15 to 17 Years						
Combined Ertugliflozin	65	8.12 (1.21)	63	7.57 (1.63)	63	-0.56 (-0.97, -0.14)
Placebo	32	8.00 (1.01)	30	8.44 (2.40)	30	0.44 (-0.43, 1.30)
Insulin Use at Screening						
No						
Combined Ertugliflozin	62	7.54 (0.91)	59	7.18 (1.40)	59	-0.34 (-0.70, 0.03)
Placebo	31	7.58 (0.78)	29	7.71 (1.91)	29	0.18 (-0.58, 0.93)
Yes						
Combined Ertugliflozin	49	8.69 (1.12)	46	8.12 (1.77)	46	-0.58 (-1.16, -0.01)
Placebo	24	8.57 (0.93)	23	9.20 (2.28)	23	0.56 (-0.36, 1.48)

Treatment	Baseline		Week 54		Change From Baseline in A1C at Week 54	
	N	Mean (SD)	N	Mean (SD)	N	Mean[a] (95% CI)
Geographic region						
EU						
Combined Ertugliflozin	12	7.94 (1.05)	11	7.20 (1.67)	11	-0.73 (-1.70, 0.24)
Placebo	8	7.79 (0.55)	8	6.85 (0.95)	8	-0.94 (-1.86, -0.01)
United States						
Combined Ertugliflozin	5	8.52 (1.67)	4	6.08 (0.38)	4	-2.38 (-4.51, -0.24)
Placebo	5	7.98 (0.83)	5	8.10 (1.35)	5	0.12 (-1.43, 1.67)
Other						
Combined Ertugliflozin	94	8.04 (1.15)	90	7.71 (1.64)	90	-0.32 (-0.66, 0.01)
Placebo	42	8.06 (1.06)	39	8.72 (2.34)	39	0.64 (-0.07, 1.34)

Treatment Policy Full Analysis Set includes all the available data, including data following initiation of rescue therapy as well as data collected after the last dose of study treatment in any participants who remain in the study after discontinuing study treatment.

[a] Based on $Mean_{54} \pm Z_{0.025}*SD/N^{0.5}$.

For baseline and Week 54, N is the number of participants with non-missing assessments at the specific timepoint. For change from baseline, N is the number of participants with non-missing assessments at baseline and the specific timepoint.

CI = Confidence Interval, SD = Standard Deviation.

Source: [P059MK8835: adam-adsl; adbase; adeff]

Rapporteur's comment

Primary endpoint was met. The LS mean reduction from baseline A1C at Week 24 was significantly greater in the combined ertugliflozin group than in the placebo group (-0.68%, *p*=0.007). Sensitivity analyses supported the primary endpoints. The participants were stratified based on Age: 10 to 14 years of age OR 15 to 17 years of age and based on Insulin use: Yes OR No.

Sub-group analyses showed greater reduction in A1C for the sub-group of participants 15-17 years than for the younger group. Participants with insulin use at screening showed greater A1C reduction than those without. These findings seem in line with what would be expected since patients with insulin and older patients are assumed to have more advanced diabetes and thereby possibly more easily gain from treatment with ertugliflozin.

Key secondary endpoint

Key secondary efficacy hypotheses were assessed only under the TP estimand and tested in accordance with the multiplicity strategy. All other secondary and tertiary endpoints were assessed only under the TE estimand. Under the TP estimand, the LS mean reduction from baseline in A1C at Week 24 was significantly greater in the dose-optimized ertugliflozin group than in the placebo group (-0.66%, p=0.021). See Table 15.

Table 15 Dose-Optimized Weighted ANCOVA of Change from Baseline in A1C (%) at Week 24. Treatment Policy Full Analysis Set, Washout Imputation

	Baseline		Week 24		Change from Baseline		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[a]
Dose-Optimized Ertugliflozin[b]	89	7.93 (1.14)	85	7.26 (1.48)	89	-0.68 (1.38)	-0.42 (-0.76, -0.08)
Placebo	55	8.01 (0.97)	53	8.13 (1.92)	55	0.14 (1.90)	0.25 (-0.22, 0.72)
Pairwise Comparison						Difference in LS Mean (95% CI)[a]	p-Value[a]
Dose-Optimized Ertugliflozin vs Placebo						-0.66 (-1.23, -0.10)	0.021
Root Mean Squared Error of Change = 1.724							

Treatment Policy FAS includes all data following initiation of rescue therapy as well as data collected after the discontinuation of study medication.

For Baseline and Week 24, N is the number of subjects with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of subjects in the population.

[a] Based on an ANCOVA model including terms for Baseline A1C, treatment, age (10 to 14 years/15 to 17 years), and insulin use (yes/no) at Screening and calculated by Rubin's Rule.

[b] Randomized to ertugliflozin and either did not meet the re-randomization criterion at Week 12 or were re-randomized to ertugliflozin 15 mg.

ANCOVA = Analysis of Covariance, CI = Confidence Interval, LS = Least Squares, SD = Standard Deviation.

Source: [P059MK8835: adam-adeff]

Under the TP estimand, the LS mean reduction from baseline in A1C at Week 24 was significantly greater in the ertugliflozin 5-mg group than in the placebo group (-0.86%, p=0.001). See Table 16.

Table 16. 5 mg Ertugliflozin Weighted ANCOVA of Change from Baseline in A1C (%) at Week 24. Treatment Policy Full Analysis Set, Washout Imputation

	Baseline		Week 24		Change from Baseline		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[a]
5 mg Ertugliflozin[b]	85	7.81 (1.12)	81	7.07 (1.33)	85	-0.76 (1.29)	-0.54 (-0.86, -0.22)
Placebo	55	8.01 (0.97)	53	8.13 (1.92)	55	0.14 (1.90)	0.32 (-0.11, 0.76)
Pairwise Comparison						Difference in LS Mean (95% CI)[a]	p-Value[a]
5 mg Ertugliflozin vs Placebo						-0.86 (-1.39, -0.33)	0.001
Root Mean Squared Error of Change = 1.599							

Treatment Policy FAS includes all data following initiation of rescue therapy as well as data collected after the discontinuation of study medication.

For Baseline and Week 24, N is the number of subjects with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of subjects in the population.

[a] Based on an ANCOVA model including terms for Baseline A1C, treatment, age (10 to 14 years/15 to 17 years), and insulin use (yes/no) at Screening and calculated by Rubin's Rule.

[b] Randomized to ertugliflozin and either did not meet the re-randomization criterion at Week 12 or were re-randomized to ertugliflozin 5 mg.

ANCOVA = Analysis of Covariance, CI = Confidence Interval, LS = Least Squares, SD = Standard Deviation.

Source: [P059MK8835: adam-adeff]

Secondary efficacy endpoints

Change From Baseline in A1C at Week 54

The treatment effect observed for the combined ertugliflozin group relative to the placebo group in A1C at Week 24 persisted at Week 54 (treatment difference: -1.03%, p=0.003). See Table 17 and Figure 5. Results of analyses of change from baseline over time and summary descriptions of change from baseline in A1C at Week 54 were similar to A1C results at Week 24.

Table 17 Constrained Longitudinal Data Analysis of Change from Baseline in A1C (%) at Week 54. Treatment Effect Full Analysis Set

	Baseline		Week 54		Change from Baseline		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[a]
Combined Ertugliflozin	111	8.05 (1.16)	84	7.40 (1.51)	111	-0.40 (1.57)	-0.22 (-0.59, 0.16)
Placebo	55	8.01 (0.97)	30	7.89 (2.21)	55	0.21 (2.16)	0.81 (0.24, 1.38)
Pairwise Comparison						Difference in LS Means (95% CI)[a]	p-Value[a]
Combined Ertugliflozin vs. Placebo						-1.03 (-1.70, -0.35)	0.003
Root Mean Squared Error of Change = 1.83							

Treatment Effect Full Analysis Set excludes data following initiation of rescue therapy as well as data collected more than 5 days after the discontinuation of study medication.

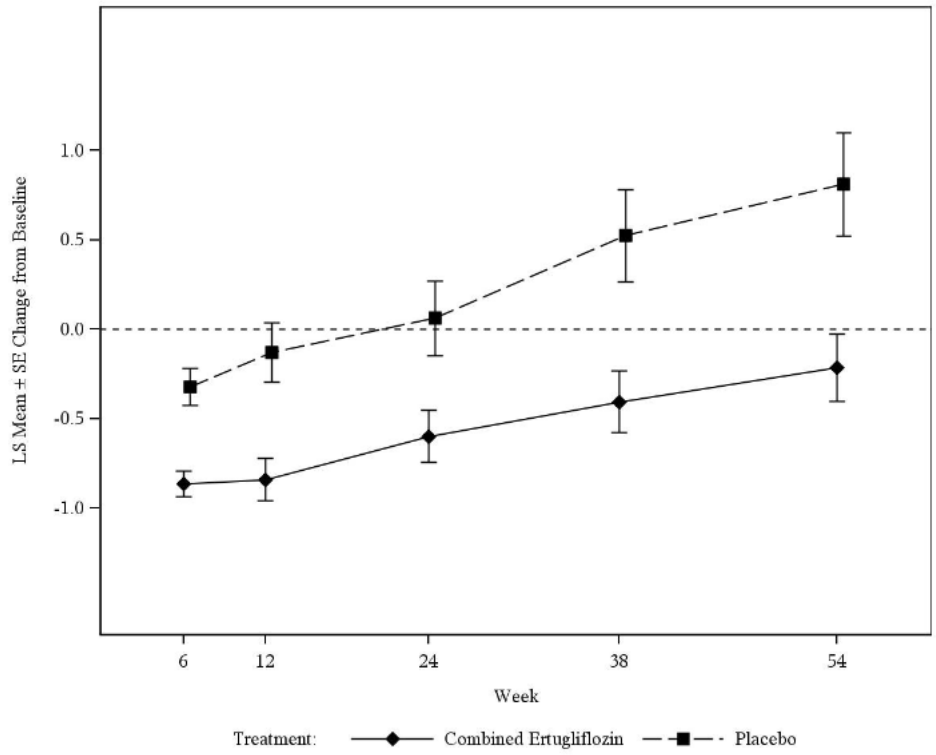
For baseline and Week 54, N is the number of subjects with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of subjects in the population.

[a]Based on a cLDA model including terms for treatment, time, age (10 to 14 years/15 to 17 years), insulin use (yes/no), interaction of time by treatment with the constraint that the mean baseline is the same for all treatment groups.

CI = Confidence Interval, LS = Least Square, SE = Standard Error, cLDA = Constrained Longitudinal Data Analysis.

Source: [P059MK8835: adam-adeff]

Figure 5 Constrained Longitudinal Data Analysis of Change from Baseline in A1C (%) Over Time. Weeks 0 to 54. (LS Mean ± SE) by Treatment Group. Treatment Effect Full Analysis Set



Fasting Plasma Glucose at Weeks 24 and 54

The improvements in A1C at Week 24 in the ertugliflozin group were supported by improvements in FPG at Week 24. The LS mean reduction from baseline in FPG at Week 24 was greater in the combined ertugliflozin group compared with the placebo group (-29.0 mg/dL, $p<0.001$), see Table 18.

Table 18 Constrained Longitudinal Data Analysis of Change from Baseline in FPG (mg/dL) at Week 24. Treatment Effect Full Analysis Set

	Baseline		Week 24		Change from Baseline		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[a]
Combined Ertugliflozin	111	143.8 (46.2)	100	123.1 (39.3)	111	-20.3 (52.5)	-20.8 (-30.8, -10.8)
Placebo	55	144.0 (44.8)	47	151.7 (60.2)	55	8.6 (57.2)	8.2 (-5.4, 21.7)
Pairwise Comparison					Difference in LS Means (95% CI)[a]		p-Value[a]
Combined Ertugliflozin vs. Placebo					-29.0 (-44.4, -13.6)		<0.001
Root Mean Squared Error of Change = 43.7							

Treatment Effect Full Analysis Set excludes data following initiation of rescue therapy as well as data collected more than 5 days after the discontinuation of study medication.

For baseline and Week 24, N is the number of subjects with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of subjects in the population.

[a]Based on a cLDA model including terms for treatment, time, age (10 to 14 years/15 to 17 years), insulin use (yes/no), interaction of time by treatment with the constraint that the mean baseline is the same for all treatment groups.

CI = Confidence Interval, LS = Least Square, SE = Standard Error, cLDA = Constrained Longitudinal Data Analysis.

Source: [P059MK8835: adam-adcff]

The treatment effect observed for the combined ertugliflozin group relative to the placebo group in FPG at Week 24 persisted at Week 54 (-33.1 mg/dL, *p*=0.001), see Table 19.

Table 19 Constrained Longitudinal Data Analysis of Change from Baseline in FPG (mg/dL) at Week 54. Treatment Effect Full Analysis Set

	Baseline		Week 54		Change from Baseline		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[a]
Combined Ertugliflozin	111	143.8 (46.2)	88	126.4 (45.4)	111	-14.4 (53.8)	-12.1 (-23.7, -0.5)
Placebo	55	144.0 (44.8)	33	145.8 (58.5)	55	15.5 (62.1)	21.0 (3.6, 38.4)
Pairwise Comparison						Difference in LS Means (95% CI)[a]	p-Value[a]
Combined Ertugliflozin vs. Placebo						-33.1 (-53.0, -13.1)	0.001
Root Mean Squared Error of Change = 51.7							

Treatment Effect Full Analysis Set excludes data following initiation of rescue therapy as well as data collected more than 5 days after the discontinuation of study medication.

For baseline and Week 54, N is the number of subjects with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of subjects in the population.

[a]Based on a cLDA model including terms for treatment, time, age (10 to 14 years/15 to 17 years), insulin use (yes/no), interaction of time by treatment with the constraint that the mean baseline is the same for all treatment groups.

CI = Confidence Interval, LS = Least Square, SE = Standard Error, cLDA = Constrained Longitudinal Data Analysis.

Source: [P059MK8835: adam-adefl]

Analyses of change from baseline over time and summary descriptions of change from baseline in FPG at Week 54 were similar to FPG results at Week 24.

Rapporteur's comment:

Key secondary endpoints consisted of change from baseline in A1C for the dose-optimized ertugliflozin group and for the ertugliflozin 5-mg group, respectively, compared to placebo. Both groups showed significantly greater reduction from baseline in A1C than placebo at week 24, thus supporting the results of the primary endpoint.

For the other secondary endpoints, results also supported the primary endpoint results. The change from baseline on A1C at week 54, FPG at Week 24 and FPG at Week 54 for ertugliflozin (5 mg or 15 mg, all doses combined) showed greater reduction than the placebo group.

As the MAH has informed that a type II variation application for extension of indication is planned to be submitted, explorative endpoints will be assessed and discussed in this future Type II variation report.

Safety results

Safety analyses were performed on the All participants as treated (APaT) population, which consisted of all 166 participants who received at least 1 dose of study medication. Safety analyses were performed in weeks 24 and 54. All analyses used the combined ertugliflozin group (5 mg and 15 mg) compared with the placebo group, with the exception of adjudicated ketoacidosis, which was reported by treatment arm.

The mean duration of exposure to ertugliflozin 5 and 15 mg was 300.6 and 266.8 days, respectively. The mean duration of exposure to placebo was 346.2 days. The mean duration of exposure in the individual ertugliflozin groups compared with the placebo group reflects the re-randomization from ertugliflozin 5 to 15 mg at Week 12 for participants who met glycemic criteria.

The incidences of AEs were generally comparable across treatment groups through Week 54, see Table 20.

Table 20 Analysis of Adverse Event Summary, Weeks 0 to 54, All Participants as Treated

	Combined Ertugliflozin		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	111		55		
with one or more adverse events	71	(64.0)	42	(76.4)	-12.4 (-25.9, 2.8)
with no adverse event	40	(36.0)	13	(23.6)	
with drug-related[b] adverse events	13	(11.7)	2	(3.6)	8.1 (-1.6, 16.1)
with serious adverse events	4	(3.6)	0	(0.0)	3.6
with serious drug-related[b] adverse events	0	(0.0)	0	(0.0)	0.0
who died	0	(0.0)	0	(0.0)	0.0
discontinued drug due to an adverse event	0	(0.0)	1	(1.8)	-1.8
discontinued drug due to a drug-related[b] adverse event	0	(0.0)	0	(0.0)	0.0
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0.0
discontinued drug due to a serious drug-related[b] adverse event	0	(0.0)	0	(0.0)	0.0

[a] Based on Miettinen & Nurminen method.
[b] Determined by the investigator to be related to the drug.
CIs were computed only for those endpoints where at least ≥8 participants in the combined ertugliflozin group or ≥2 participants in the placebo group had events.
All entries in this table reflect events that occurred during the Treatment Period + 14 days.
Adverse event terms are from MedDRA Version 27.1

Source: [P059MK8835: adam-adsl; adae]

AEs were reported for 64.0% of participants in the combined ertugliflozin group and 76.4% in the placebo group. Drug-related AEs were reported in 11.7% of participants in the combined ertugliflozin group and 3.6% in the placebo group. SAEs were reported for 4 participants (all in the combined ertugliflozin group). No SAEs were considered to be drug-related by the investigator. One participant, in the placebo group, discontinued study medication due to an AE. No participants died. The most frequently reported drug-related AEs were in the ertugliflozin 5-mg dose group. No meaningful

differences in AE summary measures were observed through Week 54 relative to Week 24. No AEs related to acceptability or palatability with study medication were reported in the study.

Most Frequently Reported Adverse Events

The incidence of AEs by SOC were generally similar in the combined ertugliflozin and placebo groups at Week 54, see Table 21. The 95% CIs for the between-group differences in incidences of AEs included 0 for all SOCs, see Figure 6. The incidences of specific AEs were generally similar in the combined ertugliflozin and placebo groups. The most frequently reported (≥10%) AE in both treatment groups was hypoglycemia at Week 54. At Week 54, pyrexia was the only specific AE that occurred at a higher incidence (95% CI for the between-group difference in the incidence excluded 0) in the combined ertugliflozin group (7.2%) than in the placebo group (0.0%). Headache, polyurea, gastritis, and rash were also reported more frequently in the combined ertugliflozin group than in the placebo group, but the 95% CIs for the between-group differences included 0. The specific AEs that occurred at a higher incidence (95% CI for the between-group difference in the incidence excluded 0) in the placebo group were musculoskeletal chest pain and anxiety. The results were similar for AEs at Week 24 and Week 54.

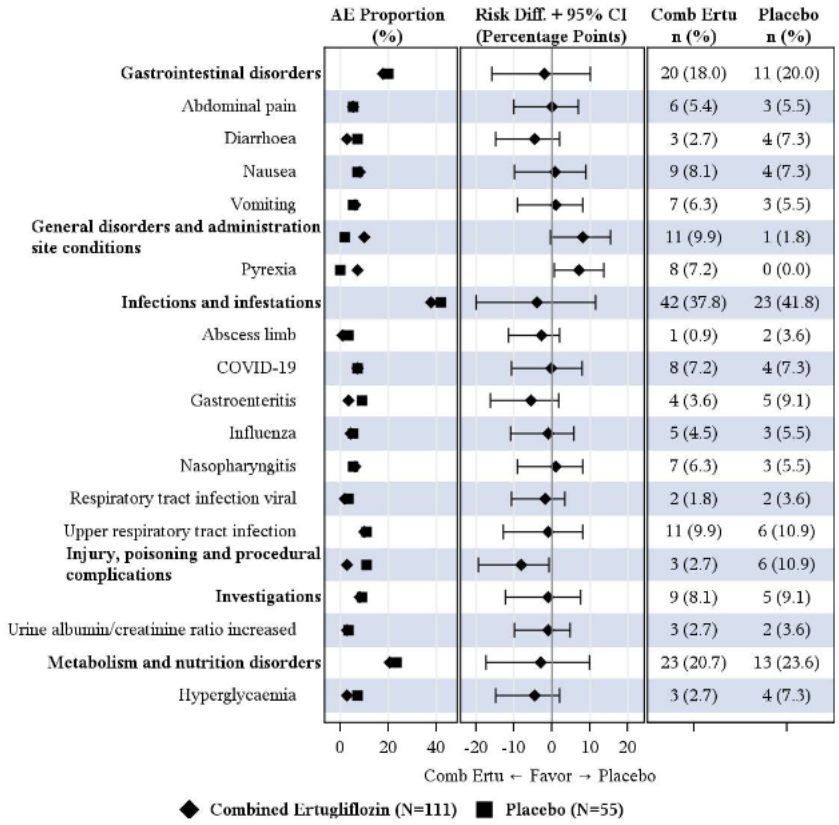
Table 21 Analysis of Participants With Adverse Events (Incidence ≥ 2% in One or More Treatment Groups) Weeks 0 to 54 Weeks 0 to 54.

	Combined Ertugliflozin		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	111		55		
with one or more adverse events	71	(64.0)	42	(76.4)	-12.4 (-25.9, 2.8)
with no adverse events	40	(36.0)	13	(23.6)	
Eye disorders	**3**	**(2.7)**	**0**	**(0.0)**	**2.7**
Gastrointestinal disorders	**20**	**(18.0)**	**11**	**(20.0)**	**-2.0 (-15.9, 10.0)**
Abdominal pain	6	(5.4)	3	(5.5)	-0.0 (-10.0, 7.0)
Diarrhoea	3	(2.7)	4	(7.3)	-4.6 (-14.8, 1.9)
Gastritis	4	(3.6)	0	(0.0)	3.6
Nausea	9	(8.1)	4	(7.3)	0.8 (-9.9, 9.0)
Vomiting	7	(6.3)	3	(5.5)	0.9 (-9.1, 8.1)
General disorders and administration site conditions	**11**	**(9.9)**	**1**	**(1.8)**	**8.1 (-0.4, 15.5)**
Pyrexia	8	(7.2)	0	(0.0)	7.2 (0.5, 13.6)
Infections and infestations	**42**	**(37.8)**	**23**	**(41.8)**	**-4.0 (-19.9, 11.5)**
Abscess limb	1	(0.9)	2	(3.6)	-2.7 (-11.5, 1.9)
COVID-19	8	(7.2)	4	(7.3)	-0.1 (-10.7, 7.9)
Gastroenteritis	4	(3.6)	5	(9.1)	-5.5 (-16.3, 1.8)
Influenza	5	(4.5)	3	(5.5)	-1.0 (-10.8, 5.8)
Nasopharyngitis	7	(6.3)	3	(5.5)	0.9 (-9.1, 8.1)
Pharyngitis	3	(2.7)	1	(1.8)	0.9
Respiratory tract infection viral	2	(1.8)	2	(3.6)	-1.8 (-10.7, 3.4)
Upper respiratory tract infection	11	(9.9)	6	(10.9)	-1.0 (-12.8, 8.2)
Urinary tract infection	3	(2.7)	1	(1.8)	0.9
Injury, poisoning and procedural complications	**3**	**(2.7)**	**6**	**(10.9)**	**-8.2 (-19.4, -0.8)**
Investigations	**9**	**(8.1)**	**5**	**(9.1)**	**-1.0 (-12.2, 7.5)**
Urine albumin/creatinine ratio increased	3	(2.7)	2	(3.6)	-0.9 (-9.9, 4.7)
Metabolism and nutrition disorders	**23**	**(20.7)**	**13**	**(23.6)**	**-2.9 (-17.4, 9.8)**
Hyperglycaemia	3	(2.7)	4	(7.3)	-4.6 (-14.8, 1.9)
Hypertriglyceridaemia	1	(0.9)	2	(3.6)	-2.7 (-11.5, 1.9)
Hypoglycaemia	14	(12.6)	7	(12.7)	-0.1 (-12.5, 9.9)
Musculoskeletal and connective tissue disorders	**4**	**(3.6)**	**3**	**(5.5)**	**-1.9 (-11.6, 4.6)**
Musculoskeletal chest pain	0	(0.0)	2	(3.6)	-3.6 (-12.4, -0.2)
Nervous system disorders	**14**	**(12.6)**	**5**	**(9.1)**	**3.5 (-8.1, 12.9)**
Headache	10	(9.0)	3	(5.5)	3.6 (-6.7, 11.5)
Psychiatric disorders	**1**	**(0.9)**	**3**	**(5.5)**	**-4.6 (-14.1, 0.5)**
Anxiety	0	(0.0)	2	(3.6)	-3.6 (-12.4, -0.2)
Renal and urinary disorders	**8**	**(7.2)**	**5**	**(9.1)**	**-1.9 (-13.1, 6.4)**
Polyuria	4	(3.6)	0	(0.0)	3.6
Respiratory, thoracic and mediastinal disorders	**11**	**(9.9)**	**1**	**(1.8)**	**8.1 (-0.4, 15.5)**
Oropharyngeal pain	3	(2.7)	1	(1.8)	0.9
Skin and subcutaneous tissue disorders	**7**	**(6.3)**	**6**	**(10.9)**	**-4.6 (-16.1, 3.9)**
Rash	4	(3.6)	0	(0.0)	3.6

[a] Based on Miettinen & Nurminen method.
Every participant is counted a single time for each applicable row and column.
CIs were computed only for those endpoints where at least ≥8 participants in the combined ertugliflozin group or ≥2 participants in the placebo group had events.
All entries in this table reflect events that occurred during the Treatment Period + 14 days.
Adverse event terms are from MedDRA Version 27.1

Source: [P059MK8835: adam-adsl; adae]

Figure 6 Rainfall Plot for Adverse Events (Incidence ≥ 8 Participants in the Combined Ertugliflozin Group or ≥ 2 Participants in the Placebo Group) Weeks 0 to 54 All Participants as Treated.



Drug-related AEs were reported in 11.7 % of participants in the combined ertugliflozin group and 3.6% in the placebo group through Week 54. See Table 22. The most frequently reported drug-related AEs in the combined ertugliflozin group were hypoglycemia (2.7%) and polyuria (2.7%). No meaningful differences in drug-related AEs were observed at Week 24 relative to Week 54.

Table 22 Analysis of Participants With Drug-Related Adverse Events (Incidence > 0% in One or More Treatment Groups) Weeks 0 to 54 All Participants as Treated

	Combined Ertugliflozin		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	111		55		
with one or more drug-related[b] adverse events	13	(11.7)	2	(3.6)	8.1 (-1.6, 16.1)
with no drug-related[b] adverse events	98	(88.3)	53	(96.4)	
Gastrointestinal disorders	**2**	**(1.8)**	**2**	**(3.6)**	**-1.8 (-10.7, 3.4)**
Nausea	1	(0.9)	2	(3.6)	-2.7 (-11.5, 1.9)
Vomiting	1	(0.9)	0	(0.0)	0.9
Infections and infestations	**3**	**(2.7)**	**0**	**(0.0)**	**2.7**
Vulvitis	1	(0.9)	0	(0.0)	0.9
Vulvovaginal mycotic infection	2	(1.8)	0	(0.0)	1.8
Injury, poisoning and procedural complications	**1**	**(0.9)**	**0**	**(0.0)**	**0.9**
Upper limb fracture	1	(0.9)	0	(0.0)	0.9
Metabolism and nutrition disorders	**5**	**(4.5)**	**1**	**(1.8)**	**2.7**
Hypoglycaemia	3	(2.7)	1	(1.8)	0.9
Increased appetite	1	(0.9)	0	(0.0)	0.9
Polydipsia	1	(0.9)	0	(0.0)	0.9
Nervous system disorders	**1**	**(0.9)**	**0**	**(0.0)**	**0.9**
Dizziness	1	(0.9)	0	(0.0)	0.9
Renal and urinary disorders	**6**	**(5.4)**	**0**	**(0.0)**	**5.4**
Glycosuria	1	(0.9)	0	(0.0)	0.9
Microalbuminuria	1	(0.9)	0	(0.0)	0.9
Polyuria	3	(2.7)	0	(0.0)	2.7
Renal and urinary disorders	**6**	**(5.4)**	**0**	**(0.0)**	**5.4**
Urethral pain	1	(0.9)	0	(0.0)	0.9

[a] Based on Miettinen & Nurminen method.
[b] Determined by the investigator to be related to the drug.
Every participant is counted a single time for each applicable row and column.
CIs were computed only for those endpoints where at least ≥8 participants in the combined ertugliflozin group or ≥2 participants in the placebo group had events.
All entries in this table reflect events that occurred during the Treatment Period + 14 days.
Adverse event terms are from MedDRA Version 27.1

Source: [P059MK8835: adam-adsl; adae]

Serious Adverse Events and Other Clinically Meaningful Adverse Events

There were no deaths due to AEs reported in this study. SAEs were reported for 4 participants in the combined ertugliflozin group and none in the placebo group through Week 54, see Table 23. The SAEs reported were COVID-19 pneumonia, post procedural infection and foot and tibia fracture (in the same participant), hyperglycemia, and hypoglycemia. None of these SAEs were considered related to study medication by the investigator. The foot fracture was the only SAE that was reported through Week 24.

Table 23 Analysis of Participants With Serious Adverse Events (Incidence > 0% in One or More Treatment Groups) Weeks 0 to 54 All Participants as Treated

	Combined Ertugliflozin		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	111		55		
with one or more serious adverse events	4	(3.6)	0	(0.0)	3.6
with no serious adverse events	107	(96.4)	55	(100.0)	
Infections and infestations	**2**	**(1.8)**	**0**	**(0.0)**	**1.8**
COVID-19 pneumonia	1	(0.9)	0	(0.0)	0.9
Post procedural infection	1	(0.9)	0	(0.0)	0.9
Injury, poisoning and procedural complications	**1**	**(0.9)**	**0**	**(0.0)**	**0.9**
Foot fracture	1	(0.9)	0	(0.0)	0.9
Tibia fracture	1	(0.9)	0	(0.0)	0.9
Metabolism and nutrition disorders	**2**	**(1.8)**	**0**	**(0.0)**	**1.8**
Hyperglycaemia	1	(0.9)	0	(0.0)	0.9
Hypoglycaemia	1	(0.9)	0	(0.0)	0.9

[a] Based on Miettinen & Nurminen method.
Every participant is counted a single time for each applicable row and column.
CIs were computed only for those endpoints where at least ≥8 participants in the combined ertugliflozin group or ≥2 participants in the placebo group had events.
All entries in this table reflect events that occurred during the Treatment Period + 14 days.
Adverse event terms are from MedDRA Version 27.1

Source: [P059MK8835: adam-adsl; adae]

Discontinuations Due to Adverse Events

One AE, in the placebo group, led to discontinuation of study medication through Week 54 and none at Week 24.

Rapporteur's comment:

The AE profile, in terms of overall frequency and incidence and types of AEs, was similar in the combined ertugliflozin group and the placebo group through Week 54. AEs were reported for 64.0% of participants in the combined ertugliflozin and 76.4% in the placebo group. The most frequently reported AEs (≥10.0%) in both groups were hypoglycemia and upper respiratory tract infection. Pyrexia was the only specific AE that occurred at a higher incidence in the combined ertugliflozin group (7.2%) versus the placebo group.

For the combined ertugliflozin group, a higher incidence of AEs considered drug-related by the investigator. The most frequently (>2.0%) reported drug-related AEs in the combined ertugliflozin group were hypoglycemia (2.7%) and polyurea (2.7%).

Four SAEs were reported for the combined ertugliflozin group, compared to zero for placebo. None of the SAEs were considered drug-related by the investigator. One participant in the placebo group discontinued study medication due to an AE. No deaths were reported.

In general, the AE information does not give rise to safety concerns in the population studied.

It was however considered worth looking into the fact that the SAEs hypoglycemia and hyperglycemia were considered not related to study medication. Narratives for these two cases were assessed and brief information as follows:

Hypoglycaemia case: A female participant on insulin and metformin at study start. At day 10 a non-serious mild hypoglycaemia caused by skipped, delayed, or small meal/snack. Background insulin dose was adjusted multiple times during the study. Study medication was uptitrated to 15 mg at day 86. Day 189 metformin was increased from 1000 mg daily to 1500 mg. On Day 262 the participant was hospitalised due to severe hypoglycaemia, presenting with altered consciousness and a home glucometer reading of 55 mg/dL. No precipitating factors were identified by the investigator. The participant was treated with glucose. The investigator considered hypoglycaemia not related to study medication. Hypoglycemia resolved after 12 hours with no new episodes of hypoglycaemia during hospitalization. On Day 263 insulin doses were reduced, and the participant was discharged. No action was taken with study medication in response to the event. Repeated events (14 events) of moderate hypoglycaemia (nonserious), which were treated with glucose or no treatment reported, occurred from day 265 to day 287. During this period, insulin and metformin doses were adjusted. For some of these events precipitating factor was reported as insulin use. On Day 288 study medication was discontinued due to the hypoglycaemia discontinuation criteria, with the last dose

administered on Day 276. The participant agreed to continue in the study off study medication.

Events of hypoglycaemia were reported on 8 separate days from day 289 to day 321, i.e. after having stopped study medication.

Hyperglycaemia case: A male participant not on insulin at study start. On Day 232 the participant experienced polyuria, polydipsia, and weakness; no change in compliance or the dose of metformin or study medication was reported. On Day 233 the participant was admitted to the hospital due to

moderate dehydration. Laboratory test results showed increased glucose, while other parameters were unremarkable. A urinalysis also showed increased glucose (4+). The participant was diagnosed with severe hyperglycaemia, which was probably caused by dietary factors. Treatment included human insulin and IV fluids (sodium chloride). On Day 234 a urinalysis showed persistent increased glucose (4+) and in addition ketones (1+) were detected. The investigator considered hyperglycaemia not related to study medication. On Day 235 glucose levels remained increased in the morning and insulin glargine was added to the treatment regimen. Hyperglycaemia resolved, and the participant was discharged. No action was taken with study medication in response to the event. Although the presentation of this event was unlikely ketoacidosis, it was adjudicated as an unclassifiable diagnosis of ketoacidosis due to the absence of laboratory data for acid/base status. Another hyperglycaemia episode occurred during which the participant was unaffected. At Day 241, glucose levels had gradually improved but remained increased and treatment with insulin glargine and metformin continued.

It is concluded that for the participant with hypoglycaemia some of the hypoglycaemia episodes were not associated with the study medication. The numerous episodes post-study medication indicate that the participant had problems with glycemic control not related to study drug. However, it cannot be completely ruled out that all of the hypoglycaemia episodes, including the serious one, were not associated with the study medication. This issue is not considered to impact the overall benefit-risk balance in adolescents. Therefore, no further investigation is deemed necessary.

For the hyperglycaemia case, it is agreed with the investigator that the participant´s hyperglycaemia episodes were most probably not related to the study drug.

Adverse Events of Special Interest (AESIs)

The protocol prespecified (Tier 1) AEs were symptomatic hypoglycemia, AEs associated with urinary tract infections (UTIs), genital mycotic infections (females), and hypovolemia. See Table 24. Through Week 54, the incidence of AEs of symptomatic hypoglycemia was comparable between the 2 treatment groups. UTIs were comparable between the 2 treatment groups. The incidence of genital mycotic infections in female participants was comparable between the 2 treatment groups. There were no AEs of genital mycotic infections reported in male participants. No meaningful differences in Tier 1 AEs were observed at Week 24 relative to Week 54.

Table 24 Analysis of Tier-1 Safety Endpoints for Adverse Events of Urinary Tract Infections and Hypovolemia, and Episodes of Symptomatic Hypoglycemia and of Genital Mycotic Infections (only females). Weeks 0 to 54. ll Participants as Treated

	Combined Ertugliflozin		Placebo		Difference in % vs Placebo	
	n	(%)	n	(%)	Estimate (95% CI)[a]	p-value[a]
Participants in population	111		55			
with one or more adverse events of Urinary Tract Infections[b]	4	(3.6)	1	(1.8)	1.8 (-6.3, 7.4)	0.528
with one or more adverse events of Hypovolemia[b]	1	(0.9)	0	(0.0)	0.9 (-5.7, 4.9)	0.481
with one or more adverse events of Symptomatic Hypoglycemia[c]	12	(10.8)	6	(10.9)	-0.1 (-12.0, 9.3)	0.985

[a] Based on Miettinen & Nurminen method.
Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.
[b] Including Rescue Approach.
[c] Excluding Rescue Approach.
Urinary Tract Infections adverse events were defined by a pre-specified sponsor-generated custom MedDRA query.
Hypovolemia adverse events were defined by a pre-specified sponsor-generated custom MedDRA query.
Adverse event terms are from MedDRA Version 27.1

Source: [P059MK8835: adam-adsl; adae; adhypo]

	Combined Ertugliflozin		Placebo		Difference in % vs Placebo	
	n	(%)	n	(%)	Estimate (95% CI)[a]	p-valuea
Participants in population	68		30			
with one or more adverse events of Genital Mycotic Infectionsb	3	(4.4)	1	(3.3)	1.1 (-12.7, 9.6)	0.805

[a] Based on Miettinen & Nurminen method.
Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.
[b] Including Rescue Approach.
Genital Mycotic Infections adverse events were defined by a pre-specified sponsor-generated custom MedDRA query.
Adverse event terms are from MedDRA Version 27.1

Source: [P059MK8835: adam-adsl; adae]

Hypoglycemia

Through Week 54, in participants on background insulin therapy, the incidences of overall hypoglycemia, documented hypoglycemia, symptomatic hypoglycemia, and asymptomatic hypoglycemia were comparable in the combined ertugliflozin and placebo groups. The number of hypoglycemic (symptomatic or asymptomatic) episodes was higher in the combined ertugliflozin group (102 episodes) than in the placebo group (15 episodes). In the combined ertugliflozin group, more episodes of hypoglycemia were symptomatic (58 episodes) than asymptomatic (44 episodes). The number of symptomatic (7 episodes) and asymptomatic (8 episodes) episodes was similar in the placebo group. No meaningful differences in the occurrence of hypoglycemia were observed at Week 24 relative to Week 54.

Through Week 54, in participants not on background insulin therapy, the incidence of overall hypoglycemia, symptomatic hypoglycemia, and asymptomatic hypoglycemia was comparable in the combined ertugliflozin and placebo groups. Documented hypoglycemia with blood glucose values ≥54 mg/dL (≥3.0 mmol/L) and ≤70 mg/dL (≤3.9 mmol/L) were less frequent in the combined ertugliflozin group (12.9%) than in the placebo group (22.6%). Documented hypoglycemia with blood glucose

values <54 mg/dL (<3.0 mmol/L) occurred only in the combined ertugliflozin group (6.5%). No events of severe hypoglycemia were reported for either group. The number of hypoglycemic episodes was higher in the combined ertugliflozin group (91 episodes) than in the placebo group (21 episodes). In the combined ertugliflozin group, fewer episodes of hypoglycemia were symptomatic (4 episodes) than asymptomatic (87 episodes) (documented hypoglycemia). In the placebo group, only 1 episode of hypoglycemia was symptomatic. No meaningful differences in the occurrence of hypoglycemia were observed at Week 24 relative to Week 54.

Urinary Tract Infections

The incidence of UTIs was low and comparable in the combined ertugliflozin and placebo groups through Week 54. All reported UTIs were classified as mild in severity, with no serious UTIs reported. No meaningful differences in the occurrence of UTIs were observed at Week 24 relative to Week 54.

Genital Mycotic Infections

The incidence of genital mycotic infections in female participants was low and comparable in the combined ertugliflozin and placebo groups through Week 54. All genital mycotic infections in female participants were classified as mild in severity, with no serious events reported. There were no genital mycotic infections in male participants. No meaningful differences in the occurrence of genital mycotic infections in female participants were observed at Week 24 relative to Week 54.

Hypovolemia

Through Week 54, 1 participant, in the combined ertugliflozin group, had an AE of hypovolemia. This event was severe, non-serious, considered not related to study medication, and did not lead to discontinuation of study medication.

Rapporteur's comment:

The protocol prespecified AEs of special interest were symptomatic hypoglycemia, AEs associated with urinary tract infections (UTIs), genital mycotic infections (females), and hypovolemia. The choice of these conditions and groups of diseases is acknowledged given the method of action of ertugliflozin. No imbalances were observed in these AESIs that gave rise to safety concerns.

Events of Clinical Interest and other safety topics of Interest

No participant met the biochemical criteria for DILI as defined in the protocol.

Through Week 54, the incidence of renal-related AEs was comparable in the combined ertugliflozin (5.4%) and placebo (3.6%) groups. The renal-related AE of increased urine albumin/creatinine ratio was in both treatment groups (3 participants on ertugliflozin; 2 participants on placebo), and microalbuminuria (2 participants) and hematuria (1 participant) in the combined ertugliflozin group. All

renal-related AEs were mild or moderate in severity, non-serious, and none led to discontinuation of study medication. No differences in the incidence of renal-related AEs were observed at Week 24 relative to Week 54.

Nephrocalcinosis was evaluated by abdominal ultrasounds. An independent reviewer assessed all ultrasounds for nephrocalcinosis. In the evaluation of nephrocalcinosis, approximately 52% of participants in the ertugliflozin group and 55% in the placebo group had evidence of nephrocalcinosis in 1 or both kidneys at baseline. Most participants in both groups (74.8% combined ertugliflozin, 83.6% placebo) exhibited no change from baseline in kidney status. The proportion of participants who had a 1-grade change from baseline in nephrocalcinosis in either kidney was higher in the combined ertugliflozin group (18.9%) than in the placebo group (9.1%) at Week 54. The proportion of participants who had a 2-grade change from baseline in nephrocalcinosis in either kidney was low and similar in both treatment groups at Week 54 (≤2.7%). There were no AEs of nephrocalcinosis reported. One participant in each group had an AE of nephrolithiasis that was mild in severity, nonserious, and did not lead to discontinuation of study medication.

Through Week 54, the incidence of hypersensitivity AEs was comparable in the combined ertugliflozin (5.4%) and placebo (3.6%) groups. All potential hypersensitivity AEs were mild in severity, non-serious, and none led to discontinuation of study medication. No differences in the incidence of hypersensitivity reactions were observed at Week 24 relative to Week 54.

No AEs associated with pancreatitis were reported.

Through Week 54, 2 participants in the combined ertugliflozin group and none in the placebo group had AEs of bone fracture. One participant had serious AEs of foot and tibia fracture from a sports injury considered not related to study medication by the investigator. A nonserious AE of upper limb fracture caused by trauma was considered related to study medication by the investigator.

Through Week 54, 2 participants treated with ertugliflozin had potential AEs of ketoacidosis adjudicated by the CAC. The event for the participant in the ertugliflozin 5-mg group was unclassifiable and the event for the participant in the ertugliflozin 5/15-mg group was considered unlikely to be ketoacidosis. One participant, in the placebo group, had ketonuria that was reported as mild and non-serious and did not meet the criteria for adjudication.

There were no events of amputation, diabetic foot syndrome, or Fournier’s gangrene.

One participant, in the placebo group, became pregnant during the study.

Rapporteur's comment:

No participant met the criteria for DILI. The incidences for renal-related AEs and for hypersensitivity were comparable for both groups. The data of nephrocalcinosis are not considered alarming. No cases of ketoacidosis were clearly identified. There were no reports of potential pancreatitis, amputations, diabetic foot syndrome, or Fournier’s gangrene for either group.

Clinical Laboratory Evaluation

Small mean increases from baseline in blood urea nitrogen (BUN) were observed in the combined ertugliflozin group, while mean values remained unchanged in the placebo group. These results are consistent with the higher proportion of participants with a BUN value that met pre-defined limits of change (PDLC) criteria for BUN. Through Week 54, a higher proportion of participants in the combined ertugliflozin group (12 [10.9%]) than in the placebo group (0 [0.0%]) had 1 BUN value with an increase from baseline of ≥50% to a value > ULN. Of the 12 participants in the combined ertugliflozin group who met these criteria, 6 had subsequent measurements that no longer met the PDLC criterion. For the other 6 participants, the last measurement continued to meet the criteria. In all 12 participants, creatinine levels were stable, and the changes observed in hemoglobin levels supported dehydration as the cause of the mild elevation of BUN (1 to 5 mg/dL above the ULN). No other notable differences in chemistry parameters were observed.

Small mean increases from baseline in hemoglobin (0.6 g/dL) and hematocrit (1.1%) were observed in the combined ertugliflozin group, while mean values for both parameters nearly unchanged in the placebo group. No other notable differences in hematology parameters were observed.

In male participants, there was a decrease over time in the urine NTx-creatinine ratio in both treatment groups. Notably, both groups exhibited a decrease in their respective ratios at Week 54 and at Week 24. In female participants, there was a decrease over time in the urine NTx-creatinine ratio in both treatment groups at Week 54, and an increase over time at Week 24. The change from baseline in urine NTx-creatinine ratio was comparable in both treatment groups at Week 24 and Week 54.

Both male and female participants in the combined ertugliflozin group had a decrease in bone-specific alkaline phosphatase (BSAP) levels from baseline to Week 54. The biomarker of bone turnover was consistent with changes in growth parameters. No other notable changes in bone biomarkers were observed.

Lipids Change from baseline in lipid endpoints were comparable between the combined ertugliflozin and placebo groups through Week 54. These changes were consistent with lipid changes noted in adult study with add-on metformin.

Small mean decreases from baseline in eGFR were observed in both treatment groups and the magnitude of the changes (~5 to 6 mL/min/1.73 m2) was consistent at Weeks 24 and 54.

Nephrocalcinosis was evaluated by abdominal ultrasounds at the visits indicated in the SoA. An independent reviewer assessed all ultrasounds for nephrocalcinosis. In the evaluation of nephrocalcinosis in this study, approximately 52% of participants in the ertugliflozin group and 55% in the placebo group had evidence of nephrocalcinosis in 1 or both kidneys at baseline. Most participants in both groups (74.8% combined ertugliflozin, 83.6% placebo) exhibited no change from baseline in kidney status.

Vital Signs, Physical Examinations, and Other Observations Related to Safety

Clinically meaningful abnormalities in vital signs, physical examinations, and ECGs were reported as AEs. There were no clinically meaningful findings in vital signs measurements in this study. Change from baseline in heart rate were comparable between ertugliflozin and placebo groups through Week 54. Change from baseline in height and growth velocity were comparable in the combined ertugliflozin and placebo groups through Week 54.

Tanner Staging

Mean changes from baseline in Tanner Stage results in female participants were comparable between the combined ertugliflozin and placebo groups through Week 54. Mean changes from baseline in Tanner Stage results in male participants were comparable between the combined ertugliflozin and placebo groups through Week 54.

Rapporteur's comment:

Small mean increases from baseline in blood urea nitrogen (BUN) were observed in the combined ertugliflozin group, while mean values remained unchanged in the placebo group. Mild dehydration was considered to be the cause behind the BUN elevation. Other than this, no clinically relevant differences between the ertugliflozin group and the placebo group in results of laboratory safety endpoints, vital signs, or growth and development endpoints were observed. No DILI events were reported.

Rapporteur's comment:

According to the applicant, no notable differences were observed for the incidences of AEs overall, AEs by SOC, and specific AEs. Incidences of hypoglycaemia (symptomatic or asymptomatic) were balanced between the 2 treatment groups, regardless of background insulin status. Severe hypoglycaemia was uncommon in both groups. More episodes of hypoglycaemia were reported in the combined ertugliflozin group than in the placebo group.

As earlier observed in the adult population with T2DM, treatment with ertugliflozin, and other SGLT2s, is associated with genital mycotic infections (in both males and females), UTIs, and hypovolemia. In this study in paediatric participants, these events were few, and not remarkably higher in the combined ertugliflozin group than in the placebo group.

The incidences of renal-related events, fractures, and hypersensitivity reactions were similar in the combined ertugliflozin and placebo groups through Week 54. No clinically relevant differences between groups were observed in results of laboratory safety endpoints, vital signs, or growth and development endpoints. No DILI events were reported.

Approximately 50% of all participants had nephrocalcinosis in 1 or both kidneys at baseline. The proportion of participants with treatment-emergent nephrocalcinosis or worsening of pre-existing nephrocalcinosis at Week 54 was higher in the combined ertugliflozin group than in the placebo group.

Relevant parameters for investigating general safety and tolerability were identified and studied. These included AEs, AESIs, vital signs, laboratory safety studies, renal-related events, nephrocalcinosis evaluations, and assessment of growth and development, and safety topics of interest such as ketoacidosis, volume depletion, hypersensitivity reactions, pancreatitis, bone fractures, bone turnover biomarkers, amputations, diabetic foot syndrome, and Fournier's gangrene.

No alarming imbalances or occurrence of DILI or pancreatitis were observed. The assessor agrees that ertugliflozin seems well tolerated in the population studied aged 10-17 years. No alarming safety issues have appeared, and the safety profile resembles the already known safety profile of the adult population. The MAH plans to further investigate the nephrocalcinosis data, as treatment-emergent nephrocalcinosis or worsening of pre-existing nephrocalcinosis at Week 54 was higher in the combined ertugliflozin group than in the placebo group. This is acknowledged.

Narratives were provided for all participants who experienced any event of clinical interest, Tier 1 safety events, safety topic of interest events, pregnancy, SAEs, and AEs leading to discontinuation of study medication, but not assessed as part of this P46 procedure.

2.3.3. Discussion on clinical aspects

In the EU, Steglatro (ertugliflozin) is authorised for treatment of T2DM for adults. The paediatric study MK-8835-059 (referred to as P059) was performed to evaluate ertugliflozin for paediatric patients with T2DM and inadequate glycemic control on metformin with or without insulin. The study is part of the paediatric development program described in the last approved PIP (EMEA-001533-PIP01-13-M03).

P059 was a Phase 3, multicenter, double-blind, randomised, placebo-controlled study to evaluate the safety and efficacy of ertugliflozin in pediatric participants (ages 10 to 17 years, inclusive) with T2DM on a stable dose of metformin ≥1500 mg/day with or without stable insulin. The overall study design and the duration of the study are considered adequate.

A total of 166 pediatric participants were randomised. Inclusion and exclusion criteria are considered adequate for recruiting a study population representative for the patient population and for a possible future treatment population. It is noted that according to inclusion criteria, all participants had background medication. For adults, ertugliflozin is indicated for treatment as monotherapy and as addition to other diabetes medications. The blood glucose lowering effect in children of treatment with ertugliflozin as monotherapy, will be assessed in the future Type II variation application envisaged to be submitted by the MAH.

Participants were randomized in a 2:1 ratio to either ertugliflozin 5 mg or placebo. At Week 12, participants in the ertugliflozin 5-mg group according to specified criteria, e.g. whose A1C was ≥7.0%, were rerandomized 1:1 to either continue on ertugliflozin 5 mg or uptitrate directly to ertugliflozin 15 mg. The randomisation and blinding procedures are considered adequate. Overall, the ertugliflozin and placebo groups were comparable with respect to demographic and disease characteristics, reflecting a possible future intended population. The rescue criteria and the use of insulin as rescue medication are acknowledged.

The primary efficacy endpoint was change from baseline in A1C at 24 weeks between ertugliflozin (5 mg or 15 mg, all doses combined) and placebo. Secondary efficacy endpoints included change from baseline on FPG at Week 24 for ertugliflozin (5 mg or 15 mg, all doses combined) versus placebo and changes from baseline within-group (ertugliflozin and placebo) on HbA1c and FPG at week 54. Primary safety endpoint consisted of Safety and tolerability of ertugliflozin over 24 weeks and 54 weeks measured as AEs and discontinuation of study medication due to AEs. The endpoints are acknowledged as clinically relevant.

The primary endpoint was met. The LS mean reduction from baseline A1C at Week 24 was significantly greater in the combined ertugliflozin group than in the placebo group (-0.68%, p=0.007). Sensitivity analyses supported the primary endpoints. The participants were stratified based on Age: 10 to 14 years of age OR 15 to 17 years of age and based on Insulin use: Yes OR No.

Sub-group analyses showed greater reduction in A1C for the sub-group of participants 15-17 years than for the younger group. Participants with insulin use at screening showed greater A1C reduction than those without. These findings seem in line with what would be expected since patients with insulin and older patients are assumed to have more advanced diabetes and thereby possibly more easily gain from treatment with ertugliflozin.

Key secondary endpoints consisted of change from baseline in A1C for the dose-optimized ertugliflozin group and for the ertugliflozin 5-mg group, respectively, compared to placebo. Both groups showed

significantly greater reduction from baseline in A1C than placebo at week 24, thus supporting the results of the primary endpoint.

For the other secondary endpoints, results also supported the primary endpoint results. The change from baseline on A1C at week 54, FPG at Week 24 and FPG at Week 54 for ertugliflozin (5 mg or 15 mg, all doses combined) showed greater reduction than the placebo group.

As no changes to the SmPC are proposed by the MAH within this procedure and the MAH has informed that a type II variation for extension of indication is planned to be submitted, the validity of the MAH conclusions of efficacy results of the P059 study should not be considered as finally assessed within this procedure. In general, the efficacy results indicate a benefit of treatment with ertugliflozin in children aged 10-17 years. Explorative endpoints will be assessed and discussed in the future Type II variation report.

For this procedure, it is considered of great importance to investigate whether the safety results from the use in the paediatric population in the P059 study, support the current use in the approved adult population with T2DM, or if new safety issues appeared in children with possible implications for adults.

No notable differences were observed for the incidences of AEs overall, AEs by SOC, and specific AEs. Incidences of hypoglycaemia (symptomatic or asymptomatic) were balanced between the 2 treatment groups, regardless of background insulin status. Severe hypoglycaemia was uncommon in both groups. More episodes of hypoglycaemia were reported in the combined ertugliflozin group than in the placebo group. Events of genital mycotic infections, UTIs, and hypovolemia were few, and not remarkably higher in the combined ertugliflozin group than in the placebo group.

The incidences of renal-related events and hypersensitivity reactions were similar in the combined ertugliflozin and placebo groups through Week 54. No clinically relevant differences between groups were observed in results of laboratory safety endpoints, vital signs, or growth and development endpoints. No DILI events were reported. The proportion of participants with treatment-emergent nephrocalcinosis or worsening of pre-existing nephrocalcinosis at Week 54 was higher in the combined ertugliflozin group than in the placebo group.

In conclusion, relevant parameters for investigating general safety and tolerability were identified and studied. Ertugliflozin seems well tolerated in the study population aged 10-17 years. No alarming safety issues have appeared, and the safety profile resembles the already known safety profile of the adult population. The MAH plans to further investigate the nephrocalcinosis data, which is considered adequate, since treatment-emergent nephrocalcinosis or worsening of pre-existing nephrocalcinosis at Week 54 was higher in the ertugliflozin group than in the placebo group. No new safety issues are identified for the studied paediatric population, therefore the safety in adults is considered unchanged.

The overall benefit-risk balance for the use of ertugliflozin in the adult population according to approved label is positive.

3. CHMP's overall conclusion and recommendation

The results from study P059 met the primary endpoint and demonstrated a statistically significant change in A1C from baseline to week 24 for subjects aged 10-17 years with T2DM treated with ertugliflozin (5 mg or 15 mg [doses combined]) compared to subjects treated with placebo. Treatment

with ertugliflozin is generally well-tolerated in children and adolescents aged 10-17 years, with an acceptable safety profile. Safety results were overall in line with the known safety profile for ertugliflozin in adults. The study results support a remained positive B/R for use of ertugliflozin in adults.

☒ **Fulfilled:**

No regulatory action required. The MAH has shared their plan to separately submit a separate Type II variation application to update the product information based on the results of P059 to expand the indication to children 10 years of age and older for the product Steglatro.