Clinical Study Report	
Drug Substance	dapagliflozin, saxagliptin
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A 26-Week, Multicentre, Randomised, Placebo-Controlled, Double-Blind, Parallel-Group, Phase III Trial with a 26-Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 5 and 10 mg, and Saxagliptin 2.5 and 5 mg in Paediatric Patients with Type 2 Diabetes Mellitus Who Are Between 10 and Below 18 Years of Age

Study dates: The analyses presented in this report are based on the 56-week clinical data lock date of 08 March 2023:
First patient enrolled: 11 October 2017
Last patient last visit: 01 February 2023

Phase of development: Therapeutic confirmatory (III)

International Co-ordinating Investigator: [redacted]

Sponsor's Responsible Medical Officer: [redacted]

AstraZeneca Pharmaceuticals LP
One Medimmune Way
Gaithersburg, MD 20878
United Sates of America

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study Centres

Patients were randomised at 94 sites in 21 countries. Patients were randomised at one additional site in Mexico (Site 4910), but due to an ongoing legal dispute between the building owners and site administration, the source documents could not be accessed. For this reason, all data from the 11 randomised patients at this site were excluded from the main efficacy and safety analyses, as documented in the statistical analysis plan. Sensitivity analyses including these patients showed no effect on the overall efficacy or safety results.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objective	Endpoint/variable
Primary objective	
To determine if there will be a greater mean reduction from baseline in HbA1c achieved after 26 weeks of oral double-blind add-on therapy of dapagliflozin (5 mg or 10 mg [all doses and regimens combined]) or saxagliptin (2.5 mg or 5 mg [all doses and regimens combined]) compared to placebo in paediatric T2DM patients with HbA1c levels of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.	Change from baseline in HbA1c at Week 26
Secondary objectives [a]	
a) To determine if there will be a greater mean reduction from baseline HbA1c achieved after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg (with titration to the high dose for those who do not achieve the glycaemic target of HbA1c < 7% at 12 weeks) compared to placebo in paediatric T2DM patients with HbA1c levels of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.	Change from baseline in HbA1c at Week 26
b) To determine if there will be a greater mean reduction from baseline HbA1c achieved after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg compared to placebo in paediatric T2DM patients with HbA1c levels of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.	Change from baseline in HbA1c at Week 26
c) To compare mean reduction from baseline of HbA1c at Week 26 achieved while remaining on the low-dose drug (dapagliflozin 5 mg or saxagliptin 2.5 mg) vs uptitration to the high-dose (dapagliflozin	Change from baseline in HbA1c at Week 26

Table S1 Objectives and Endpoints

Objective	Endpoint/variable
10 mg or saxagliptin 5 mg) amongst paediatric T2DM patients on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin who do not achieve an HbA1c < 7% at Week 12.	
d) To determine if there will be a greater mean reduction from baseline FPG achieved after 26 weeks of oral double-blind add-on therapy of dapagliflozin (5 mg or 10 mg [all doses and regimens combined]) or of saxagliptin (2.5 mg or 5 mg [all doses and regimens combined]) compared to placebo in paediatric T2DM patients with HbA1c levels of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.	Change from baseline in FPG at Week 26
e) To determine if there will be a greater mean reduction from baseline in FPG achieved after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg (with titration to the high dose for those who do not achieve the glycaemic target of HbA1c < 7% at 12 weeks) compared to placebo in paediatric T2DM patients with HbA1c of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.	Change from baseline in FPG at Week 26
f) To determine if there will be a greater mean reduction from baseline FPG achieved after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg compared to placebo in paediatric T2DM patients with HbA1c levels of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.	Change from baseline in FPG at Week 26
g) To compare mean reduction from baseline of FPG at Week 26 achieved while remaining on the low-dose drug (dapagliflozin 5 mg or saxagliptin 2.5 mg) vs uptitration to the high dose (dapagliflozin 10 mg or saxagliptin 5 mg) amongst paediatric T2DM patients on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin who do not achieve an HbA1c < 7% at Week 12.	Change from baseline in FPG at Week 26
h) To compare the percentage of patients with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7.0% after 26 weeks of oral double-blind add-on therapy of dapagliflozin (5 mg or 10 mg [all doses and regimens combined]) or of saxagliptin (2.5 mg or 5 mg [all doses and regimens combined]) compared to placebo in paediatric T2DM patients with HbA1c levels of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.	Percentage of patients with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26
i) To compare the percentage of patients with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7.0% after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg	Percentage of patients with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26

Table S1 Objectives and Endpoints

Objective	Endpoint/variable
(with titration to the high-dose for those who do not achieve the glycaemic target of HbA1c < 7% at 12 weeks) vs placebo in paediatric T2DM patients with HbA1c of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.	
j) To compare the percentage of patients with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7.0% after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg vs placebo in paediatric T2DM patients with HbA1c levels of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.	Percentage of patients with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26
k) To compare the percentage of paediatric T2DM patients on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7.0% at Week 26 while remaining on the low-dose drug (dapagliflozin 5 mg or saxagliptin 2.5 mg) vs uptitration to the high dose (dapagliflozin 10 mg or saxagliptin 5 mg) amongst patients who do not achieve an HbA1c < 7% at Week 12.	Percentage of patients with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26
Safety objectives	
To assess the safety and tolerability, including the incidence of AEs and events of hypoglycaemia, of dapagliflozin and saxagliptin as add-on to diet and exercise and metformin (IR or XR), or insulin, or metformin (IR or XR) plus insulin in paediatric T2DM patients when administered for up to 26 weeks of ST double-blind treatment, and, separately, up to 52 weeks of total treatment.	Incidence of AEs, SAEs, hypoglycaemic events, discontinuations due to AEs, marked abnormalities in clinical laboratory tests, vital signs, Tanner staging, measures of growth and maturation, DKA events, and safety laboratory tests.
To assess the incidence of DKA with dapagliflozin and saxagliptin as add-on to diet and exercise and metformin (IR or XR), or insulin, or metformin (IR or XR) plus insulin in paediatric T2DM patients when administered for up to 26 weeks of ST double-blind treatment, and, separately, up to 52 weeks of total treatment.	
To assess measures of growth and maturity and Tanner staging and markers of bone health in paediatric T2DM patients when administered dapagliflozin or saxagliptin as add-on to diet and exercise and metformin (IR or XR), or insulin, or metformin (IR or XR) plus insulin for up to 26 weeks of ST double-blind treatment, and, separately, for up to 52 weeks of total treatment, and for an additional 52 weeks after the study has been completed and study-related treatment has been discontinued.	
To assess the safety and tolerability of dapagliflozin (or saxagliptin) monotherapy in paediatric patients who are randomised to withdraw background metformin.	

Table S1 Objectives and Endpoints

Objective	Endpoint/variable
Exploratory objectives [b]	
To compare the percentage of patients requiring glycaemic rescue medication or discontinuing study drug due to lack of efficacy with dapagliflozin or saxagliptin against the percentage with placebo during 26 weeks of oral double-blind add-on treatment in paediatric T2DM patients with HbA1c of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.	Percentage of patients who require glycaemic rescue medication or discontinue the study drug due to lack of efficacy during the 26-week treatment period.
To assess time to initiation of glycaemic rescue medication or discontinuation of study drug due to lack of efficacy with dapagliflozin, saxagliptin, or placebo during the 26-week ST treatment period and during the 52-week ST + LT treatment period in paediatric T2DM patients with HbA1c of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.	• Time to initiation of glycaemic rescue medication or discontinuation of study drug due to lack of efficacy during the 26-week treatment period • Time to initiation of glycaemic rescue medication or discontinuation of study drug due to lack of efficacy during the 52-week treatment period.
To assess the mean change from baseline in HbA1c achieved with dapagliflozin therapy vs placebo, and separately, achieved with saxagliptin therapy vs placebo after 52 weeks of oral blinded add-on treatment in paediatric T2DM patients with HbA1c of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.	Change from baseline in HbA1c at Week 52
To assess the mean change from baseline in FPG achieved with dapagliflozin therapy vs placebo, and separately, achieved with saxagliptin therapy vs placebo after 52 weeks of oral blinded add-on treatment in paediatric T2DM patients with HbA1c of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.	Change from baseline in FPG at Week 52
To assess the percentage of patients with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7.0% after 52 weeks of oral blinded add-on therapy with dapagliflozin vs placebo, or saxagliptin vs placebo in paediatric T2DM patients with HbA1c of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.	Percentage of patients with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 52

Table S1 Objectives and Endpoints

Objective	Endpoint/variable
To assess the effect of monotherapy of dapagliflozin therapy (and separately saxagliptin therapy) for patients randomised to withdraw background metformin relative to dapagliflozin + metformin (and separately saxagliptin + metformin) and relative to placebo + metformin during the randomised withdrawal period using change in HbA1c, change in FPG, achievement of therapeutic glycaemic response (HbA1c < 7%), and time to rescue or discontinuation due to lack of glycaemic control.	• Change in HbA1c during the randomised withdrawal period • Change in FPG during the randomised withdrawal period • Percentage of patients who achieve or maintain an HbA1c level < 7% at the end of the randomised withdrawal period • Time to initiation of glycaemic rescue medication or discontinuation of study drug due to lack of efficacy using the start time of randomised withdrawal period as the reference point.
Pharmacokinetic/pharmacodynamic objective [c]	
To explore the PK and exposure-response relationship of dapagliflozin and, separately, saxagliptin and its metabolite 5-hydroxy-saxagliptin (5-OH-saxagliptin), in patients aged 10 to below 18 years with T2DM based on the collection of population PK samples.	Plasma levels of dapagliflozin, saxagliptin and its metabolite 5-OH-saxagliptin, and DPP4 activity [d] at indicated times.

[a] Note: secondary objectives are NOT presented in hierarchical testing order in this table. The hierarchical testing order is specified in Section 4.5.1 of the SAP (Appendix 16.1.9).

[b] Reported in the body of this CSR; not reported in the synopsis except where results are important for the interpretation of the primary analysis.

[c] Plasma concentrations are summarised in Section 14 of the CSR; PK data from sparse sampling were analysed using a population PK approach and are summarised in separate reports for dapagliflozin and saxagliptin.

[d] Plasma DPP4 activity was only assessed in saxagliptin randomised patients. DPP4 analyses will be summarised in a separate report.

Monotherapy refers to study drug taken after randomised metformin withdrawal.

AE, adverse event; CSR, clinical study report; DKA, diabetic ketoacidosis; DPP4, dipeptidyl-peptidase-4; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; IR, immediate release; LT, long-term; PK, pharmacokinetic; SAE, serious adverse event; SAP, statistical analysis plan; ST, short-term; T2DM, Type 2 diabetes mellitus; vs, versus; XR, extended release

Study Design

This ongoing study is a 26-week Phase IIIb, multicentre, randomised, placebo-controlled, double-blind, parallel-group study with a 26-week safety extension period plus a 4-week follow-up period to evaluate the safety and efficacy of dapagliflozin (5 mg and 10 mg), and, separately, saxagliptin (2.5 mg and 5 mg) in paediatric patients with Type 2 diabetes mellitus (T2DM). An additional post-treatment visit is scheduled at Week 104 to assess measures of growth and maturity. This report summarises the study results up to the Week 56 database lock.

After a 2-week lead-in period, patients were randomised 1:1:1 to receive dapagliflozin 5 mg, saxagliptin 2.5 mg, or placebo. Based on a blinded glycated haemoglobin (HbA1c) assessment at Week 12, patients on active treatment with HbA1c values < 7% remained on low-dose treatment while those with HbA1c values ≥ 7% were randomised 1:1 to continue on low-dose treatment or uptitrate to high-dose treatment (dapagliflozin 10 mg or saxagliptin 5 mg) starting from Week 14; patients on placebo continued on placebo (with appropriate blinding).

After completion of the 26-week short-term (ST) period, all patients were to enter the long-term (LT) treatment period. A subset of eligible patients (on background treatment with metformin only and who had HbA1c < 7.5% at Week 26 or Week 32, provided they had not initiated rescue glycaemic control therapy or been withdrawn from study drug) could undergo a third randomisation at Week 32 or Week 40 to continue or withdraw background therapy with metformin ("randomised metformin withdrawal period") to evaluate monotherapy with active study drug. Patients who did not qualify for the third randomisation at Week 32 due to an HbA1c ≥ 7.5% at Week 26 could qualify for the third randomisation at Week 40 if HbA1c was < 7.5% at Week 32. Discontinuation of background metformin occurred in an unblinded manner.

After Week 52, all patients discontinued study drug and received medication at the discretion of the treating physician until the Week 104 post-treatment visit. Adverse events (AEs) and serious adverse events (SAEs) were assessed during a Week 56 phone visit, and measures of growth and maturity will be assessed at the Week 104 visit.

Target Population and Sample Size

The target population consisted of male and female patients between 10 and < 18 years of age with T2DM (HbA1c ≥ 6.5% and ≤ 10.5%) on diet, exercise, and a stable dose of metformin, insulin, or metformin + insulin.

The sample size provides the ability to detect a 0.75% improvement over placebo for dapagliflozin or saxagliptin in change from baseline in HbA1c at Week 26 (ST) with approximately 80% power for each comparison at a 2-sided alpha level of 0.05. If 243 paediatric patients were randomised and analysed, and each treatment compared with placebo at a 2-sided alpha = 0.05 level, this would provide approximately 80% power for each comparison to detect a 0.75% reduction in HbA1c change from baseline versus (vs) placebo assuming a standard deviation of 1.7% (estimate based on a blinded review of ongoing study data).

Study Drug and Comparator: Dosage, Mode of Administration and Batch Numbers

The study drugs were dapagliflozin (5 mg or 10 mg tablet administered orally once daily), saxagliptin (2.5 mg or 5 mg tablet administered orally once daily), and matching placebo.

Table S2 Batch Numbers

Study treatment name:	Dapagliflozin 5 mg	Dapagliflozin 10 mg	Saxagliptin 2.5 mg	Saxagliptin 5 mg
Study drug	JF0085, MJ0714	HN0485, KF0352	5A87013S, KK0385	5A87014S, KK0383
Placebo to match	166075, 205378	166074, 189096	5A87015S, KK0384	

Duration of Treatment

An initial 26-week ST period was followed by a 26-week LT safety extension period. The study drug was discontinued at Week 52, after which patient treatment was left to the Investigator's discretion.

Statistical Methods

The intent-to-treat (ITT) estimand (which was estimated using data regardless of premature treatment discontinuation, regardless of rescue medication initiation, and with multiple imputation) was evaluated as the primary estimand.

The primary population for analysis was the Randomised Patients Data Set consisting of all randomised patients who received at least one dose of study drug during the treatment period. The primary analysis involved an analysis of covariance (ANCOVA) analysis of the change from baseline HbA1c at Week 26 of dapagliflozin (5 mg or 10 mg [all doses and regimens combined]) or saxagliptin (2.5 mg or 5 mg [all doses and regimens combined]) compared with placebo. The model included the baseline HbA1c value as a covariate, and treatment group (regimen) and randomisation strata as fixed effects. Missing data at the study endpoint were imputed using missing not at random (MNAR) imputation models. The modelling provides least square mean estimates and 2-sided 95% confidence intervals (CI) for mean changes from baseline within each treatment group (regimen) and differences in mean change from baseline between a treatment group and placebo.

Secondary analyses of the primary endpoint included weighted ANCOVA analyses testing the low-dose/high-dose and the low-dose regimens vs placebo. Additional ANCOVA analyses were conducted to compare uptitration to the high dose vs remaining at the low dose among patients with HbA1c $\geq$ 7% at Week 12. Similar analyses as for HbA1c were conducted for fasting plasma glucose (FPG). Similar comparisons of treatments and regimens were performed to compare the proportion of patients reaching the target of HbA1c < 7%. Logistic and weighted logistic regression analyses were performed for the analyses of these endpoints. Testing of secondary analyses followed a sequential testing procedure to control for multiplicity of testing.

The following treatment regimens were considered for analysis:

- Overall treatment (all dose regimens combined for dapagliflozin or saxagliptin).
- Low-dose/high-dose regimen: Initial treatment with the low dose (5 mg of dapagliflozin or 2.5 mg of saxagliptin) followed by uptitration to the high dose (10 mg of dapagliflozin or 5 mg of saxagliptin) for patients who did not achieve the glycaemic target of HbA1c < 7% at Week 12 (not responding and re-randomised to high dose) and continuing treatment with the low dose for those achieving the glycaemic target of HbA1c < 7% at Week 12 (responding and not re-randomised).
- Low-dose regimen: Initial treatment of the low dose (5 mg of dapagliflozin or 2.5 mg of saxagliptin) followed by continuing treatment on the low dose for those who do not achieve the glycaemic target of HbA1c < 7% at Week 12 (not responding and re-randomised to low dose) and those achieving glycaemic target of HbA1c < 7% at Week 12 (responding and not re-randomised).
- Placebo: all patients randomised to placebo.

Study Population

A total of 490 patients were enrolled and 245 patients were randomised: 81 patients to the dapagliflozin group, 88 patients to the saxagliptin group, and 76 patients to the placebo group (Randomised Patients Data Set).

All 245 randomised patients received study drug and were included in the Treated Patients Data Set. Of the randomised patients, 73 (90.1%), 82 (93.2%), and 66 (86.8%) patients in the dapagliflozin, saxagliptin, and placebo groups, respectively, completed study drug treatment throughout the 26-week double-blind ST period and 76 (93.8%), 83 (94.3%), and 68 (89.5%) patients, respectively, completed the ST period. All patients who completed the ST period entered the LT period. Of the randomised patients, 71 (87.7%), 75 (85.2%), and 56 (73.7%) patients in the dapagliflozin, saxagliptin, and placebo groups, respectively, completed study drug treatment throughout the LT period and 75 (92.6%), 79 (89.8%), and 61 (80.3%), respectively, completed the LT period.

The Randomised Patients Data Set and Treated Patients Data Set were used for the main efficacy and safety analyses, respectively.

No imbalances were observed between treatment groups at baseline that could have a potential influence on the results and their interpretation. Overall mean age was 14.5 years. Patients were evenly distributed between the ≥ 10 and < 15 years and the ≥ 15 and < 18 years age groups across the treatment groups. In total, 59.6% of patients were female and 40.4% were male. The treatment groups were generally well balanced in terms of race and ethnic groups. Approximately half of the patients (50.6%) were White. Patients were recruited across geographic regions: 97 (39.6%) patients were randomised in Latin America, 68 (27.8%)

patients were randomised in Asia/Pacific, 43 (17.6%) patients were randomised in Europe, and 37 (15.1%) patients were randomised in North America.

Overall, mean duration of T2DM at baseline was 2.48 years, ranging from 0 to 10.3 years, and the duration was < 2 years in 48.6% of patients. At baseline, mean HbA1c was 8.07% (ranging from 5.1% to 12.2%) and mean FPG was 9.03 mmol/L (ranging from 3.5 mmol/L to 82.6 mmol/L).

Background antidiabetic medication at baseline was metformin alone for the majority of patients (51.4%), followed by insulin + metformin (36.3%), and insulin alone (12.2%).

There were 88.2% of patients using metformin, and 51.8% of patients using insulin as a concomitant medication during the ST period. A higher proportion of patients in the placebo group had concomitant insulin (56.6%) compared with the dapagliflozin group (49.4%), and the saxagliptin group (50.0%).

Summary of Efficacy Results: Dapagliflozin Versus Placebo

Dapagliflozin (overall) vs placebo:

The primary analysis (ITT) demonstrated a significantly greater mean reduction from baseline in HbA1c at Week 26 in the overall dapagliflozin group (all dose regimens combined) compared with the placebo group. At Week 26, the difference in adjusted mean (standard error of the mean [SE]) change from baseline HbA1c was -0.62% (0.218%) in the dapagliflozin group and 0.41% (0.218%) in the placebo group. The difference between the groups was -1.03% (95% CI -1.57, -0.49), $p < 0.001$. A statistically significant improvement in glycaemic control was achieved at Week 6 and sustained through Week 26 with dapagliflozin vs placebo.

The secondary analyses were consistent with the primary analysis. At Week 26, there was a greater mean reduction in FPG from baseline (adjusted mean difference: -1.08 mmol/L [95% CI -2.02, -0.14], $p = 0.024$). There was a greater proportion of patients with baseline HbA1c ≥ 7% who achieved HbA1c level < 7% (odds ratio: 3.8 [95% CI 1.2, 11.7], $p = 0.019$) in the overall dapagliflozin group compared with the placebo group.

Dapagliflozin low-dose/high-dose treatment regimen vs placebo (secondary analyses):

For patients who had HbA1c ≥ 7% at Week 12 and were randomised to the uptitration group at Week 14, all 3 endpoints were consistent for this comparison. Statistically significant differences favouring dapagliflozin over placebo were observed for mean reduction from baseline HbA1c at Week 26, mean reduction from baseline FPG at Week 26, and the proportion of patients with baseline HbA1c ≥ 7% who achieved HbA1c level < 7% at Week 26.

Dapagliflozin low-dose regimen vs placebo (secondary analyses):
For patients who remained on the low-dose regimen during the study, all 3 endpoints were consistent for this comparison. Statistically significant differences favouring dapagliflozin over placebo were observed for mean reduction from baseline HbA1c at Week 26, mean reduction from baseline FPG at Week 26, and the proportion of patients with baseline HbA1c ≥ 7% who achieved HbA1c level < 7% at Week 26.

Dapagliflozin low-dose vs high-dose regimen (secondary analyses):
In patients who did not achieve HbA1c < 7% at Week 12, there were no significant differences between the group of patients who remained on 5 mg dapagliflozin compared with the group uptitrated to 10 mg dapagliflozin for mean reduction from baseline HbA1c at Week 26, mean reduction from baseline FPG at Week 26, and the proportion of patients with baseline HbA1c ≥ 7% who achieved HbA1c level < 7% at Week 26. These comparisons were not powered.

Summary of Efficacy Results – Saxagliptin Versus Placebo

Saxagliptin (overall) vs placebo:
The primary endpoint was not met; however, a numerical difference favouring saxagliptin over placebo was seen. The mean change from baseline (SE) HbA1c at Week 26 was 0.06% (0.198%) in the saxagliptin group and 0.50% (0.202%) in the placebo group, resulting in a difference of -0.44% (95% CI -0.93 to 0.05), p = 0.078. As the primary endpoint was not met, p-values for all secondary analyses are nominal.

The difference in mean change in HbA1c from baseline between overall saxagliptin and placebo during the ST period was nominally significant at Weeks 6, 12, and 20 but not at Week 26. In the weighted analysis of mean change in HbA1c from baseline during the ST + LT period, the difference between saxagliptin and placebo was nominally significant at Week 26 and Week 52 (exploratory analysis); the different results between the ST and ST + LT analyses at Week 26 were due to the handling of intermittent missing data. The primary analysis may also have been affected by an imbalance between the treatment groups in the proportion of patients who required glycaemic rescue medication and remained in the study at Week 26 (4/88 [4.5%] patients in the saxagliptin group compared with 10/76 [13.2%] patients in the placebo group).

The secondary analyses of mean change from baseline FPG at Week 26, and the proportion of patients with baseline HbA1c ≥ 7% who achieved a HbA1c level < 7% at Week 26 showed non-significant differences between overall saxagliptin and placebo, favouring saxagliptin.

Saxagliptin low-dose/high-dose treatment regimen vs placebo (secondary analyses):
No statistically significant differences between the saxagliptin low-dose/high-dose regimen vs placebo were observed for mean change from baseline HbA1c at Week 26, mean change from

baseline FPG at Week 26, and the proportion of patients with baseline HbA1c ≥ 7% who achieved HbA1c level < 7% at Week 26.

Saxagliptin low-dose regimen vs placebo (secondary analyses):
No statistically significant differences between the saxagliptin low-dose regimen vs placebo were observed for mean change from baseline HbA1c at Week 26 or mean change from baseline FPG to Week 26. The proportion of patients with baseline HbA1c ≥ 7% who achieved HbA1c level < 7% at Week 26 was nominally significant (odds ratio 3.8 [95% CI 1.1, 13.5], p = 0.042).

Saxagliptin low-dose vs high-dose (secondary analyses):
In patients who did not achieve HbA1c < 7% at Week 12, there were no significant differences between the group of patients who remained on 2.5 mg saxagliptin compared with the group uptitrated to 5 mg saxagliptin for mean change from baseline HbA1c to Week 26, mean change from baseline FPG to Week 26, and the proportion of patients with baseline HbA1c ≥ 7% who achieved HbA1c level < 7% at Week 26.

Summary of Safety Results: Dapagliflozin Versus Placebo

During the ST + LT period the percentage (%) of patients with any AE was similar in the total dapagliflozin group and placebo groups (72.8% vs 71.1%), whereas the number of AEs, reported as the incidence rate adjusted for exposure time, was lower in the total dapagliflozin group than in the placebo group (160.00 vs 182.69 per 100 patient years). There were 9 SAEs reported in the total dapagliflozin group and 5 SAEs in the placebo group. No hypoglycaemia SAEs were reported in either treatment group. There was 1 adjudicated event of diabetic ketoacidosis (DKA) reported in each of the total dapagliflozin and placebo groups. No deaths were reported in either treatment group. One non-serious AE led to discontinuation of study drug in each of the total dapagliflozin and placebo groups.

The findings from the markers of growth, maturation, and bone health, including Tanner scores and puberty status did not raise any safety concerns with dapagliflozin treatment.

Based on evaluation of clinical laboratory parameters, vital signs, and physical findings, dapagliflozin as add-on treatment to metformin, insulin, or a combination of metformin and insulin, was well tolerated when administered for 26 weeks of ST therapy and 52 weeks of total therapy in patients aged 10 to < 18 years of age with T2DM.

Summary of Safety Results: Saxagliptin Versus Placebo

During the ST + LT period, the percentage of patients with any AE was similar in the total saxagliptin and placebo groups (69.3% vs 71.1%), whereas the number of AEs, reported as the incidence rate adjusted for exposure time, was lower in the total saxagliptin group than in the placebo group (147.62 vs 182.69 per 100 patient years). There were 8 SAEs reported in the

total saxagliptin group and 5 SAEs in the placebo group. No hypoglycaemia SAEs were reported in either treatment group. No deaths were reported in either group. One AE led to discontinuation of study drug in each of the total saxagliptin and placebo groups.

The findings from the markers of growth, maturation, and bone health, including Tanner scores and puberty status did not raise any safety concerns with saxagliptin treatment.

Based on evaluation of clinical laboratory parameters, vital signs, and physical findings, saxagliptin as add-on treatment to metformin, insulin, or a combination of metformin and insulin, was well tolerated when administered for 26 weeks of ST therapy and 52 weeks of total therapy in patients 10 to < 18 years of age with T2DM.

Conclusions: Dapagliflozin Versus Placebo

- Add-on treatment with dapagliflozin resulted in a statistically significant and clinically meaningful improvement in glycaemic control in paediatric T2DM patients 10 to < 18 years of age who had HbA1c levels of 6.5% to 10.5% on diet and exercise and metformin, insulin, or metformin plus insulin at enrolment. The primary analysis (ITT) demonstrated a greater mean reduction in HbA1c from baseline to Week 26 with dapagliflozin (overall treatment) compared with placebo (adjusted mean difference -1.03% [95% CI: -1.57 to -0.49], p< 0.001).
- Safety results were consistent with the overall well-established safety profile for dapagliflozin, and no new safety concerns were identified. Safety data indicates that dapagliflozin was well-tolerated in the treated paediatric patients.

Conclusions: Saxagliptin Versus Placebo

- Add-on treatment with saxagliptin resulted in a numerical but not statistically significant improvement in glycaemic control compared with placebo in paediatric T2DM patients 10 to < 18 years of age who had HbA1c levels of 6.5% to 10.5% on diet and exercise and metformin, insulin, or metformin plus insulin at enrolment. In the primary analysis (ITT), the difference in adjusted mean change in HbA1c from baseline to Week 26 between saxagliptin (overall treatment) compared with placebo was -0.44% (95% CI -0.93 to 0.05), p = 0.078.
- Safety results were consistent with the overall well-established safety profile for saxagliptin in adults with T2DM, and no new safety concerns were identified. Safety data indicates that saxagliptin was well-tolerated in the treated paediatric patients.