EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 July 2025
EMA/273696/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invokana

International non-proprietary name: Canagliflozin

Procedure No. EMEA/H/C/002649/II/0069

Note

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

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List of abbreviations

ADR(s) adverse drug reaction
AE(s) adverse event(s)
AHA antihyperglycemic agent
BID bis in die (twice a day)
BMI body mass index
CI confidence interval
CSR clinical study report
DKA diabetic ketoacidosis
ECG electrocardiogram
eGFR estimated glomerular filtration rate
EOT end-of-treatment
EU European Union
FAS full analysis set
FOIA Freedom of Information Act
FPG fasting plasma glucose
GLP-1 RA glucagon-like peptide-1 receptor agonist
HbA1c glycated hemoglobin
ICH International Conference for Harmonisation
IIV Inter-individual variability
IR immediate-release
LS least squares
MedDRA Medical Dictionary for Regulatory Activities
MODY Maturity onset diabetes of the young
MTD maximum tolerated dose
PD(s) pharmacodynamic(s)
PDCO Pediatric Committee
PIP pediatric investigation plan
PK(s) pharmacokinetic(s)
PopPK population pharmacokinetics
PT preferred term
QD quaque die (once daily)
RTG renal threshold for glucose excretion
RUV residual unexplained variability
SCE summary of clinical efficacy
SCP summary of clinical pharmacology
SCS summary of clinical safety
SD standard deviation
SE standard error
SGLT1 sodium-glucose co-transporter 1
SGLT2 sodium-glucose co-transporter 2
T2DM Type 2 Diabetes Mellitus
TEAE(s) treatment emergent adverse event(s)
TODAY Treatment Options for Type 2 Diabetes in Adolescents and Youth (study)
UACR urinary albumin/creatinine ratio
UGE urinary glucose excretion
UTI urinary tract infection

Definitions of Terms

AUC area under the plasma concentration-time curve
AUC24h area under the plasma concentration-time curve from time 0 to 24 hours
AUCτ area under the plasma concentration-time curve during a dosing interval (τ)
Cmax maximum plasma concentration
Efp effect of placebo treatment on HbA1c at steady-state for a typical participant
Emax maximum placebo-corrected effect of canagliflozin on HbA1c at steady-state for a typical participant
t1/2 half-life
tmax time to reach the maximum concentration

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 11 July 2024 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of paediatric patients with type 2 diabetes mellitus aged 10 years old and older for INVOKANA, based on final results from study JNJ-28431754DIA3018 as well as study JNJ-28431754DIA1055. Study JNJ-28431754DIA3018 is a double-blind, placebo-controlled, 2-arm, parallel-group, multicenter Phase 3 study in participants with T2DM >10 and <18 years of age who had inadequate glycemic control (ie, HbA1c of >6.5% to <11.0%).

As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 13.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor changes to the PI and update the list of local representatives in the Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0208/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0208/2022 was completed.

The PDCO issued an opinion on compliance for the PIP P/0208/2022 (EMEA-C-001030-PIP01-10-M10).

Information relating to orphan market exclusivity

NA.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig

Timetable	Actual dates
Submission date	11 July 2024
Start of procedure	17 August 2024
CHMP Rapporteur Assessment Report	10 October 2024
PRAC Rapporteur Assessment Report	10 October 2024
PRAC Outcome	31 October 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 November 2024
Request for supplementary information (RSI)	14 November 2024
CHMP Rapporteur Assessment Report	26 February 2025
PRAC Rapporteur Assessment Report	26 February 2025
PRAC Outcome	13 March 2025
2nd Request for supplementary information (RSI)	27 March 2025
CHMP Rapporteur Assessment Report	30 June 2025
Updated CHMP Rapporteur Assessment Report	16 July 2025
CHMP opinion	24 July 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Currently Invokana is approved in adults in the following indication:
INVOKANA (canagliflozin) is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see SmPC sections 4.4, 4.5 and 5.1.

The MAH is proposing to extend the indication to the paediatric population as follows (**in bold**):
*INVOKANA (canagliflozin) is indicated for the treatment of adults **and children aged 10 years and older** with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:*

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see SmPC sections 4.4, 4.5 and 5.1.

The applicant does not propose any changes to the dosage form, route of administration, or dosing regimen via this application.

Epidemiology

Type 2 diabetes mellitus (T2DM) in children and adolescents is increasing worldwide, and the main driver is the increased prevalence and degree of childhood obesity. Childhood T2DM is still relatively rare in Europe.
In Germany, a three-fold increase in the prevalence of T2DM was reported for 10- to 19-year-olds between 2002 and 2020 (3.4 to 10.8 per 100,000) (Stahl-Pehe A et al. J Diabetes 2022; 14:840-850).

Biologic features, Aetiology and pathogenesis

In view of the pathophysiological similarities between T2DM in adults and children and adolescents aged 10 to less than 18 years, it is hypothesized that canagliflozin will also have efficacy in this paediatric population with a similar safety profile.

Clinical presentation, diagnosis

Four diagnostic tests for T2DM are currently recommended, including measurement of fasting plasma glucose, 2-hour (2-h) post-load plasma glucose after a 75 g oral glucose tolerance test (OGTT), HbA1c and a random blood glucose in the presence of signs and symptoms of diabetes.

People with fasting plasma glucose values of ≥7.0 mmol/L (126 mg/dl), 2-h post-load plasma glucose ≥ 11.1 mmol/L (200 mg/dl), HbA1c ≥ 6.5% (48 mmol/mol) or a random blood glucose ≥ 11.1 mmol/L (200 mg/dl) in the presence of signs and symptoms are considered to have diabetes (WHO 2019).

Management

The recommended treatment for paediatric T2DM is similar to the one in adults, with emphasis on a step-wise approach starting with lifestyle modifications, particularly diet and exercise, followed by the use of a single medical therapy and later by two therapies in combination. The aim is that the patient achieves and maintains low levels of glucose in the blood in order to prevent long-term complications.

For a long time, the only two approved treatment options for paediatric patients with T2DM in most countries were metformin and insulin. Recently, additional treatment options have become available in the EU for children and adolescents aged 10 to less than 18 years with type 2 diabetes, e.g. the GLP-1 receptor agonists Liraglutide (Victoza), Exenatide extended-release once-weekly injection (Bydureon), Dulaglutide (Trulicity) and the SGLT-2 inhibitors Dapagliflozin (Forxiga) and Empagliflozin (Jardiance).

2.1.2. About the product

INVOKANA (canagliflozin) is an inhibitor of sodium-glucose transporter 2 (SGLT2). The low-affinity/ high-capacity SGLT2 transporter in the proximal renal tubule reabsorbs the majority of glucose filtered by the renal glomerulus. Pharmacological inhibition of SGLT2 decreases renal glucose re-absorption and thereby increases urinary glucose excretion and lower plasma glucose in patients with T2DM. Canagliflozin as a single agent was first approved for marketing on 29 March 2013 in the US under the trade name of INVOKANA (available in 2 dose strengths of 100 mg and 300 mg) as an adjunct to diet and exercise in the treatment of T2DM in adults. The EU Marketing Authorization for canagliflozin was granted on 15 November 2013. Canagliflozin 100 mg and 300 mg film-coated tablets is currently authorized in more than 60 countries.

2.1.3. The development programme

The following table summarizes the studies supporting the present application of INVOKANA (canagliflozin) for the treatment of T2DM in children and adolescents aged 10 to less than 18 years.

Step in Development or Study	Paediatric Age Group	Status	Application where Report is submitted	Status of Application
Clinical studies				
Study 3 28431754DIA1055 Open-Label, Multicenter, Multiple Oral Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics and	≥10 to <18 years of age	Completed	Study results submitted under Type 2 Variation submitted in eCTD seq. 077 (EMEA/H/002649/II/023)	Procedure approved on 15/09/2016

Safety of Canagliflozin in Older Children and Adolescents ≥10 to <18 years of age with Type 2 Diabetes Mellitus and Currently on a Stable Dose of Metformin				
Study 4 28431754DIA3018 A Randomized, Multicenter, Double-Blind, Parallel-Group, Placebo-Controlled Study to Investigate the Efficacy and Safety of Canagliflozin in Children and Adolescents (≥10 to <18 years) with Type 2 Diabetes Mellitus	≥10 to <18 years of age	Completed	Study Results submitted on 13 March 2024, under Art.46 application – eCTD seq. 0217 (EMEA/H/C/002649/P46/19)	Assessment is on-going

2.1.4. General comments on compliance with GCP

All clinical studies included in this submission were conducted and reported in accordance with the ethical principles originating from the Declaration of Helsinki and in accordance with ICH Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

For the environmental risk assessment, the MAH refers to the ERA submitted as part of the previous variation for Invokana (EMEA/H/C/2649/II/46). This is acceptable since in the previous ERA, the $PEC_{surfacewater}$ was calculated with the default Fpen (1 %) which includes the new patient group applied for here, i.e. paediatric patients ≥10 to <18 years of age. The assessment of the data previously provided for ERA indicated no risks were identified; Consequently, this is still valid for this variation application.

2.2.2. Discussion on non-clinical aspects

The provided rationale for not providing an updated ERA is acceptable.

2.2.3. Conclusion on the non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP. The provided rationale for not providing an updated ERA is also considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

Study DIA1055
The study sites were not inspected. The company confirms that this study was conducted in line with the requirements of Directive 2001/20/EC, the ethical principles in the Declaration of Helsinki and with the Good Clinical Practice and applicable regulatory requirements.

Study DIA3018
The company confirms that the study was conducted in accordance with the ethical principles in the Declaration of Helsinki and consistent with Good Clinical Practices and applicable regulatory requirements. Known instances of non-conformance were documented and are not considered to have an impact on the overall conclusions of this study.

2.3.2. Pharmacokinetics

Study 28431754DIA1055 (DIA1055)

Title of study
Open-Label, Multicenter, Multiple Oral Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Canagliflozin in Older Children and Adolescents ≥10 to <18 years of age with Type 2 Diabetes Mellitus and Currently on a Stable Dose of Metformin

Objectives/Endpoints

Primary objective
To evaluate the pharmacokinetics of canagliflozin after multiple oral doses of canagliflozin in children and adolescent subjects with Type 2 Diabetes Mellitus (T2DM) who were ≥10 to <18 years of age and on a stable dose of metformin.

Pharmacokinetic parameters to be determined:

$C_{max,ss}$	maximum observed plasma concentration during a dosing interval at steady-state
t_{max}	time to reach the maximum observed plasma concentration
AUC_{τ}	area under the plasma concentration-time curve during a dosing interval (τ)
$t_{1/2,\lambda}$	elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$
λ_z	first-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve
CL_{ss}/F	total clearance of drug at steady-state after extravascular administration, uncorrected for absolute bioavailability calculated as: D/AUC_{τ}

Secondary objectives:

- Evaluate the pharmacodynamic effects of canagliflozin on plasma glucose levels, urinary glucose excretion, and the renal threshold for glucose after multiple oral doses. For details, please see section below on pharmacodynamics.
- Assess the acceptability of the canagliflozin tablets
- Assess the safety and tolerability

Design

Open-label, sequential, multiple-dose (14 days of dosing), multi-center study of canagliflozin in 2 dose groups of approximately 8 subjects per dose group (up to approximately 16 children and adolescents in total). Subjects who were diagnosed with T2DM and on a stable regimen of metformin (≥1,000 mg per day) for ≥8 weeks before screening were enrolled. Subjects were instructed to continue to take their stable dose of metformin throughout the study.

The study consisted of 4 phases:

(1) Screening Phase: ~3 weeks (Days -25 to -4)

(2) Baseline Phase: 3 days (Days -3 to -1)
Subjects received placebo with ~180 mL water on Day -1 after an overnight fast of ≥8 hours. About 10 min later, subjects received a standardized breakfast. Serial blood samples were drawn immediately before dosing and at selected time points for up to 24 hours.

(3) Open-Label Treatment Phase: 17-day Treatment Period (Days 1 through 17)

- Dose Group 1: Eight subjects received one 100-mg tablet of canagliflozin daily for 14 days.
- Dose Group 2: Based upon PK, PD and safety data from the first 5 subjects who completed Dose Group 1, nine (9) additional subjects were enrolled into Dose Group 2 to receive one 300 mg tablet of canagliflozin daily for 14 days.

In both groups, the first dose of study drug was administered in the morning of Day 1 after an overnight fast of ≥8 hours. About 10 min later, subjects received a standardized breakfast. Subjects were instructed to continue daily oral doses of canagliflozin with metformin for Day 2 to Day 13 at approximately the same time each morning before the first meal of the day. The clinical study center contacted the subjects each day to remind them to take their dose of study medication as well as metformin, to query potential adverse events and to ensure compliance with study-related procedures. Time and amount of each dose as well as the daily fasting self-glucose monitoring value was documented in a study diary.

Subjects received their final dose of study drug in the morning of Day 14 (after an overnight fast of ≥8 hours), immediately followed by administration of a questionnaire to assess the acceptability of the canagliflozin tablet. Approximately 10 minutes after dosing, subjects received a standardized breakfast and remained at the study center for collection of PK, PD and safety assessments for 24 hours (until the morning of Day 15).

(4) Safety Follow-up Phase: 7 - 10 days after the last study-related procedure on day 17 or at the time of early withdrawal

During the last 3 days of Screening (ie., Days -6, -5, and -4) and on a daily basis during the entire treatment outpatient period (Day 2 to Day 13 and Day 15 to follow-up), subjects were to record the fasting self-monitored fingerstick glucose levels (before the first meal of the day). The subjects had to report the results to the clinic weekly, or at any time where values exceeded pre-specified limits (>270 mg/dL or <50 mg/dL). On Day -1, Day 1 and again on Day 14 and Day 15, the study staff monitored the subject's fasting glucose levels via a fingerstick blood sample.

Changes in conduct – study amendments

The original protocol (issued 26 September 2013) had 5 amendments as specified below.

- Amendment INT-5 (21 September 2015): The overall reason for the amendment was to enhance study recruitment. The window period for screening safety assessments was widened from 7 days to 10 days. Updated information on diabetic ketoacidosis and handling of subjects surrounding this event was added. Subjects who were on metformin XR for at least 8 weeks prior to screening and switched to metformin immediate release (IR; at the same total daily dose) which was well tolerated for at least 2 weeks prior to Day -1 were allowed to participate in the study. The concurrent use of insulin with metformin to achieve sufficient glycemic control was allowed.
- Amendment INT-4 (16 September 2014): The overall reason for the amendment was to ensure protocol consistency with health authority agreements for study design. Administration of AHAs for up to 7 days in the 8 to 2 weeks prior to the screening visit was not permitted as per this amendment.
- Amendment INT-3 (09 September 2014): The overall reason for the amendment was to adjust and clarify the language of the Inclusion and Exclusion criteria, modify rules related to concomitant medications, and update the calculation of estimated glomerular filtration rate (eGFR; using Schwartz formula).
- Amendment INT-2 (30 Oct 2013): The overall reason for the amendment was to correct a typo defining the value of a non-acceptable eGFR in exclusion criterion 8 and Inclusion of contraceptive injection as an effective birth control method.
- Amendment INT-1 (18 October 2013): The overall reason for the amendment was to address a comment from the US FDA regarding the definition of renal function inclusion criteria and general clarifications of admission days and a few procedures. The restriction on male subjects for use of effective birth control method was removed as per this amendment.

Study drug, dose, and mode of administration

The formulations supplied for this study were:

- Canagliflozin, 100 mg (1×100 mg), capsule-shaped yellow tablets - oral
- Canagliflozin, 300 mg (1×300-mg), capsule-shaped white tablets - oral
- Placebo capsule-shaped white tablets (Day -1 dosing only).

Background therapy

Stable regimen of metformin immediate release (IR) monotherapy of at least 1,000 mg/day for at least 8 weeks before screening

Number of patients

Planned: A total of 16 subjects were planned to be enrolled in the study.

Analyzed: A total of 17 subjects (8 subjects from Group 1 receiving 100 mg and 9 subjects from Group 2 receiving 300 mg canagliflozin) completed the study and were included in the analysis.

Main inclusion and exclusion criteria

Diagnosis and Main Criteria for Inclusion: Medically stable male or female subjects ranging in age from ≥10 to <18 years, with diagnosis of T2DM without pancreatic autoimmunity and who were on a stable regimen of metformin immediate release (IR) monotherapy of at least 1,000 mg/day for at least 8 weeks before screening. Subjects had to be able to swallow whole tablets and had to have normal renal function (estimated glomerular filtration rate [eGFR] ≥90 ml/min/1.73 m^2 as assessed by Schwartz formula), ALT or AST <2.0×ULN and a HbA1c of ≥6.1% to ≤10%.

Subjects with history of type 1 diabetes mellitus (T1DM), history of maturity onset diabetes of the young (MODY) and any secondary form of diabetes were excluded.

Pharmacokinetic Results
A total of 17 subjects were enrolled, the majority were black or African American, female, with a median age of 15 years. The 3-fold range between minimum and maximum BMI (range: 18.0 to 55.3 kg/m^2; mean: 38.17 kg/m^2) and body weight (range: 48.5 to 168.6 kg; mean: 107.15 kg) from subjects included within this study was notable and is representative of adult BMI and body weight ranges.

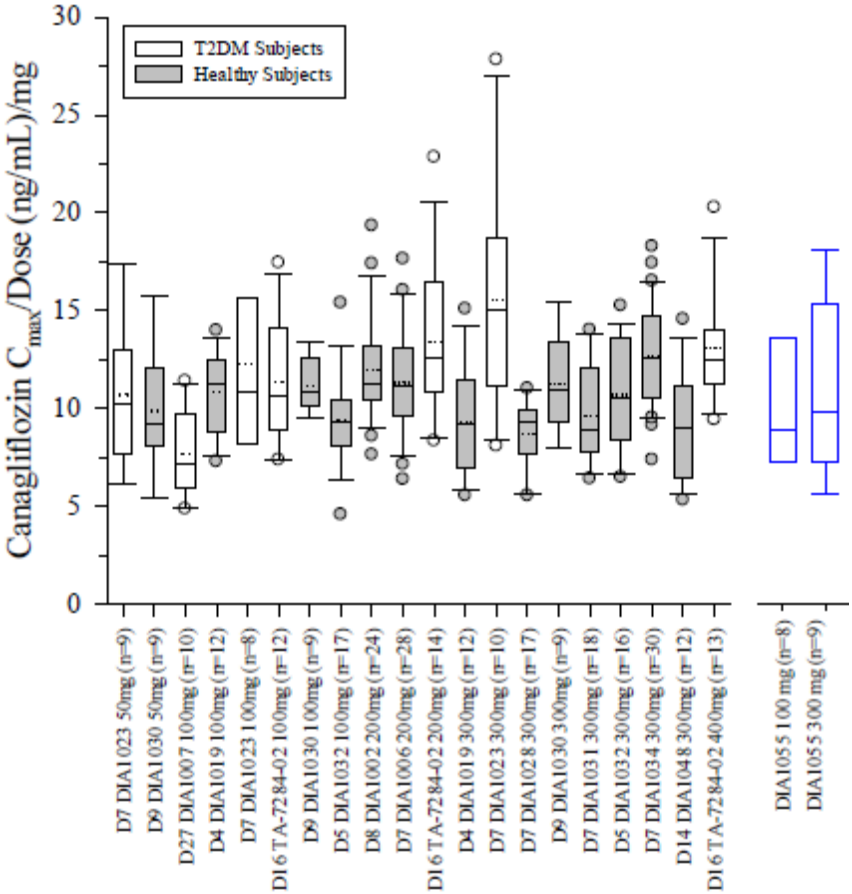
Pharmacokinetic

Mean (SD) Plasma Canagliflozin Pharmacokinetic Parameters
(Study 28431754DIA1055: Pharmacokinetic Analysis Set)

Parameters	Canagliflozin 100 mg (Group 1) n= 8	Canagliflozin 300 mg (Group 2) n= 9
C_{max} (ng/mL)	951 (429)	3,260 (1,330)
C_{max}/Dose (ng/mL/mg)	9.51 (4.29)	10.9 (4.42)
t_{max} (h)[a]	1.64 (1.00 – 1.98)	2.44 (1.00 - 4.00)
AUC_T (h*ng/mL)	6,190 (1,770)	28,392 (12,412)
AUC_T/Dose (h*ng/mL/mg)	61.9 (17.7)	94.6 (41.4)
$t_{1/2}$ (h)	11.3 (2.5)	15.2 (6.9)
λ_z (1/h)	0.0644 (0.0151)	0.0528 (0.0183)
CL_{ss}/F (L/h)	17.5 (5.78)	12.3 (6.90)

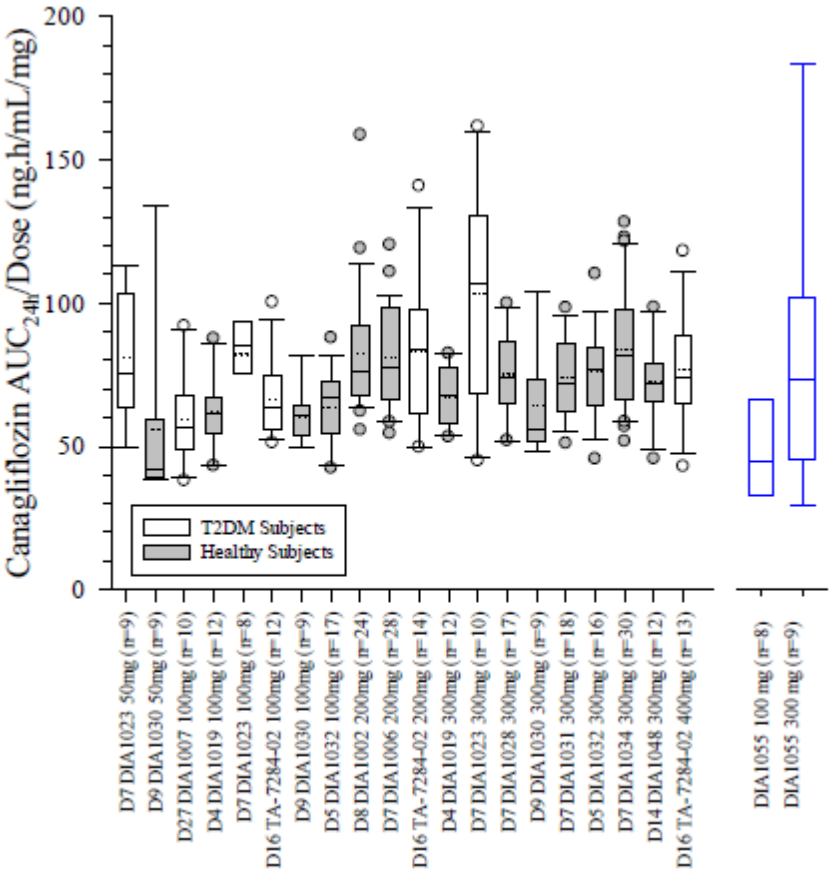
[a] Mean (range)

Dose-Normalized C_{max} Values of Canagliflozin Following Multiple-Dose Administration of 50 to 400 mg QD in Healthy Adult Subjects and Subjects with T2DM and Pediatric T2DM Subjects Receiving 100 mg or 300 mg (DIA-1055)



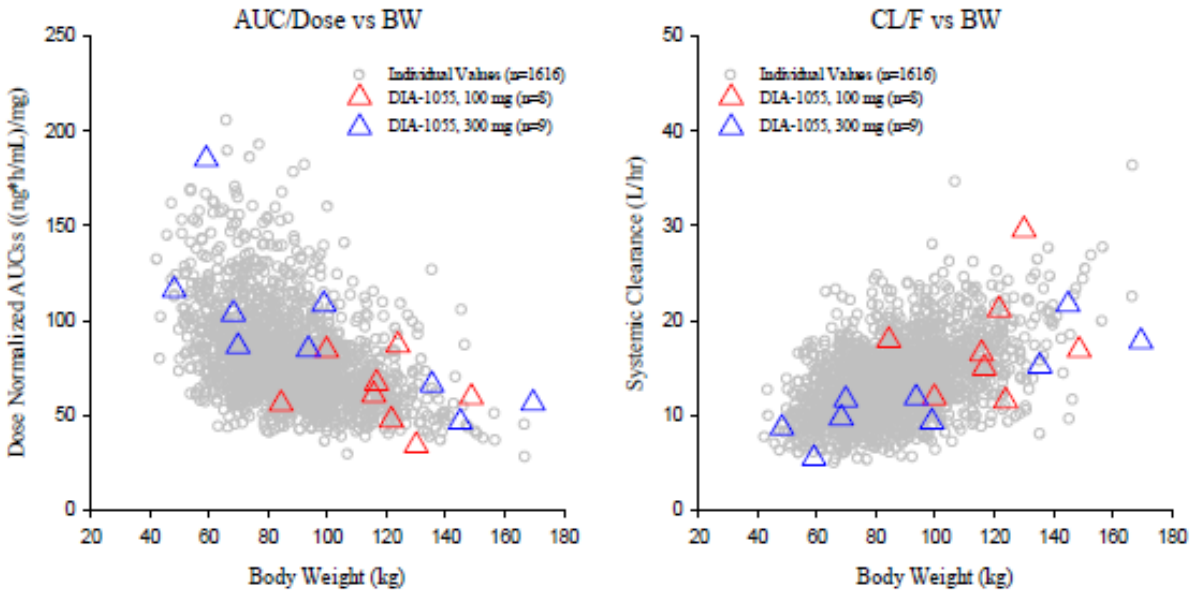
Note: different sampling time-points were utilized between studies, and may impact estimation of C_{max}

Dose-Normalized AUC_{tau} Values of Canagliflozin Following Multiple-Dose Administration of 50 to 400 mg QD in Healthy Adult Subjects and Subjects with T2DM and Pediatric T2DM Subjects Receiving 100 mg or 300 mg (DIA-1055)



Note: different sampling time-points were utilized between studies, and may impact estimation of AUC_{tau}

Dose-Normalized AUC24h Values of Canagliflozin vs. Body Weight Following Multiple-Dose Administration of 25 to 1600 mg in Healthy Subjects, Subjects with T2DM, and Obese Subjects



Note: Population PK and DIA-1055 defined AUC defined as AUC = Dose/CL)

Study 28431754DIA3018 (DIA3018)

Study DIA3018 was conducted in children and adolescents (≥10 to <18 years) with T2DM who had inadequate glycaemic control. The primary objectives of the study were:
a) To assess the effect of canagliflozin relative to placebo on HbA1c after 26 weeks of treatment, and
b) to assess the overall safety and tolerability of canagliflozin.
(For further details please see the Clinical Efficacy section below).
PK blood samples were collected at Week 12, Week 26, Week 52 (EOT) and at the early withdrawal visit for determination of plasma trough concentrations of canagliflozin in all participants.

The mean plasma canagliflozin concentrations were higher for the 300 mg dose vs the 100 mg dose. The data suggest that the mean plasma canagliflozin concentration for the 100 mg dose is consistent between the Week 12 and Week 26 visits. The mean plasma canagliflozin concentration at Week 52 is lower, probably due to the inclusion of EOT values that may not have been taken in a similar time frame following the last dose of study intervention. The data were variable across all visits and doses, but overall, were within the concentration range observed in the canagliflozin adult dataset and in paediatric participants during Study DIA1055.

Descriptive Statistics of Canagliflozin Plasma Concentration (ng/mL) Data; Full Analysis Set

	100 mg			300 mg	
	Week 12	Week 26	Week 52/EOT	Week 26	Week 52/EOT
N	80	57	56	15	14
Mean	344.2	304.3	186.5	503.7	988.5
CV (%)	202.9	425.9	294.4	185.1	209.8
SE	78.1	171.7	73.4	240.8	554.2
SD	698.4	1296.0	549.2	932.5	2073.7
Median	90.7	65.5	59.4	5.3	160.8

Minimum[a]	0	0	0	0	0
Maximum	4640	9530	3910	3330	7540

BQL=below the lower limit of quantification; CV=coefficient of variation; EOT=end of treatment; SD=standard deviation; SE=standard error.

[a] BQL data are represented by concentration values of 0.

Population pharmacokinetic analysis

Previously, a PopPK model for canagliflozin for adults had been developed based on data from nine Phase 1 (ie, DIA1001, DIA1002, DIA1003, DIA1007, DIA1008, DIA1019, DIA1023, DIA1030, and TA7284-02), two Phase 2 (ie, DIA2001, OBE2001), and three Phase 3 (ie, DIA3004, DIA3005, and DIA3009) clinical studies in healthy adults and adult patients with T2DM. The dataset used for model development included 9,061 rich and sparse plasma concentrations from a total of 1,616 participants. This PopPK model for adults consisted of an open 2-compartment disposition model with first-order elimination and a sequential zero- and first-order absorption after a lag time. Inter-individual variability (IIV) was quantified on the model parameters for Vc/F, ke, k32, ka, and Tlag, assuming a lognormal distribution. The CL/F was derived from the estimated apparent volume of distribution and the estimated ke through CL/F=Vc/F*ke. An additive error model was used to quantify the residual unexplained variability (RUV) on the log-transformed plasma concentration scale, assuming different variances for rich and sparse PK data. As the Phase 2 and 3 PK data were sparse and therefore less informative with respect to the absorption and distribution characteristics of canagliflozin, the PopPK parameters describing absorption (ka, Tlag, and D1) and distribution (Vc/F, k23, and k32), including their covariate and random effects, were fixed to the estimated values from the PopPK model built on Phase 1 data.

Non-linear mixed effects modeling software NONMEM (Version 7.4 and higher, ICON plc) and the FOCE with INTERACTION (FOCE-I) estimation option was used for the PopPK analysis.

The final adult PopPK model included statistically significant covariates of sex, age, and body weight on Vc/F, BMI on ka, BMI and over-encapsulation (over-encapsulated versus non-encapsulated tablets) on Tlag, and eGFR and total daily dose on ke. The covariate effects were deemed not clinically relevant and therefore no dose adjustment based on those covariates was warranted.

An external model evaluation was performed to verify the predictive performance of the previously developed adult PopPK model for paediatric studies DIA1055 and DIA3018. In total, 330 canagliflozin concentrations from 90 paediatric patients with T2DM were included in the PopPK analysis dataset (age range 10.0 – 17.0 years, body weight range 44.8 – 170 kg). Based on the results of the external evaluation, the previously developed PopPK model in adults was not deemed to adequately describe the data in paediatric patients with T2DM from studies DIA1055 and DIA3018. In particular, the model appeared to underestimate the general trend of the paediatric data at a population level, while at an individual level the paediatric data were well described by the model. Therefore, a model update was performed.

The base model structure remained the same for the updated paediatric model, but the inclusion of covariates was retested. Compared with the adult PopPK model, covariate effects of age, eGFR, and BMI were removed, while covariate effects of body weight and sex on Vc, over-encapsulation on Tlag, and total daily dose on ke were retained in the paediatric PopPK model. No additional covariate effects were identified in the paediatric PopPK model. In order to estimate PK metrics for the paediatric patients, all parameters were fixed to the estimates from the adult model except for the residual error variances, which were re-estimated based on the data from studies DIA1055 and DIA3018. Final model parameters for the paediatric-adjusted model are displayed in Table 1 below.

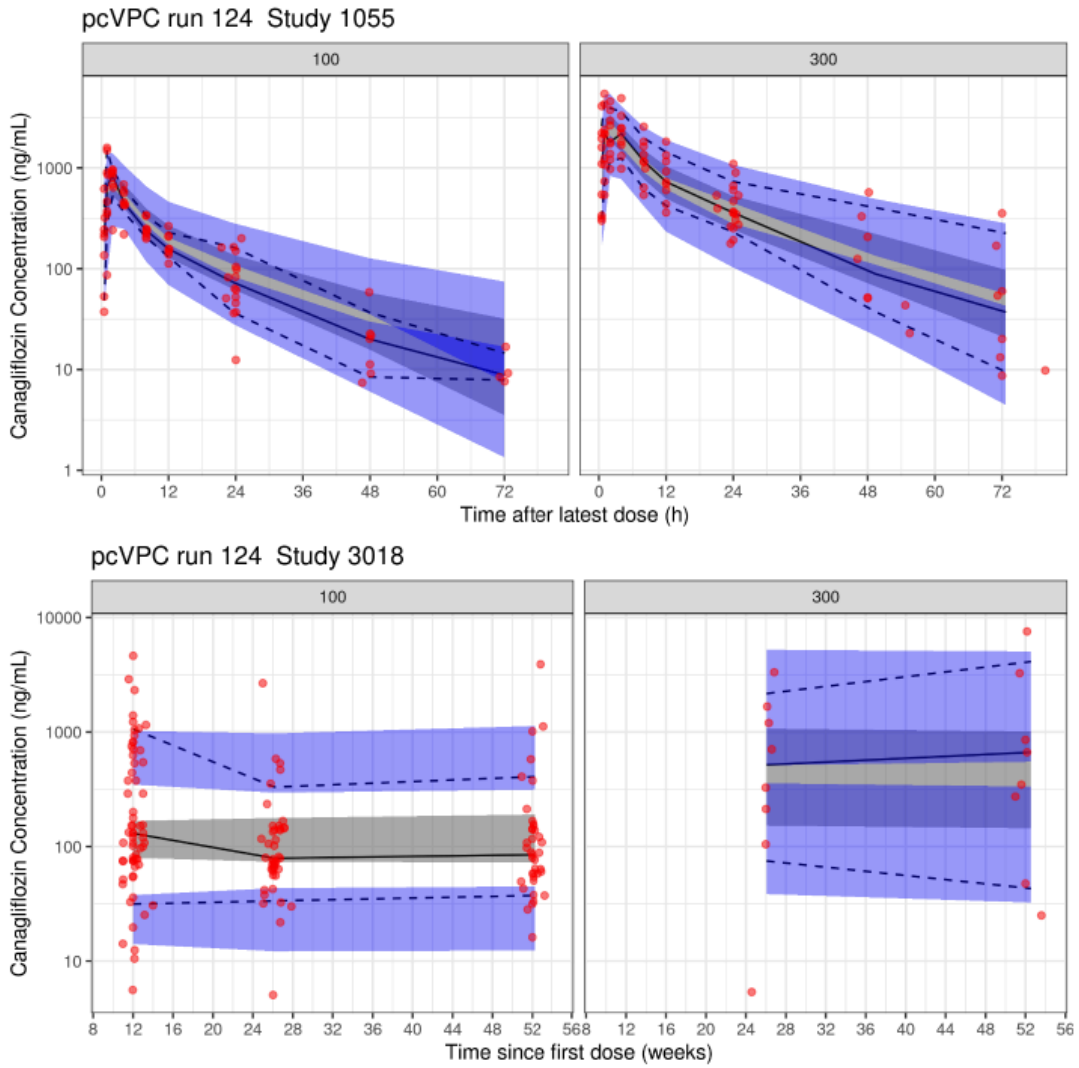
Table 1 Parameter estimates of the final paediatric PopPK Model for Canagliflozin (run124)

Parameter	Population Mean Estimate	RSE (%)	IIV (CV%)	Shrinkage (%)
V_c/F (L) (males)	99.3 FIX		14.6 FIX	70.1
k_e (h^{-1})	0.145 FIX		23.1 FIX	39.1
k_a (h^{-1})	3.68 FIX		188 FIX	51.6
T_{lag} (h) (non-encaps. tablets)	0.147 FIX		93.6 FIX	65.7
D_1 (h)	0.604 FIX			
k_{23} (h^{-1})	0.101 FIX			
k_{32} (h^{-1})	0.0856 FIX		36.2 FIX	65.1
V_c/F (L) (females)	82.6 FIX			
T_{lag} (h) (over-encaps. tablets)	0.262 FIX			
Body weight on V_c/F	0.583 FIX			
Total daily dose on k_e	-0.0631 FIX			
Residual error (SD %) Phase 1 pediatric	22.7	13.4		
Residual error (SD %) Phase 2 and 3 pediatric	114	9.12		

FIX = model parameters, including covariate and random effects, were fixed to the estimates obtained from the adult PopPK model[1]

CV% calculated as $\left(\sqrt{\exp(\omega^2) - 1}\right) * 100$

Visual predictive checks (pcVPCs) are shown in Figure 1 below.



Observed concentrations (red dots) with median (solid lines) and 10th, 90th percentiles (dashed lines). Areas show the simulation-based 95% PIs, in grey for the median and in blue for the 10th and 90th percentiles (N=1,000).

Figure 1: pcVPC of the Final paediatric PopPK Model (run 124) for Canagliflozin in DIA1055 (Top) and DIA3018 (Bottom) by Dose

Simulations

Based on the final paediatric PopPK model (run124) and the previously developed adult PopPK model, canagliflozin exposure metrics AUC24h and Cmax at steady state were simulated in paediatric and adult patients with T2DM, respectively in order to support bridging from QD to BID dosing of canagliflozin for the use of CANA/MET in paediatric patients with T2DM. The concentration - time profiles at steady state following 50 mg BID, 100 mg QD, 150 mg BID, and 300 mg QD canagliflozin administration were simulated. Canagliflozin PK was simulated including IIV and Phase 1 RUV, as the simulations should reflect an adequately characterized PK profile based on a rich sampling schedule. The MAH concluded that the simulations show that AUC24h at steady state, reflecting the total daily exposure, is similar between QD and BID dosing for the same total daily dose of canagliflozin, in both paediatric and adult T2DM patients.

2.3.3. Pharmacodynamics

Study DIA1055

One of the secondary objectives of Study DIA1055 was to evaluate the pharmacodynamic effects of canagliflozin on plasma glucose levels, urinary glucose excretion, and the renal threshold for glucose after multiple oral doses (for study description see Pharmacokinetics section above). The following parameters were addressed:

Renal Threshold for Glucose	
$RT_{G,t1-t2}$	Renal threshold for glucose excretion calculated over the 0-12 and 12-24h time intervals.
24-h mean RT_G	The 24-h mean renal threshold for glucose excretion, calculated as the average of the values obtained over the 0-12h and 12-24h intervals.
Plasma Glucose	
FPG	Fasting plasma glucose.
$M\Delta PG_{0-2h}$	Mean concentration for postprandial incremental plasma glucose excursion during the 0- to 2-hour interval, calculated as the positive incremental (above pre-meal) AUC over 0-2h divided by the 2 h time interval.
$M\Delta PG_{0-4h}$	Mean concentration for postprandial incremental plasma glucose excursion during the 0- to 4-hour interval, calculated as the positive incremental (above pre-meal) AUC over 0-4h divided by the 4 h time interval.
MPG_{0-4h}	Mean concentration of plasma glucose during the 0- to 4-hour interval, calculated as AUC over 0 to 4h divided by the 4-hour time interval.
MPG_{0-24h}	Mean concentration for plasma glucose during the 0- to 24-hour interval, calculated as AUC over 0 to 24h divided by the 24-hour time interval.
Urinary Glucose Excretion	
UGE_{t1-t2}	urinary glucose excretion, equal to the amount of urine glucose excreted into the urine over the time intervals 0 to 12 hours and 12 to 24 hours, abbreviated as UGE_{0-12h} and UGE_{12-24h}, respectively, calculated for each interval by multiplying the urinary volume with the urinary glucose concentration.
UGE_{0-24h}	cumulative daily urinary glucose excretion, equal to the amount of plasma glucose excreted into the urine over the entire urine collection interval, 0 to 24 hours, calculated as the sum of UGE_{0-12h} and UGE_{12-24h}.

Results:

Renal Threshold for Glucose (RT_G)

On day 14, 100 mg of canagliflozin resulted in a mean RT_G of

- 74 mg/dL (4.11 mmol/L) from 0 to 12 h
- 95 mg/dL (5.27 mmol/L) from 12 to 24 h
- 85 mg/dL (4.72 mmol/L) over 24 h (24-hour mean RT_G)

On day 14, 300 mg of canagliflozin resulted in a mean RT_G of

- 67 mg/dL (3.72 mmol/L) from 0 to 12 h
- 72 mg/dL (4 mmol/L) from 12 to 24 h
- 69 mg/dL (3.83 mmol/L) over 24 h (24-hour mean RTG)

The results are depicted in Figure 1 below:

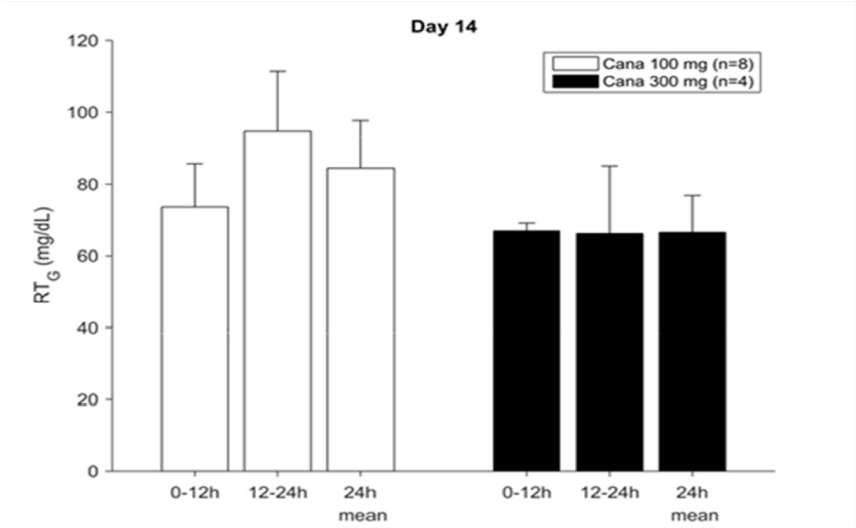


Figure 1: Mean (SD) RT_G values on day 14 after 100 mg (left) and 300 mg (right) of Canagliflozin

Urinary Glucose Excretion

Day -1:
15 of the 17 subjects had UGE_{0-24h} <0.18 g; 2 subjects in the 100 mg cohort had high plasma glucose concentrations and an UGE of 13 g and 29 g.

Day 14:
Mean ± SD for UGE_{0-24h}
100 mg canagliflozin: 74 ± 37 g; 300 mg canagliflozin: 69 ± 27 g

With both doses, UGE was higher in the 0-12-hour period than from 12 to 24 hours - see Figure 2 below.

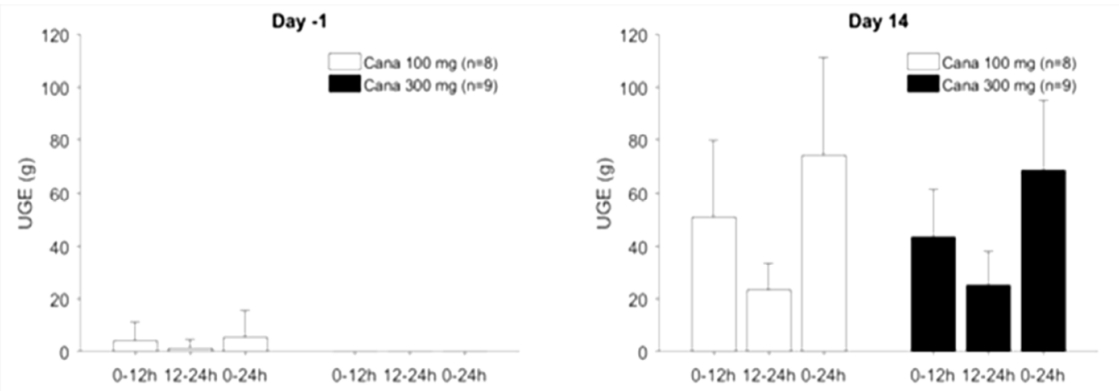


Figure 2: Mean (SD) UGE values on day 1 (left) and day 14 (right) for subjects receiving 100 mg or 300 mg of canagliflozin

Plasma Glucose
Both doses of canagliflozin reduced plasma glucose throughout the full 24 h period, leading to reduced mean plasma glucose (MPG_{0-4h} and MPG_{0-24h}) between Day -1 and 14 in each group (see Figure 3 below).

MPG_{0-4h} (mean ± SD):
- 100 mg: reduction from 164 ± 69 mg/dL (9.1 mmol/L) to 120 ± 32 mg/dL (6.7 mmol/L)
- 300 mg: reduction from 119 ± 18 mg/dL (6.6 mmol/L) to 104 ± 12 mg/dL (5.8 mmol/L)

$MPG_{0\text{-}24h}$ (mean ± SD):

- 100 mg: reduction from 147 ± 59 mg/dL (8.1 mmol/L) to 115 ± 23 mg/dL (6.4 mmol/L)
- 300 mg: reduction from 110 ± 11 mg/dL (6.1 mmol/L) to 96 ± 10 mg/dL (5.3 mmol/L)

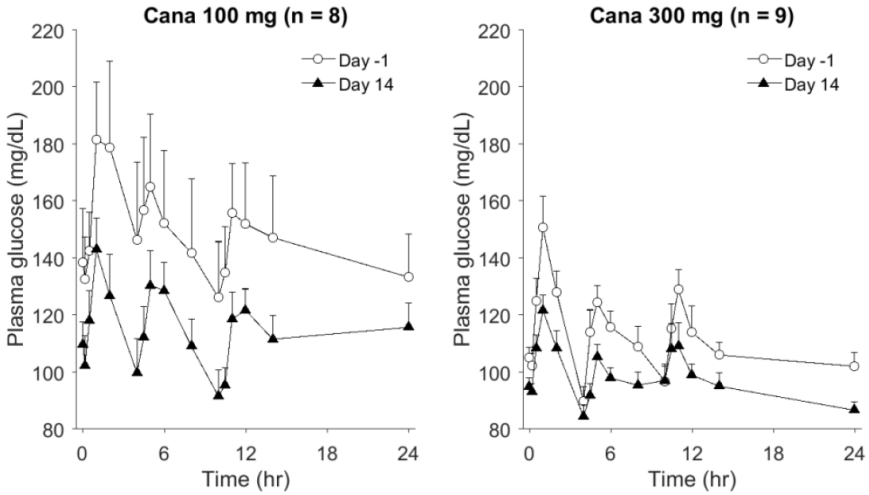


Figure 3: Mean (+SE) plasma glucose profiles on day-1 and day 14 after 100 mg (left) or 300 mg (right) of canagliflozin

The MAH has provided an additional analysis (Figure 4 below) to investigate the effects of canagliflozin in subjects with different baseline plasma glucose. Relatively small reductions in plasma glucose were seen in subjects with only modest hyperglycemia at baseline, but much greater reductions in subjects with higher baseline plasma glucose.

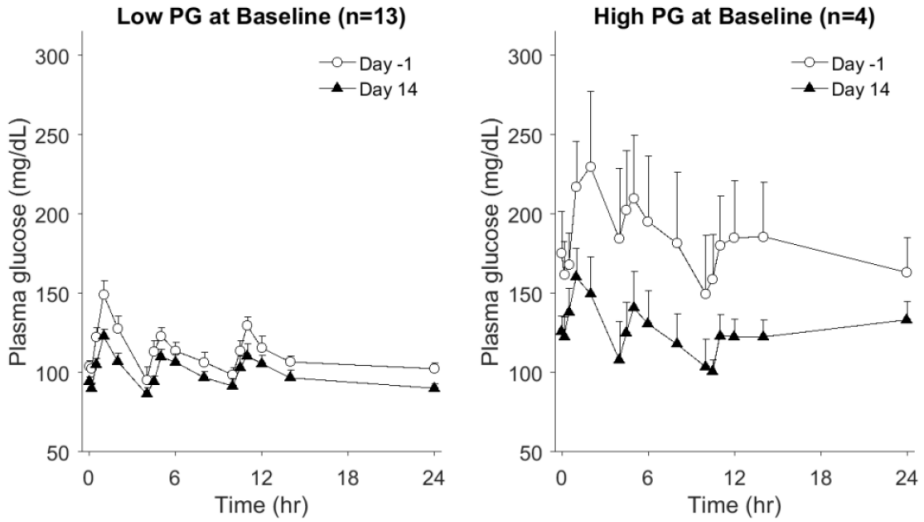


Figure 4: Mean (+SE) plasma glucose profiles on day-1 and day 14 for subjects with baseline fasting plasma glucose levels below (left) and above (right) 126 mg/dL. All four subjects in the higher baseline plasma glucose group were in the 100 mg cohort.

Fasting Plasma Glucose (FPG)

At both the 100 mg and the 300 mg dose, canagliflozin led to clear reductions in FPG (mean ± SD):

- 100 mg: reduction from 143 ± 58 mg/dL (Day -1; n=7) to 110 ± 24 mg/dL (Day 14; n=8)
- 300 mg: reduction from 107 ± 10 mg/dL (Day -1; n=7) to 100 ± 11 mg/dL (Day 14; n=8)

Mean incremental plasma glucose concentrations ($M\Delta PG_{0\text{-}2\ h}$ and $M\Delta PG_{0\text{-}4\ h}$)

Numerical reductions in incremental plasma glucose concentrations were observed in both dose groups, with no clear differential effect of the 300 mg dose compared to the 100 mg group on the postprandial excursions in these subjects – see **Table 1** below:

Table 1: Mean (SD) incremental plasma glucose values ($M\Delta PG_{0\text{-}2h}$ and $M\Delta PG_{0\text{-}4h}$) following breakfast, on Day-1 and Day 14 for subjects receiving 100 mg or 300 mg of canagliflozin

		N	Day -1, Mean (SD)	Day 14, Mean (SD)
Breakfast $M\Delta PG_{0\text{-}2h}$	100 mg	8	28 (20)	19 (12)
	300 mg	9	25 (14)	16 (11)
Breakfast $M\Delta PG_{0\text{-}4h}$	100 mg	8	28 (29)	15 (13)
	300 mg	9	17 (10)	12 (11)

Acceptability of canagliflozin tablets:

Administration of canagliflozin 100 mg and 300 mg tablets appeared to be acceptable with reference to perception of taste, smell, ability to swallow, or feelings after taking the dosage in paediatric T2DM subjects in the age range studied in this study.

2.3.4. PK/PD modelling

For population PK analysis of study DIA3018, please see section above.

2.3.5. Discussion on clinical pharmacology

PK exposures in paediatric T2DM subjects receiving 100 mg once-daily and 300 mg once-daily doses of canagliflozin were consistent with those of adult subjects.

In study DIA1055, the pharmacodynamic effects of canagliflozin (100 mg and 300 mg) on RT_G, UGE and plasma glucose concentration were determined as secondary endpoints. Both doses caused a similar reduction of RT_G during the first 12 hours, but only the 300 mg dose maintained the effect throughout the entire 24-hour period. This is consistent with the findings in adults, where 100 mg yielded near-maximal effects over the first 12 hours with a modest attenuation of the effect in the overnight period, while doses of ≥300 mg resulted in sustained near-maximal effects throughout the full 24 hours.

Urine glucose excretion (UGE) was almost undetectable at baseline in most of the subjects. The increase in UGE by canagliflozin was higher in the 0-12 h period, but less pronounced from 12 to 24 h, which might be due to higher plasma glucose concentrations during daytime as compared to the overnight period. Mean UGE in the pediatric population was modestly lower than in most of the Phase 1 studies in adult T2DM populations, which may be due to the relatively low plasma glucose concentrations seen in the subjects in this study. Of note, mean RT_G was suppressed to a range of ~65-95 mg/dL (3.6-5.3 mmol/L), which is similar to the effects seen in adults with T2DM. The 100 mg and the 300 mg dose did not differ relevantly in their effect on UGE, possibly because the plasma glucose concentrations at baseline were considerably lower in the 300 mg-group than in the 100 mg group. This might have precluded the detection of an additional effect of the 300 mg dose. This also pertains to $MPG_{0\text{-}4h}$ and $MPG_{0\text{-}24h}$, where this imbalance between the two dosing groups with regard to baseline glucose may also have confounded the comparison between the effect of the 100 mg and the 300 mg dose.

Many of the subjects started with plasma glucose concentrations below the values typically found in T2DM subjects, and the overall magnitude of the mean reductions in plasma glucose was only modest. When the effects of canagliflozin were analyzed in dependence on the levels of glucose control at baseline, consistent with the results from adult populations, relatively small reductions in plasma glucose were seen in subjects who had only modest hyperglycemia at baseline, but much greater reductions in plasma glucose were seen in subjects with higher baseline plasma glucose. Of note, all four subjects with higher baseline plasma glucose were in the 100 mg cohort, while all individuals treated with 300 mg were in the group with lower plasma glucose at baseline. Thus, again, this renders it rather difficult to conclude on any additional benefit provided by the 300 mg dose.

The blood glucose-lowering effects of canagliflozin were confirmed by the reduction in FPG as well as of post-prandial glucose excursions after 2 and 4 hours ($M\Delta PG_{0\text{-}2\ h}$ and $M\Delta PG_{0\text{-}4\ h}$). However, as already mentioned above, baseline plasma glucose was higher in the 100 mg than in the 300 mg cohort, and no relevant difference was seen between the 100 mg and the 300 mg dose.

A population pharmacokinetic analysis for study DIA 3018 was submitted. It is noted that the estimated relationship between body weight and clearance and body weight and volume from the adult popPK model was retained in the pediatric popPK model (estimated exponent of 0.583 for volume and clearance). As a sensitivity analysis, paediatric popPK model has been updated to include fixed allometric exponents (exponent of body weight on Vc/F of 1.0 and -0.25 on ke (corresponding to a body weight effect on CL/F with an exponent of 0.75; run131).

The figures indicate that exposure in lower weight paediatric patients exceeds exposure in adults with the approved doses. Thus, a warning was inserted in section 4.4 regarding potentially increased DKA risk in children receiving 300 mg of canagliflozin. Moreover, information was added to section 4.2 (subsection on "Paediatric population") indicating that caution is advised, when the 300 mg dose is administered, specifically in children with a body weight <50 kg and in section 5.2.

2.3.1. Conclusions on clinical pharmacology

PK exposures in paediatric T2DM subjects receiving 100 mg once-daily and 300 mg once-daily doses of canagliflozin appears to be consistent with those of adult subjects. Similarly as in adults, canagliflozin reduced RT_G, increased UGE, lowered plasma glucose concentrations and reduced the post-prandial excursions in plasma glucose in the pediatric population. A separate analysis according to high and low baseline plasma glucose showed that the plasma glucose-lowering effect of canagliflozin is increased in subjects with higher plasma glucose levels. Except for a more prolonged effect of 300 mg in comparison to 100 mg on RT_G, no relevant difference was seen between the two dosing groups in the other analyses. This may be due to the lower baseline plasma glucose in the 300 mg as compared to the 100 mg cohort, which may confound the detection of a potential additional effect of the 300 mg dose.

2.4. Clinical efficacy

2.5. Main study

Study JNJ-28431754DIA3018 (DIA3018)

Title of study

A Randomized, Multicenter, Double-Blind, Parallel-Group, Placebo-Controlled Study to Investigate the Efficacy and Safety of Canagliflozin in Children and Adolescents (≥10 to <18 years) with Type 2 Diabetes Mellitus

Methods

Design

DIA3018 was a randomized, double blind, placebo-controlled, 2-arm, parallel group, multi-center study that evaluated canagliflozin in male or female participants ≥10 to<18 years of age with type 2 diabetes mellitus (T2DM). The study lasted approximately 59 weeks and comprised the following parts:

Pre-treatment phase

- 1-week screening phase (screening visit at week -3)
- 2-week single-blind placebo run-in period (week -2 to baseline/day 1 – one placebo tablet matching canagliflozin 100 mg once daily)

Double-blind treatment phase

- 52-week double-blind placebo-controlled treatment phase (incl. a 26-week core double-blind treatment period and a 26-week double-blind extension treatment period)
- Re-randomization at week 13: Subjects who have a Week 12 HbA1c of ≥7.0% and eGFR ≥60 mL/min/1.73m^2 are re-randomized 1:1 to either remain on double-blind canagliflozin 100 mg (or matching placebo) or to up-titrate to double-blind canagliflozin 300 mg (or matching placebo). A double-dummy approach is used to maintain the subjects blinded to dose assignments. For details, please see section on "Blinding" below.

Post-treatment phase

- 30-day follow-up post-treatment (telephone follow-up contact or optional study visit, at the discretion of the investigator, 30 days after the last dose)

The design is depicted in the **Figure 1** below (taken from study protocol):

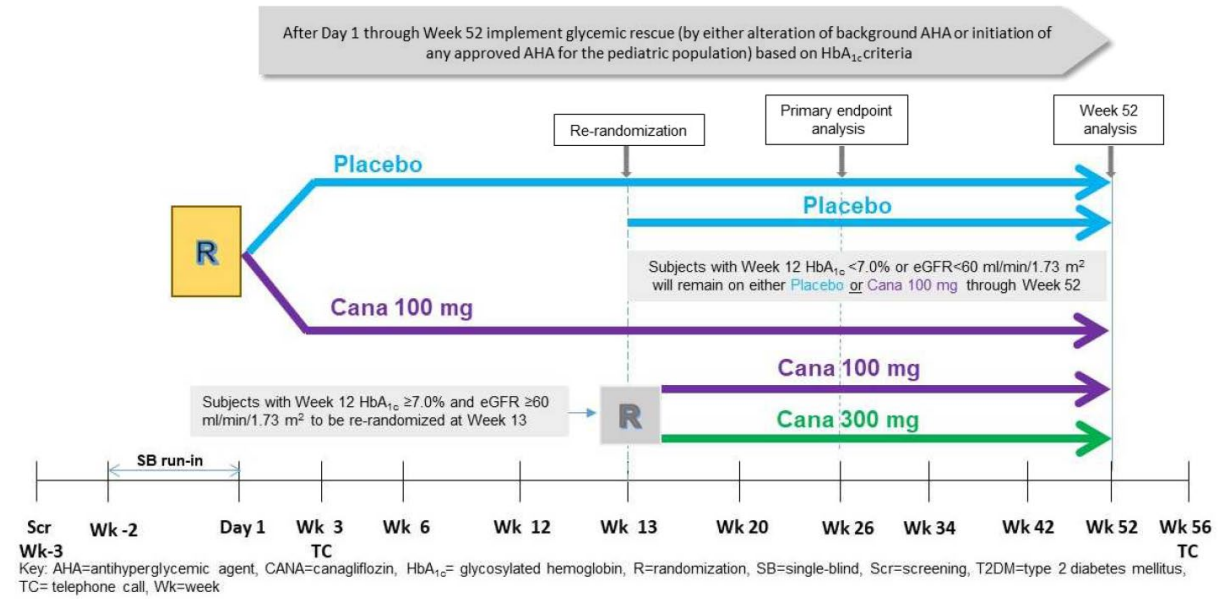


Figure 1: Design of Study JNJ28431754-DIA3018

Study participants

Main inclusion criteria

- Male or female ≥10 to<18 years of age at the time of screening
- Diagnosis of T2DM
- Random C-peptide at screening >0.6 ng/mL/>0.2 nmol/L
- Absence of pancreatic autoimmunity (GAD, and islet cell antigen 2 [IA2] antibody negative)
- Inadequate glycemic control (i.e., HbA1c of ≥6.5% to ≤11.0%) and
  - on diet and exercise only for at least 4 weeks prior to screening, or
  - on diet and exercise and a stable dose of metformin monotherapy ≥1,000 mg per day or MTD per day (defined by the investigator) for ≥8 weeks prior to screening, or
  - on diet and exercise and a stable insulin monotherapy regimen for at least 8 weeks prior to screening and ≤15% change in the total daily dose of insulin [averaged over 1 week to account for day to day variability]), or
  - on diet and exercise and a stable combination therapy with metformin and insulin for at least 8 weeks prior to screening. It is noted that metformin prolonged release was replaced by the immediate release form at the same/nearest appropriate daily dose).

Main exclusion criteria (shortened list)

Participants were not eligible for this study if they

- had a history of diabetic ketoacidosis [DKA], T1DM, pancreas or β-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy or MODY.
- were on any antihyperglycemic agents [AHA] other than metformin or insulin within 8 weeks of the first dose of study agent
- had severe hypoglycemia within 6 months prior to Day 1
- had renal and cardiovascular issues
- had gastrointestinal issues (known significant liver disease)

- had laboratory results (including persistent elevated ketone levels, eGFR<60mL/min/1.73m^2, alanine aminotransferase level >5.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN at screening)
- had other conditions (e.g., history of malignancy within 5 years before screening, major surgery within 12 weeks before screening or planned surgery during study participation, non-traumatic amputation within past 12 months etc.)
- were on certain medications (SGLT2 inhibitors, corticosteroids or immunosuppressive agents, anticonvulsants, any active investigational drug or medical device within 12 weeks before start of treatment)
- had general exclusions listed in the protocol.

Treatments

Study drug, dose, and mode of administration
Canagliflozin 100 mg and 300 mg tablets with matching placebo tablets for each dose strength were supplied for this study. The study agent was to be swallowed as a whole with liquid and not chewed, divided, dissolved, or crushed.

On Day 1, participants were randomly assigned in a 1:1 ratio to canagliflozin 100 mg or matching placebo. At Week 13, participants who had a Week 12 HbA1c of ≥7.0% and an eGFR ≥60 mL/min/1.73m^2 were re-randomized to either remain on double-blind canagliflozin 100 mg (or matching placebo) or up-titrated to double-blind canagliflozin 300 mg (or matching placebo).

Background therapy
Please see inclusion criteria and stratification criteria used at randomization.

Objectives

Primary
- To assess the effect of canagliflozin relative to placebo on glycated hemoglobin (HbA1c) after 26 weeks of treatment (change in HbA1c from baseline at Week 26)
- To assess the overall safety and tolerability of canagliflozin, based on:
  - Collection/monitoring of adverse events
  - Collection of potential hypoglycemic episodes (from diary provided to participants)
  - Ketone monitoring
  - Physical examinations
  - Body weight
  - Vital signs (blood pressure, pulse rate)
  - Safety laboratory tests (incl. chemistry, hematology, urinalysis)
  - Self-measured blood glucose (SMBG)
  - Bone turnover markers (serum osteocalcin and serum collagen type 1 CTx)
  - Markers of calcium and phosphate homeostasis (calcium, magnesium, phosphate, PTH 25-hydroxy Vitamin D, calcitonin, urinary excretion of calcium and phosphate)
  - Urinary ACR
  - Assessment of growth velocity and Tanner Staging

Major Secondary

- After 26 weeks of treatment, to assess the effect of canagliflozin relative to placebo for the subset of participants taking background metformin (with or without insulin) on HbA1c
- After 26 weeks of treatment, to assess the effect of canagliflozin relative to placebo on:
  - Fasting plasma glucose (FPG)
  - Proportion of participants with HbA1c <7.5%, <7.0% and <6.5%
  - Time to rescue therapy and proportion of participants receiving rescue therapy
  - Body weight
- After 52 weeks of treatment, to assess the effect of canagliflozin relative to placebo on:
  - HbA1c and FPG
  - Proportion of participants with HbA1c <7.5%, <7.0% and <6.5%
  - Time to rescue therapy and proportion of participants receiving rescue therapy
  - Body weight

Additional Secondary

- After 12 weeks of treatment to assess the effects of canagliflozin relative to placebo on HbA1c
- After 26 weeks of treatment, to assess the effect of canagliflozin 100 mg relative to placebo on HbA1c
- After 26 weeks of treatment, to assess the effect of canagliflozin 100 mg followed by a dose increase to 300 mg relative to placebo on HbA1c
- After 26 weeks and 52 weeks of treatment, to assess the effect of canagliflozin relative to placebo on:
  - Body mass index (BMI)
  - Fasting plasma lipids (i.e., LDL-C, HDL-C, total cholesterol, non-HDL-C, LDL-C to HDL-C ratio, non-HDL-C to LDL-C ratio, and triglycerides)
  - Systolic and diastolic blood pressure
  - Growth velocity and Tanner Staging
  - Markers of calcium and phosphate homeostasis, (calcium, magnesium, phosphate, parathyroid hormone [PTH], 25-hydroxy Vitamin D, calcitonin; urinary excretion of calcium and phosphate)
  - Bone turnover markers (serum osteocalcin and serum collagen type 1 carboxy-telopeptide [CTx])
  - Urinary albumin/creatinine ratio (ACR)

Note: Growth velocity and Tanner staging, markers of calcium and phosphate homeostasis as well as bone turnover markers and urinary albumin/creatinine ratio (ACR) are discussed in the Safety section of this AR.

Estimands

Clinical scientific question: What is the mean treatment difference at Week 26 on change from baseline in HbA1c from treatment assignment to either canagliflozin or placebo in children and adolescents with T2DM who have inadequate glycemic control, regardless of treatment discontinuation or initiation of rescue medication?

The primary efficacy estimand is described according to the following attributes:

- Population: children and adolescents (≥10 to <18 years) with T2DM who have an HbA1c ≥6.5% to ≤11.0%.
- Variable: change in HbA1c from baseline to Week 26.
- Treatment: canagliflozin (100 mg or 300 mg) vs placebo.

- Intercurrent events (ICEs) (events that preclude observation of the variable or affect its interpretation): treatment discontinuation or initiation of rescue medication; ICEs are addressed with the treatment policy strategy, targeting the effect of treatment assignment, regardless of the occurrence of ICE.
- Population-level summary: difference in means versus placebo.

A similar estimand deviating only in the population attribute was defined for the evaluation of the primary endpoint in the subset of participants with background metformin (with or without insulin).

Sample size

Number of patients

Number of Participants (planned and analyzed):

- Number planned: 146 (73 per arm);
- Number analysed: 171 (87 receiving placebo and 84 receiving canagliflozin)

Randomisation

Participants were randomly assigned in a 1:1 ratio to once daily administration of canagliflozin 100 mg, or placebo. Dynamic randomization (i.e., covariate-adjusted randomization) was used in an effort to maintain balance between treatment groups with respect to the following stratification factors:

- AHA background
  - diet and exercise only
  - metformin monotherapy (while on diet and exercise)
  - insulin monotherapy (while on diet and exercise)
  - combination of metformin and insulin (while on diet and exercise)
- Age group
  - ≥10 to <15 years old
  - ≥15 to <18 years old

In dynamic randomization, a new participant was sequentially assigned to a particular treatment group by taking into account the specific covariates and previous assignments of participants. This approach used the method of minimization by assessing the imbalance of sample size among the covariates listed above.

Participants who at Week 12 had an HbA1c of ≥7.0% and an eGFR ≥60 mL/min/1.73m^2 were re-randomized in a 1:1 ratio to either remain on double-blind canagliflozin 100 mg (or matching placebo) or to up-titrate to double-blind canagliflozin 300 mg (or matching placebo).

Blinding

A placebo control was used, and randomization was employed to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes are evenly balanced across treatment groups. Blinded treatment helped to reduce potential bias during data collection and evaluation of clinical endpoints. The 2-week single-blind placebo run-in period before randomization allows sufficient time for investigators to assess whether subjects demonstrate compliance with study procedures and have no difficulty with administration of the study drug.

Blinding remains ensured after re-randomization at week 13 (see section on Study design above) by using the following double-dummy approach:

- Subjects initially randomized to placebo and undergoing re-randomization at Week 13, will continue receiving 1 tablet of placebo matching canagliflozin 100 mg and will ADD 1 tablet of placebo matching canagliflozin 300 mg for the remainder of the double-blind treatment period.
- Subjects initially randomized to canagliflozin 100 mg and re-randomized to remain on canagliflozin 100 mg at Week 13, will continue receiving 1 tablet of canagliflozin 100 mg and will ADD 1 tablet of placebo matching canagliflozin 300 mg for the remainder of the double-blind treatment period.
- Subjects initially randomized to canagliflozin 100 mg and re-randomized to up-titrate to canagliflozin 300 mg at Week 13, will switch to 1 tablet of placebo matching canagliflozin 100 mg and will ADD 1 tablet of canagliflozin 300 mg for the remainder of the double-blind treatment period.

Subjects not undergoing re-randomization (i.e, HbA1c of <7.0% or eGFR <60 mL/min/1.73m^2) at Week 13 will continue to receive 1 tablet of canagliflozin 100 mg or 1 tablet of placebo matching canagliflozin 100 mg for the remainder of the double-blind treatment period.

Statistical methods

Analysis sets

Unless otherwise specified, all analyses will use the Full Analysis set (FAS). The FAS includes all subjects who are randomly assigned to a treatment group, have received at least one dose of study drug and have a baseline HbA1c measurement (according to their randomized assignment).

The 26-week/52-week per protocol (PP) analysis set consists of all FAS subjects who complete the 26-week/52-week double-blind treatment period and have no major protocol deviations.

The subjects who complete the 26-week/52-week double-blind treatment period are defined as those subjects who receive study drug and have non-missing HbA1c measurement at Week 26/52.

The safety analysis set consists of the subjects who are randomized and take at least 1 dose of study drug.

Primary analysis

The primary efficacy endpoint was the change in HbA1c from baseline at Week 26 in the overall study population. The primary analysis was based on the FAS dataset, including all HbA1c measurements collected from randomization to Week 26, including the measurements collected after treatment discontinuation or initiation of rescue medication. The primary analysis was to be based on a pattern mixture model (PMM), that multiply imputed missing data following ICEs based on comparable subjects within the same treatment arm that had observations following the ICE. Data missing of patients not having an ICE were multiply imputed in a similar way but based on the overall study population. A total of 1000 multiple imputations will be performed. Each of the multiply imputed datasets will be analyzed using analysis of covariance (ANCOVA) with terms for treatment, stratification factors, and baseline HbA1c and results will be combined with Rubin's rules.

Secondary analysis of the primary efficacy endpoint

The secondary analysis was based on a subset of participants on background metformin (with or without insulin) from the FAS dataset. Evaluation was otherwise identical to the primary analysis.

Sensitivity analyses

- Multiple imputation based on the "copy reference" approach
- A tipping point analysis: This analysis starts with a MAR MI model. Then each imputed value is made worse by a difference Delta in increments of 0.1 starting at zero until results reach statistical non-significance.
- The primary efficacy endpoint will be analysed using an MMRM
- Use of last observation carried forward (LOCF) method for missing week 26 data followed by an ANCOVA model as described for the primary analysis.
- A re-randomization test (Proschan 2011) (utilizing the MMRM) will be used to determine the p-value for the treatment comparison of the primary efficacy endpoint accounting for the same minimization algorithm as employed in the study.
- Analysis of the primary endpoint based on the 26-week PP analysis set using an MMRM.

Comparison by dose

The comparisons by dose (canagliflozin 100 mg without up-titration after Week 12 and canagliflozin 100 mg up-titrate to 300 mg after Week 12) to placebo will be tested for reference purpose by using the weights in the analyses described below.

- Canagliflozin 100 mg with no dose increase versus placebo:
  All subjects start with a weight of 1. After Week 12, subjects who are re-randomized to continue canagliflozin 100 mg will have a weight of 2. The subjects who are re-randomized to up-titrate to canagliflozin 300 mg will have a weight of 0.
- Canagliflozin 100 mg followed by a dose increase to 300 mg versus placebo:
  All subjects start with a weight of 1. After Week 12, subjects who are re-randomized to continue canagliflozin 100 mg will have a weight of 0. The subjects who are re-randomized to up-titrate to canagliflozin 300 mg will have a weight of 2.

Multiplicity

To strongly control the family-wise error rate at the 5% significance level, a sequential testing procedure was applied. The primary endpoint was first tested in all participants (i.e, full analysis set [FAS]) (primary analysis of the primary efficacy endpoint), and if the results were significant (2-sided alpha level of 0.05), a test for the subset of participants on a background of metformin (with or without insulin) followed (secondary analysis of the primary efficacy endpoint). All other endpoints/evaluations are exploratory and supportive in nature.

Analyses of secondary endpoints

Continuous endpoints will be analysed with an MMRM model. For the endpoints with post-baseline assessments taken only at Week 26 and Week 52, an analysis of covariance (ANCOVA) model similar to the primary efficacy endpoint will be used at Week 26.

The categorical secondary efficacy endpoint of maintaining HbA1c <7.0% (and HbA1c <6.5% and HbA1c <7.5%) will be analysed longitudinally using a generalized linear mixed model in the FAS population.

The time to event data (e.g., time to receiving rescue therapy or discontinuing due to need for rescue therapy) will be plotted using the KM method. The difference in proportion of subjects receiving rescue therapy or discontinuing due to need for rescue therapy between canagliflozin and placebo with 95% confidence intervals will be provided.

Results

Participant flow

Study Disposition

Overall study population

Table 1 below shows the disposition of subjects within the overall study population. The study randomized 171 participants (canagliflozin 100 mg/300 mg: n=84; placebo: n=87). Of the 84 participants on canagliflozin, 33 participants were re-randomized at Week 13 (100 mg canagliflozin: n=16; 300 mg canagliflozin: n=17).

The number of participants who completed the 26-week core treatment period was balanced between both treatment groups (placebo: n=77 [88.5%]; canagliflozin: n=72 [85.7%]). Comparable numbers of participants completed the 52-week treatment period (73 participants [83.9%] receiving placebo vs 69 participants [82.1%] receiving canagliflozin).

For the overall study, 24/87 participants (27.6%) receiving placebo were initiated on rescue medication prior to Week 26, compared to 5/84 participants (6.0%) receiving canagliflozin.

Table 1: Study Disposition (overall study), Study JNJ28431754-DIA3018; all Randomized Subjects

	Placebo	**Canagliflozin**			**Total**
		100 mg	300 mg	Combined	
Analysis set: All Randomized	87	67	17	84	171
Safety Analysis Set	87 (100.0%)	67 (100.0%)	17 (100.0%)	84 (100.0%)	171 (100.0%)
Full Analysis Set	87 (100.0%)	67 (100.0%)	17 (100.0%)	84 (100.0%)	171 (100.0%)
26-Week Core Treatment Period					
Subjects re-randomized at week 13	60 (69.0%)	16 (23.9%)	17 (100.0%)	33 (39.3%)	93 (54.4%)
Initiated rescue medication prior to week 26[a]	24 (27.6%)	3 (4.5%)	2 (11.8%)	5 (6.0%)	29 (17.0%)
Completed 26-week core treatment period[b]	77 (88.5%)	58 (86.6%)	14 (82.4%)	72 (85.7%)	149 (87.1%)
PP analysis set in 26-week core treatment period	50 (57.5%)	53 (79.1%)	10 (58.8%)	63 (75.0%)	113 (66.1%)
52-Week Treatment Period					
Initiated rescue medication prior to week 52	40 (46.0%)	7 (10.4%)	3 (17.6%)	10 (11.9%)	50 (29.2%)
Completed 52-week treatment period[b]	73 (83.9%)	55 (82.1%)	14 (82.4%)	69 (82.1%)	142 (83.0%)
PP analysis set in 52-week treatment period	31 (35.6%)	48 (71.6%)	11 (64.7%)	59 (70.2%)	90 (52.6%)
Completed 52-week trial period	75 (86.2%)	60 (89.6%)	14 (82.4%)	74 (88.1%)	149 (87.1%)
Discontinued treatment prior to week 52	14 (16.1%)	12 (17.9%)	3 (17.6%)	15 (17.9%)	29 (17.0%)
Discontinued trial prior to week 52	12 (13.8%)	7 (10.4%)	3 (17.6%)	10 (11.9%)	22 (12.9%)

a: A subject is considered to have initiated rescue medication prior to week 26 if the day of initiation of the medication is prior to the lower limit of Week 26 Analysis Visit window (Day 163 to 211).

b: It is possible that the number of subjects who completed 52-week treatment period is more than the number of subjects completed 26-week core treatment period due to the definition of the completed 26-week core treatment period. The subjects who complete the 26-week core double-blind treatment period are defined as those subjects who receive study drug and have non-missing HbA1c measurement at Week 26. In the case that the subjects discontinue from the treatment or have drug interruption at Week 26, the HbA1c measurement needs to be taken no later than the last dose of study drug at Week 26 plus 7 days and the subjects' last dose date needs to be on or after Day 163 based on the definition of analysis visit windows in the SAP.

Disposition of participants in the individual treatment groups:

Add-on to metformin monotherapy: n=79 [46.2%] (placebo: n=40; canagliflozin: n=39):
- 92.5% on placebo and 84.6% on canagliflozin completed the 26-week core treatment period.
- 82.5% on placebo and 79.5% on canagliflozin completed the 52-week treatment period.
- 20.0% on placebo and 5.1% on canagliflozin: rescue medication prior to week 26.

Add-on to insulin monotherapy: n=19 [11.1%] (placebo: n=10; canagliflozin: n=9):
- 90.0% on placebo and 88.9% on canagliflozin completed the 26-week core treatment period.
- 90.0% on placebo (all who completed the 26-week core treatment period) and 66.7% on canagliflozin completed the 52-week treatment period.
- 30.0% on placebo and 11.1% on canagliflozin: rescue medication prior to Week 26.

Add-on to metformin and insulin: n=50 [29.2%] (placebo: n=27; canagliflozin: n=23):
- 81.5% on placebo and 82.6% on canagliflozin completed the 26-week core treatment period.
- All participants receiving placebo and canagliflozin, who completed the 26-week treatment period, also completed the 52-week treatment period.
- 44.4% on placebo and 4.3% on canagliflozin: rescue medication prior to Week 26.

Add-on to diet and exercise only: n=23 [13.5%] (placebo: n=10; canagliflozin: n=13):
- 90.0% on placebo and 92.3% on canagliflozin completed the 26-week treatment period.
- 90.0% on placebo and 100.0% on canagliflozin completed the 52-week treatment period
- 10.0% on placebo and 7.7% on canagliflozin: rescue medication prior to Week 26.

Combination of add-on to metformin and add-on to metformin and insulin treatment groups
129 participants (75.4%) were on background metformin (with or without insulin), 67 of which received placebo and 62 received canagliflozin. Table 2 below shows the disposition of participants in the add-on to metformin treatment group (with or without insulin).

A total of 59/67 participants (88.1%) on placebo completed the 26-week core treatment period, compared to 52/62 participants (83.9%) on canagliflozin. The number of participants who completed the 52-week treatment period was comparable between the two groups (55/67 participants [82.1%] vs 50/62 participants [80.6%], respectively).

Twenty of 67 participants (29.9%) on placebo were initiated on rescue medication prior to Week 26, compared to 3/62 participants (4.8%) on canagliflozin.

Table 2: Study Disposition (Treatment group metformin with and w/o insulin), Study JNJ28431754-DIA3018; all Randomized Subjects

	Placebo	**Canagliflozin**			**Total**
		100 mg	300 mg	Combined	
Analysis set: All Randomized	67	50	12	62	129
Safety Analysis Set	67	50	12	62	129

	(100.0%)	(100.0%)	(100.0%)	(100.0%)	(100.0%)
Full Analysis Set	67 (100.0%)	50 (100.0%)	12 (100.0%)	62 (100.0%)	129 (100.0%)
26-Week Core Treatment Period					
Subjects re-randomized at week 13	45 (67.2%)	11 (22.0%)	12 (100.0%)	23 (37.1%)	68 (52.7%)
Initiated rescue medication prior to week 26[a]	20 (29.9%)	1 (2.0%)	2 (16.7%)	3 (4.8%)	23 (17.8%)
Completed 26-week core treatment	59 (88.1%)	43 (86.0%)	9 (75.0%)	52 (83.9%)	111 (86.0%)
PP analysis set in 26-week core treatment period	36 (53.7%)	40 (80.0%)	7 (58.3%)	47 (75.8%)	83 (64.3%)
52-Week Treatment Period					
Initiated rescue medication prior to week 52	33 (49.3%)	5 (10.0%)	2 (16.7%)	7 (11.3%)	40 (31.0%)
Completed 52-week treatment period[b]	55 (82.1%)	41 (82.0%)	9 (75.0%)	50 (80.6%)	105 (81.4%)
PP analysis set in 52-week treatment period	20 (29.9%)	35 (70.0%)	9 (75.0%)	44 (71.0%)	64 (49.6%)
Completed 52-week trial period	57 (85.1%)	45 (90.0%)	9 (75.0%)	54 (87.1%)	111 (86.0%)
Discontinued treatment prior to week 52	12 (17.9%)	9 (18.0%)	3 (25.0%)	12 (19.4%)	24 (18.6%)
Discontinued trial prior to week 52	10 (14.9%)	5 (10.0%)	3 (25.0%)	8 (12.9%)	18 (14.0%)

a: A subject is considered to have initiated rescue medication prior to week 26 if the day of initiation of the medication is prior to the lower limit of Week 26 Analysis Visit window (Day 163 to 211).

b: It is possible that the number of subjects who completed 52-week treatment period is more than the number of subjects completed 26-week core treatment period due to the definition of the completed 26-week core treatment period. The subjects who complete the 26-week core double-blind treatment period are defined as those subjects who receive study drug and have non-missing HbA1c measurement at Week 26. In the case that the subjects discontinue from the treatment or have drug interruption at Week 26, the HbA1c measurement needs to be taken no later than the last dose of study drug at Week 26 plus 7 days and the subjects' last dose date needs to be on or after Day 163 based on the definition of analysis visit windows in the SAP.

Treatment Disposition

All randomized subjects

Not re-randomized participants:

- Out of 51 participants, 43 (84.3%) completed treatment with canagliflozin 100 mg, while 8 (15.7%) discontinued treatment.
- Out of 27 participants on placebo, 19 (70.4%) completed treatment and 8 (29.6%) were discontinued.

Participants re-randomized at week 13:

- Out of 16 participants who received canagliflozin 100 mg, 12 (75.0%) completed treatment.
- Out of 17 participants who received canagliflozin 300 mg, 14 (82.4%) completed treatment.
- Out of 60 participants on placebo, 54 (90%) completed treatment and 6 (10.0%) were discontinued.

In both above-mentioned participant groups, there were no apparent differences in reasons for discontinuation between participants on canagliflozin and those on placebo. Table 3 below summarizes the reasons for discontinuation of treatment:

Table 3: Subject Disposition; All Randomized Subjects (Study JNJ28431754-DIA3018)

Analysis set: All Randomized	Not Re-Randomized		Re-Randomized at Week 13		
	Placebo	Cana 100 mg	Placebo	Cana 100 mg	Cana 300 mg
	27	51	60	16	17

Treated	27 (100.0%)	51 (100.0%)	60 (100.0%)	16 (100.0%)	17 (100.0%)
On treatment	0	0	0	0	0
Completed treatment	19 (70.4%)	43 (84.3%)	54 (90.0%)	12 (75.0%)	14 (82.4%)
Discontinued treatment	8 (29.6%)	8 (15.7%)	6 (10.0%)	4 (25.0%)	3 (17.6%)
Reasons for treatment discontinuation					
Adverse event	1 (3.7%)	1 (2.0%)	0	0	0
Lost to follow-up	3 (11.1%)	0	0	1 (6.3%)	0
Non-compliance with study drug	0	0	1 (1.7%)	0	1 (5.9%)
Physician decision	1 (3.7%)	0	0	0	0
Pregnancy	0	1 (2.0%)	0	0	0
Protocol violation	0	1 (2.0%)	0	0	0
Site terminated by sponsor	0	1 (2.0%)	0	0	0
Subject refused further study treatment	0	1 (2.0%)	0	1 (6.3%)	0
Use of non-approved AHA as rescue therapy	0	0	1 (1.7%)	0	0
Withdrawal by parent/guardian	2 (7.4%)	0	1 (1.7%)	0	0
Withdrawal by subject	1 (3.7%)	1 (2.0%)	2 (3.3%)	2 (12.5%)	2 (11.8%)
Other	0	2 (3.9%)	1 (1.7%)	0	0
Discontinued study[a]	8 (29.6%)	3 (5.9%)	4 (6.7%)	4 (25.0%)	3 (17.6%)
Reasons for study discontinuation					
Lost to follow-up	3 (11.1%)	0	1 (1.7%)	1 (6.3%)	0
Non-compliance with study drug	0	0	1 (1.7%)	0	1 (5.9%)
Physician decision	1 (3.7%)	0	0	0	0
Site terminated by sponsor	0	1 (2.0%)	0	0	0
Withdrawal by parent/guardian	2 (7.4%)	0	0	0	0
Withdrawal by subject	2 (7.4%)	2 (3.9%)	2 (3.3%)	3 (18.8%)	2 (11.8%)
Other	0	0	0	0	0
Completed Week 52 Visit	19 (70.4%)	49 (96.1%)	56 (93.3%)	12 (75.0%)	14 (82.4%)
Died (from any data source)	0	0	0	0	0

[a]Subjects who discontinued from study are included in the "discontinued from treatment" category. Only the reasons for study discontinuation with n≥1 instances are listed. Therefore, the following reasons for study discontinuation were omitted from the table: adverse event, refusal of further study treatment, use of non-approved AHA as rescue therapy, protocol violation and pregnancy.

Background metformin (with or without insulin) group

The number of subjects in the add-on metformin group who completed treatment is provided in Table 4 below:

Table 4: Subject Disposition –Subjects on Background Metformin (with or without Insulin); All Randomized Subjects (Study JNJ28431754-DIA3018)

Analysis set: All Randomized	**Not Re-Randomized**		**Re-Randomized at Week 13**		
	Placebo	Cana 100 mg	Placebo	Cana 100 mg	Cana 300 mg
	22	39	45	11	12
Treated	22 (100.0%)	39 (100.0%)	45 (100.0%)	11 (100.0%)	12 (100.0%)
On treatment	0	0	0	0	0
Completed treatment	14 (63.6%)	32 (82.1%)	41 (91.1%)	9 (81.8%)	9 (75.0%)
Discontinued treatment	8 (36.4%)	7 (17.9%)	4 (8.9%)	2 (18.2%)	3 (25.0%)
Reasons for treatment discontinuation					
Adverse event	1 (4.5%)	0	0	0	0
Lost to follow-up	3 (13.6%)	0	0	1 (9.1%)	0

Non-compliance with study drug	0	0	1 (2.2%)	0	1 (8.3%)
Physician decision	1 (4.5%)	0	0	0	0
Pregnancy	0	1 (2.6%)	0	0	0
Protocol violation	0	1 (2.6%)	0	0	0
Site terminated by sponsor	0	1 (2.6%)	0	0	0
Subject refused further study treatment	0	1 (2.6%)	0	1 (9.1%)	0
Use of non-approved AHA as rescue therapy	0	0	1 (2.2%)	0	0
Withdrawal by parent/guardian	2 (9.1%)	0	1 (2.2%)	0	0
Withdrawal by subject	1 (4.5%)	1 (2.6%)	0	0	2 (16.7%)
Other	0	2 (5.1%)	1 (2.2%)	0	0
Discontinued study[a]	8 (36.4%)	3 (7.7%)	2 (4.4%)	2 (18.2%)	3 (25.0%)
Reasons for study discontinuation					
Lost to follow-up	3 (13.6%)	0	1 (2.2%)	1 (9.1%)	0
Non-compliance with study drug	0	0	1 (2.2%)	0	1 (8.3%)
Physician decision	1 (4.5%)	0	0	0	0
Site terminated by sponsor	0	1 (2.6%)	0	0	0
Withdrawal by parent/guardian	2 (9.1%)	0	0	0	0
Withdrawal by subject	2 (9.1%)	2 (5.1%)	0	1 (9.1%)	2 (16.7%)
Other	0	0	0	0	0
Completed Week 52 Visit	14 (63.6%)	37 (94.9%)	43 (95.6%)	9 (81.8%)	9 (75.0%)
Died (from any data source)	0	0	0	0	0

[a]Subjects who discontinued from study are included in the "discontinued from treatment" category. Only the reasons for study discontinuation with n≥1 instances are listed. Therefore, the following reasons for study discontinuation were omitted from the table: adverse event, refusal of further study treatment, use of non-approved AHA as rescue therapy, protocol violation and pregnancy.

Participants who reached week 13

Table 5 shows that the number of participants who reached Week 13 were comparable for both treatment groups (83/87 [95.4%] vs 80/84 [95.2%]).

Sixty participants (69.0%) receiving placebo were re-randomized at Week 13 while 23 participants (26.4%) were not randomized. The most commonly reported reason for not-re-randomization was HbA1c <7% (n=20; 87.0%).

Of the 80 participants who received canagliflozin 100 mg and reached Week 13, 16 participants (19.0%) remained on canagliflozin 100 mg and 17 (20.2%) were re-randomized to canagliflozin 300 mg. Forty-seven participants (56.0%) were not re-randomized (most common reason in 43/47 [91.5%] participants: HbA1c <7.0%).

Table 5: Summary of Re-Randomization; All Randomized Subjects (Study JNJ28431754-DIA3018)_

	Prior to Re-Randomization	
	Placebo	Cana 100 mg
Analysis set: All Randomized	87	84
Not Reached Week 13[a]	4 (4.6%)	4 (4.8%)
Reached Week 13	83 (95.4%)	80 (95.2%)
Re-randomized at Week 13	60 (69.0%)	33 (39.3%)
Remain on placebo	60 (69.0%)	0
Remain on 100 mg cana	0	16 (19.0%)
Re-randomized to 300 mg cana	0	17 (20.2%)
Not re-randomized	23 (26.4%)	47 (56.0%)
Reason not re- randomized		
HbA1c value <7.0%	20 (87.0%)	43 (91.5%)

eGFR <60 mL/min/1.73 m2	0	0
Both HbA1c value <7.0% and eGFR <60 mL/min/1.73 m2	0	1 (2.1%)
Other	2 (8.7%)	1 (2.1%)
<Missing>	1 (4.3%)	2 (4.3%)

[a]Subjects who reached Week 13 means the subjects had at least one visit after Week 12 and did not withdraw study drug before Week 12.

Conduct of the study

Changes in conduct – study amendments

Global amendments

The study period was from 28 Jul 2017 to 20 Sept 2023. There were 4 amendments to the original protocol, the first and second of which were adopted before any study-related procedures had begun:

(1) From 27 March 2017 (substantial): Modification of study design to allow the assessment of canagliflozin when used with and without titration which is more reflective of how canagliflozin may be used in this pediatric population, and to add ketone monitoring procedures, and some minor editorial changes

(2) From 25 August 2017 (substantial): Changes in the statistical analysis and minor editorial changes

(3) From 25 June 2018 (substantial): Independently powered subset of participants on a background of diet and exercise only, where superiority of canagliflozin *vs* placebo can be assessed

(4) From 14 August 2020: Due to slower than expected recruitment and a high rate of screen failures, the power calculation was modified resulting in a reduced sample size. In addition, minor modifications to the inclusion and exclusion criteria have been made.

Local amendments

- 2/EU-1 (25 August 2017): To amend the study protocol in EU countries to reflect the recommendation from the EMA PDCO on ketone monitoring, and inclusion of all changes associated with global Amendment 2.
- 2/ISR-1 (14 June 2018): reflects recommendations from Israel Ministry of Health on hypo- and hyperglycemia.
- 2/IND-1 (08 February 2018): upon request from CDSCO/India to add a BMI inclusion criterion.
- 3/IND-1 (10 October 2018), 3/ISR-1 (10 October 2018): same changes as in Amendment 3.
- 3/EU-1 (10 October 2018): reflected consistencies across all protocol amendments (ie, local vs. global).
- 4/EU-1 (10 November 2020), 4/IND-1 (27 August 2020): same changes as in Amendment 4, with power calculation modified with the EMA's approval in the European version.

Protocol deviations

All major protocol deviations (pd) for the FAS are summarized in the below. A total of 53 participants (31%) reported major deviations (placebo: n=30 [34.5%]; canagliflozin: n=23 [27%]). The most common protocol deviations were "Other" (n=37 [21.6%]) and participants who entered but did not satisfy criteria (n=21 [12.3%]). The remaining protocol deviations occurred in <3% of participants. See Table 6 below.

Table 6: Summary of subjects with major protocol deviations through Week 26; FAS (Study JNJ28431754-DIA3018)

Analysis set: Full	Placebo	Canagliflozin			Total
		100 mg	300 mg	Combined	
	87	67	17	84	171
Subjects with major protocol deviations	30 (34.5%)	19 (28.4%)	4 (23.5%)	23 (27.4%)	53 (31.0%)
Other[a]	20 (23.0%)	15 (22.4%)	2 (11.8%)	17 (20.2%)	37 (21.6%)
Entered but did not satisfy criteria	11 (12.6%)	8 (11.9%)	2 (11.8%)	10 (11.9%)	21 (12.3%)
Received a disallowed concomitant treatment	5 (5.7%)	0	0	0	5 (2.9%)
Developed withdrawal criteria but not withdrawn	1 (1.1%)	0	0	0	1 (0.6%)
Minor pd - investigational product	0	1 (1.5%)	0	1 (1.2%)	1 (0.6%)
Minor pd - study procedures	1 (1.1%)	0	0	0	1 (0.6%)
[a] "other": =protocol deviations like administrative issues, intermittent missed doses, and diary issues. Note: Subjects may appear in more than one category.					

One participant receiving canagliflozin continued on a low dose of metformin XR throughout the duration of the study.

Treatment compliance

Study agent compliance ≥75% at Week 26 was comparable across treatment groups with 76/87 participants [87.4%] receiving placebo and 75/84 participants [89.3%] receiving canagliflozin – see Table 7 below.

Table 7: Summary of study agent compliance through week 26; FAS (Study JNJ28431754-DIA3018)

Analysis set: Full	Placebo	Canagliflozin		
		100 mg	300 mg	Combined
	87	67	17	84
Compliance category <75%	3 (3.4%)	4 (6.0%)	1 (5.9%)	5 (6.0%)
≥75%	76 (87.4%)	60 (89.6%)	15 (88.2%)	75 (89.3%)
Missing	8 (9.2%)	3 (4.5%)	1 (5.9%)	4 (4.8%)

Treatment compliance through Week 52 was similarly comparable between the groups (data not shown here).

Baseline data

Demographics and baseline disease characteristics

Overall, demographic and baseline characteristics were comparable across the treatment groups. More than two thirds of the patients were female in the placebo and total canagliflozin group. The proportion of female participants was 67.9% (n=55) in the age group ≥10 to <15 years and 68.9% (n=62) in those aged ≥15 to <18 years.

Mean baseline HbA1c was markedly lower (by 0.5 %) in the canagliflozin arm as compared to placebo-treated patients (7.8 vs. 8.3, respectively), which went along with a slightly shorter mean duration of disease, a higher baseline eGFR and a higher fasting serum triglyceride value in the canagliflozin group in comparison to the placebo arm.

None of the subjects had any microvascular complication (i.e., medical history of diabetic neuropathy, diabetic retinopathy, or diabetic nephropathy) at baseline. In none of the subjects, severe hypoglycaemia was reported.

Table 8 summarizes baseline demographics and clinical characteristics.

Table 8: Summary of demographics and baseline characteristics; FAS (Study JNJ-28431754DIA3018)

Analysis set: Full	Placebo	Canagliflozin			Total
		100 mg	300 mg	Combined	
	87	67	17	84	171
Age (years)					
N	87	67	17	84	171
Mean (SD)	14.4 (2.04)	14.2 (2.00)	14.5 (2.07)	14.3 (2.00)	14.3 (2.02)
Median	15.0	15.0	15.0	15.0	15.0
Range	(10; 17)	(10; 17)	(10; 17)	(10; 17)	(10; 17)
10 to <15	42 (48.3%)	33 (49.3%)	6 (35.3%)	39 (46.4%)	81 (47.4%)
15 to <18	45 (51.7%)	34 (50.7%)	11 (64.7%)	45 (53.6%)	90 (52.6%)
Sex					
N	87	67	17	84	171
Female	60 (69.0%)	49 (73.1%)	8 (47.1%)	57 (67.9%)	117 (68.4%)
Male	27 (31.0%)	18 (26.9%)	9 (52.9%)	27 (32.1%)	54 (31.6%)
Race					
N	87	67	17	84	171
American Indian or Alaska Native	4 (4.6%)	1 (1.5%)	3 (17.6%)	4 (4.8%)	8 (4.7%)
Asian	38 (43.7%)	29 (43.3%)	5 (29.4%)	34 (40.5%)	72 (42.1%)
Black or African American	13 (14.9%)	4 (6.0%)	2 (11.8%)	6 (7.1%)	19 (11.1%)
White	31 (35.6%)	33 (49.3%)	7 (41.2%)	40 (47.6%)	71 (41.5%)
Multiple	1 (1.1%)	0	0	0	1 (0.6%)
Ethnicity					
N	87	67	17	84	171
Hispanic or Latino	29 (33.3%)	23 (34.3%)	10 (58.8%)	33 (39.3%)	62 (36.3%)
Not Hispanic or Latino	57 (65.5%)	44 (65.7%)	7 (41.2%)	51 (60.7%)	108 (63.2%)
Not reported	1 (1.1%)	0	0	0	1 (0.6%)
Weight					
N	87	67	17	84	171
Mean (SD)	79.9 (25.31)	81.8 (24.67)	81.0 (21.86)	81.6 (24.01)	80.8 (24.62)
Median	75.2	75.1	79.5	75.9	75.2
Range	(41; 162)	(47; 161)	(45; 134)	(45; 161)	(41; 162)
Height					
N	87	67	17	84	171
Mean (SD)	160.9 (9.88)	160.7 (10.07)	163.3 (10.04)	161.2 (10.06)	161.0 (9.94)
Median	161.0	158.4	163.0	159.5	161.0
Range	(141; 186)	(144; 190)	(143; 186)	(143; 190)	(141; 190)
Body Mass Index, kg/m²					
N	87	67	17	84	171
Mean (SD)	30.5 (7.66)	31.3 (7.38)	30.1 (6.61)	31.1 (7.21)	30.8 (7.43)
Median	29.2	30.4	28.2	29.9	29.8
Range	(18; 57)	(19; 50)	(21; 42)	(19; 50)	(18; 57)
Underweight <18.5	1 (1.1%)	0	0	0	1 (0.6%)
Normal 18.5 to <25	20 (23.0%)	17 (25.4%)	4 (23.5%)	21 (25.0%)	41 (24.0%)
Overweight 25 to <30	28 (32.2%)	15 (22.4%)	7 (41.2%)	22 (26.2%)	50 (29.2%)
Obese ≥30	38 (43.7%)	35 (52.2%)	6 (35.3%)	41 (48.8%)	79 (46.2%)

Baseline HbA1c (%)					
N	87	67	17	84	171
Mean (SD)	8.3 (1.35)	7.5 (1.20)	8.8 (1.30)	7.8 (1.31)	8.0 (1.35)
Median	8.0	7.3	8.7	7.5	7.8
Range	(6; 11)	(6; 11)	(7; 11)	(6; 11)	(6; 11)
<7%	16 (18.4%)	25 (37.3%)	1 (5.9%)	26 (31.0%)	42 (24.6%)
7 to <8%	25 (28.7%)	21 (31.3%)	4 (23.5%)	25 (29.8%)	50 (29.2%)
8 to <9%	16 (18.4%)	10 (14.9%)	5 (29.4%)	15 (17.9%)	31 (18.1%)
9 to ≤10%	19 (21.8%)	9 (13.4%)	4 (23.5%)	13 (15.5%)	32 (18.7%)
>10%	11 (12.6%)	2 (3.0%)	3 (17.6%)	5 (6.0%)	16 (9.4%)
Baseline FPG (mmol/L)					
N	85	64	17	81	166
Mean (SD)	8.7 (3.67)	8.1 (3.08)	10.4 (2.97)	8.6 (3.18)	8.6 (3.43)
Median	7.8	7.0	10.2	7.5	7.7
Range	(3; 25)	(3; 18)	(6; 17)	(3; 18)	(3; 25)
Duration of Diabetes (years)					
N	87	67	17	84	171
Mean (SD)	2.3 (1.77)	1.8 (2.20)	1.6 (1.29)	1.7 (2.04)	2.0 (1.92)
Median	1.9	1.1	1.1	1.1	1.5
Range	(0; 10)	(0; 14)	(0; 4)	(0; 14)	(0; 14)
Baseline eGFR (ml/min/1.73 m²)					
N	87	67	17	84	171
Mean (SD)	151.1 (29.71)	163.2 (34.52)	166.1 (30.85)	163.8 (33.65)	157.3 (32.25)
Median	146.0	165.0	169.0	166.0	155.0
Range	(66; 284)	(84; 277)	(112; 235)	(84; 277)	(66; 284)
Baseline Systolic Blood Pressure (mmHg)					
N	87	67	17	84	171
Mean (SD)	114.9 (12.34)	116.4 (13.41)	112.3 (12.10)	115.5 (13.19)	115.2 (12.73)
Median	114.3	115.0	113.0	114.5	114.3
Range	(80; 149)	(93; 152)	(91; 139)	(91; 152)	(80; 152)
Baseline Diastolic Blood Pressure (mmHg)					
N	87	67	17	84	171
Mean (SD)	72.0 (8.07)	73.9 (8.47)	69.5 (8.58)	73.0 (8.63)	72.5 (8.34)
Median	72.3	73.7	69.0	72.7	72.7
Range	(51; 94)	(55; 93)	(55; 96)	(55; 96)	(51; 96)
Baseline Serum Triglycerides (mmol/L) – Fasting					
N	82	61	17	78	160
Mean (SD)	1.6 (1.19)	1.8 (1.06)	3.1 (3.90)	2.1 (2.08)	1.8 (1.70)
Median	1.3	1.6	2.0	1.6	1.4
Range	(0; 9)	(0; 6)	(1; 18)	(0; 18)	(0; 18)
Baseline Serum HDL Cholesterol (mmol/L) – Fasting					
N	78	61	17	78	156
Mean (SD)	1.1 (0.24)	1.1 (0.25)	0.9 (0.17)	1.0 (0.25)	1.1 (0.25)
Median	1.1	1.1	0.9	1.0	1.1
Range	(1; 2)	(0; 2)	(1; 1)	(0; 2)	(0; 2)
Baseline Serum LDL Cholesterol (mmol/L) – Fasting					
N	77	61	17	78	155
Mean (SD)	2.7 (0.82)	2.5 (0.86)	2.4 (0.86)	2.5 (0.86)	2.6 (0.85)
Median	2.6	2.5	2.2	2.5	2.5
Range	(1; 5)	(1; 5)	(1; 5)	(1; 5)	(1; 5)
Baseline Serum Cholesterol (mmol/L) – Fasting					
N	82	61	17	78	160
Mean (SD)	4.5 (0.91)	4.4 (1.08)	4.6 (1.41)	4.5 (1.15)	4.5 (1.03)
Median	4.4	4.4	4.3	4.3	4.4
Range	(3; 7)	(2; 7)	(3; 9)	(2; 9)	(2; 9)
Baseline Serum Non-HDL Cholesterol (mmol/L) - Fasting					
N	77	61	17	78	155
Mean (SD)	3.4 (0.88)	3.4 (1.07)	3.7 (1.40)	3.4 (1.15)	3.4 (1.02)
Median	3.3	3.3	3.4	3.3	3.3
Range	(2; 6)	(1; 6)	(2; 8)	(1; 8)	(1; 8)
Baseline Serum LDL Cholesterol/HDL Cholesterol (mol/mol) - Fasting					
N	77	61	17	78	155

Mean (SD)	2.5 (0.89)	2.5 (1.03)	2.7 (0.65)	2.5 (0.96)	2.5 (0.92)
Median	2.2	2.4	3.0	2.6	2.3
Range	(1; 5)	(1; 5)	(2; 4)	(1; 5)	(1; 5)
Baseline Serum Non-HDL Cholesterol/LDL Cholesterol (mol/mol) - Fasting					
N	76	60	15	75	151
Mean (SD)	1.2 (0.30)	1.2 (0.29)	1.3 (0.39)	1.2 (0.31)	1.2 (0.30)
Median	1.1	1.2	1.1	1.2	1.1
Range	(1; 2)	(1; 2)	(1; 2)	(1; 2)	(1; 2)
Baseline Calcium (mmol/L)					
N	87	67	17	84	171
Mean (SD)	2.5 (0.10)	2.5 (0.09)	2.4 (0.12)	2.4 (0.10)	2.4 (0.10)
Median	2.5	2.5	2.4	2.5	2.5
Range	(2; 3)	(2; 3)	(2; 3)	(2; 3)	(2; 3)
Baseline Magnesium (mmol/L)					
N	87	67	17	84	171
Mean (SD)	0.8 (0.07)	0.8 (0.08)	0.8 (0.06)	0.8 (0.07)	0.8 (0.07)
Median	0.8	0.8	0.8	0.8	0.8
Range	(1; 1)	(1; 1)	(1; 1)	(1; 1)	(1; 1)
Baseline Phosphate (mmol/L)					
N	87	67	17	84	171
Mean (SD)	1.4 (0.21)	1.4 (0.21)	1.4 (0.23)	1.4 (0.22)	1.4 (0.21)
Median	1.4	1.4	1.4	1.4	1.4
Range	(1; 2)	(1; 2)	(1; 2)	(1; 2)	(1; 2)
Baseline Parathyroid Hormone, Intact (pmol/L)					
N	82	65	17	82	164
Mean (SD)	4.6 (2.19)	5.2 (4.16)	3.7 (1.27)	4.9 (3.79)	4.7 (3.09)
Median	4.2	4.4	3.8	4.0	4.1
Range	(1; 12)	(1; 33)	(2; 6)	(1; 33)	(1; 33)
Baseline 25-Hydroxy Vitamin D (nmol/L)					
N	87	65	17	82	169
Mean (SD)	47.4 (23.58)	48.6 (18.24)	45.9 (12.52)	48.1 (17.17)	47.8 (20.66)
Median	45.0	45.0	51.0	45.5	45.0
Range	(13; 189)	(12; 106)	(23; 61)	(12; 106)	(12; 189)
Baseline Calcitonin (pmol/L)					
N	82	64	17	81	163
Mean (SD)	1.8 (10.69)	0.6 (0.07)	0.6 (0.00)	0.6 (0.06)	1.2 (7.58)
Median	0.6	0.6	0.6	0.6	0.6
Range	(1; 97)	(1; 1)	(1; 1)	(1; 1)	(1; 97)
Baseline Urine Calcium (mmol/L)					
N	83	63	17	80	163
Mean (SD)	2.4 (2.67)	2.3 (2.16)	3.6 (2.89)	2.6 (2.37)	2.5 (2.52)
Median	1.7	1.7	3.0	1.9	1.8
Range	(0; 16)	(0; 12)	(0; 12)	(0; 12)	(0; 16)
Baseline Urine Phosphate (mmol/L)					
N	81	56	17	73	154
Mean (SD)	19.0 (14.40)	21.4 (14.28)	24.5 (18.40)	22.1 (15.26)	20.5 (14.84)
Median	16.7	23.3	19.0	22.5	18.5
Range	(1; 77)	(1; 61)	(1; 60)	(1; 61)	(1; 77)
Baseline Osteocalcin (ug/L)					
N	86	65	16	81	167
Mean (SD)	41.6 (32.18)	42.9 (31.83)	32.2 (18.46)	40.8 (29.88)	41.2 (31.00)
Median	30.1	32.8	29.4	32.3	30.7
Range	(9; 160)	(8; 195)	(9; 72)	(8; 195)	(8; 195)
Baseline Serum Collagen Type 1 Beta Carboxy Telopeptide (ug/L)					
N	69	56	14	70	139
Mean (SD)	7.8 (4.10)	8.9 (4.40)	9.5 (9.39)	9.0 (5.67)	8.4 (4.97)
Median	6.5	8.7	7.2	8.2	7.6
Range	(2; 20)	(2; 24)	(3; 41)	(2; 41)	(2; 41)
Baseline Serum Type I Collagen C-Telopeptides MMP (ug/L)					
N	13	8	2	10	23
Mean (SD)	6.8 (3.87)	6.0 (4.00)	4.1 (0.49)	5.6 (3.63)	6.3 (3.73)
Median	6.3	5.3	4.1	4.4	5.8
Range	(1; 14)	(1; 13)	(4; 4)	(1; 13)	(1; 14)
Baseline Urine Albumin/Creatinine (mg/g)					
N	78	58	15	73	151

Mean (SD)	65.0 (278.31)	35.8 (101.29)	68.2 (191.34)	42.4 (124.16)	54.1 (217.46)
Median	8.8	9.1	15.0	10.0	9.0
Range	(2; 2103)	(3; 605)	(4; 757)	(3; 757)	(2; 2103)
<30 mg/g	66 (84.6%)	50 (86.2%)	11 (73.3%)	61 (83.6%)	127 (84.1%)
30 to 300 mg/g	10 (12.8%)	5 (8.6%)	3 (20.0%)	8 (11.0%)	18 (11.9%)
>300 mg/g	2 (2.6%)	3 (5.2%)	1 (6.7%)	4 (5.5%)	6 (4.0%)

Note: N's for each parameter reflect non-missing values.

As shown in Table 9 below, most of the patients (>70%) in study DIA3018 come from a non-European and non-US-American background.

Table 9: Number of Subjects by Country; Full Analysis Set (Study JNJ28431754-DIA3018)

Analysis set: Full Analysis	**Placebo**	**Canagliflozin**			**Total**
		100 mg	300 mg	Combined	
	87	67	17	84	171
Brazil	8 (9.2%)	3 (4.5%)	1 (5.9%)	4 (4.8%)	12 (7.0%)
China	3 (3.4%)	1 (1.5%)	0	1 (1.2%)	4 (2.3%)
India	3 (3.4%)	5 (7.5%)	1 (5.9%)	6 (7.1%)	9 (5.3%)
Malaysia	18 (20.7%)	10 (14.9%)	2 (11.8%)	12 (14.3%)	30 (17.5%)
Mexico	16 (18.4%)	14 (20.9%)	6 (35.3%)	20 (23.8%)	36 (21.1%)
Philippines	11 (12.6%)	10 (14.9%)	2 (11.8%)	12 (14.3%)	23 (13.5%)
Poland	3 (3.4%)	3 (4.5%)	0	3 (3.6%)	6 (3.5%)
Russian Federation	3 (3.4%)	7 (10.4%)	0	7 (8.3%)	10 (5.8%)
United States	22 (25.3%)	14 (20.9%)	5 (29.4%)	19 (22.6%)	41 (24.0%)

Prior and Concomitant Therapies

Prior Therapies

156 out of 171 participants (91.2%) received one or more prior medications, with comparable number of participants across treatment groups. Antihyperglycaemic therapies were used by 148/171 participants (86.5%), of which, biguanides were used by 129 participants (75.4%). Other drugs used in diabetes included fast-acting (76 participants [44.4%]), long-acting (49 participants [28.7%]), intermediate- or long-acting combined with fast-acting (11 participants [6.4%]), and intermediate-acting (10 participants [5.8%]) insulins and analogues for injection. Other diabetes agents were used by <5% of participants.

Concomitant Therapies

One or more concomitant medications were administered to 171 participants (97.1%), with comparable number of affected participants across treatment groups.

*Antihyperglycemic drugs (*n=153 [89.5%])

- Metformin (n=132 [77.2%])
- Insulins and fast-acting insulin analogues (n=78 [45.6%])
- Long-acting insulins (n=56 [32.7%])
- Intermediate- or long-acting combined with fast-acting insulins (n=13 [7.6%])
- Intermediate-acting insulins (n=12 [7.0%])
- Other diabetes agents: <5% of participants.

Other medications:

- Vitamins (n=50 [29.2%]),
- Analgesics (n=39 [22.8%])
- Antibacterials for systemic use (n=38 [22.2%]),

- Anti-inflammatory and antirheumatic products (n=28 [16.4%])
- Antihistamines for systemic use (n=28 [16.4%])
- Vaccines (n=19 [11.1%])
- Psychoanaleptics (n=16 [9.4%])
- Lipid-modifying agents (n=17 [9.9%])
- Drugs for acid-related disorders (n=15 [8.8%])
- Nasal preparation (n=11 [6.4%])
- Agents acting on the renin-angiotensin system (n=13 [7.6%])
- Cough and cold preparation (n=14 [8.2%])
- Drugs for obstructive airway diseases (n=13 [7.6%])
- Sex hormones and modulators of the genital system (n=10 [5.8%])
- Drugs for functional gastrointestinal disorders (n=10 [5.8%])
- Other medications were received by <5% of study participants.

Numbers analysed

The sizes of the analysis sets and the proportions of placebo-and canagliflozin-treated patients were taken from Table 1 above (=Table 2 in the clinical study report)

- **Full analysis set (FAS)**
  All participants who were randomly assigned to a treatment group, who received at least one dose of study agent and had a baseline HbA1c measurement.
  - 171 participants randomized
  - Canagliflozin 100 mg or 300 mg: 84/171 (of the 84 participants on canagliflozin, 33 participants were re-randomized at Week 13 (100 mg canagliflozin: n=16; 300 mg canagliflozin: n=17).
  - placebo: 87/171

- **26-week per protocol (PP) analysis set**
  All FAS participants who completed the 26-week double-blind treatment period (i.e., who received study agent and had non-missing HbA1c measurement at Week 26) and had no major protocol deviations that could affect the interpretation of the primary efficacy endpoint (e.g, initiation of glycaemic rescue therapy) within the 26-week core double-blind treatment period.
  - 137 participants belong to the 26-week PP analysis set
  - Canagliflozin 100 mg or 300 mg: 67/137
  - placebo: 70/137

- **52-week PP analysis set**
  All FAS participants who completed the 52-week double-blind treatment period and had no major protocol deviations that could affect the interpretation of the efficacy endpoint (e.g., initiation of glycemic rescue therapy) within the 52 weeks of treatment.
  - 129 participants belong to the 52-week PP analysis set
  - Canagliflozin: 65/129
  - placebo: 64/129

For further information, see above, section on Participant flow/study disposition.

Outcomes and estimation

Primary efficacy endpoint

Canagliflozin caused a statistically significant improvement with respect to change from baseline in HbA1c at Week 26 compared to placebo (LS means difference = -0.76% [SE: 0.249; 95% CI: -1.25, -0.27; p=0.002]) - see Table 10 below.

Table 10: Primary analysis of the primary efficacy endpoint (primary estimand, treatment policy strategy): change from baseline in HbA1c (%) at Week 26 using pattern mixture model – all subjects; FAS (Study JNJ-28431754DIA3018)

	Placebo (N=87)	Cana (N=84)
Observed Value at Baseline		
N	87	84
Mean (SD)	8.3 (1.35)	7.8 (1.31)
Observed Value at Week 26		
N	80	77
Mean (SD)	8.6 (2.01)	7.3 (1.78)
Change from Baseline at Week 26		
N	80	77
Mean (SD)	0.3 (1.56)	-0.4 (1.44)
Subjects with intercurrent events	30	10
Subjects discontinued treatment prior to Week 26	9	5
Subjects received rescue medication prior to Week 26	24	5
Summary of results at Week 26 applying Rubin's rules to combine the ANCOVA results across the imputed datasets based on pattern mixture model[a]		
LS Mean (SE)	0.39 (0.191)	-0.37 (0.194)
Difference [Cana-Placebo] in LS Means (SE)		-0.76 (0.249)
95% CI		(-1.25, -0.27)
p-value		0.002

[a]: Imputed datasets are analyzed using analysis of covariance (ANCOVA) with terms for treatment, stratification factors (AHA background and age group), and baseline HbA1c.
A subject is considered to have received rescue medication prior to Week 26 if the day of initiation of the medication is prior to the lower limit of Week 26 Analysis Visit window (Day 163 to 211). Same rule applies for subjects who discontinued treatment prior to Week 26.

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Secondary analysis of primary efficacy endpoint on background metformin

Canagliflozin caused a statistically significant improvement in change from baseline in HbA1c at Week 26 compared to placebo in participants on background metformin (with or without insulin; LS means difference = -0.77% [SE: 0.308; 95% CI: -1.38, -0.17; p=0.012]) – see Table 11 below.

Table 11: Secondary Analysis of the primary efficacy endpoint (primary estimand, treatment policy strategy): change from baseline in HbA1c (%) at Week 26 using pattern mixture model – subjects on background metformin (with or without insulin); FAS (Study JNJ-28431754DIA3018)

	Placebo (N=67)	Cana (N=62)
Observed Value at Baseline		
N	67	62
Mean (SD)	8.4 (1.37)	7.8 (1.37)
Observed Value at Week 26		
N	62	56
Mean (SD)	8.7 (2.10)	7.4 (1.82)
Change from Baseline at Week 26		
N	62	56
Mean (SD)	0.3 (1.63)	-0.4 (1.50)
Subjects with intercurrent events	26	7
Subjects discontinued treatment prior to Week 26	8	4
Subjects received rescue medication prior to Week 26	20	3
Summary of results at Week 26 applying Rubin's rules to combine the ANCOVA results across the imputed datasets based on pattern mixture model[a]		
LS Mean (SE)	0.46 (0.221)	-0.32 (0.220)
Difference [Cana-Placebo] in LS Means (SE)		-0.77 (0.308)
95% CI		(-1.38, -0.17)
p-value		0.012

[a]: Imputed datasets are analyzed using analysis of covariance (ANCOVA) with terms for treatment, stratification factors (AHA background and age group), and baseline HbA1c.
A subject is considered to have received rescue medication prior to Week 26 if the day of initiation of the medication is prior to the lower limit of Week 26 Analysis Visit window (Day 163 to 211). Same rule applies for subjects who discontinued treatment prior to Week 26.

[tefa1c03m.rtf] [PROD/jnj-28431754b/dia3018/dbr_final_re2/re_csr/tefa1c03m.sas] 28DEC2023, 17:43

Secondary efficacy endpoints

Change from Baseline in FPG (LOCF)

The LS mean change in FPG from baseline was significantly greater in the canagliflozin group than in the placebo group at both Week 26 and Week 52 – see Table 12 below

Table 12: Change from Baseline in FPG (Conventional Unit; mg/dL) at Week 26 and 52 - LOCF; Full Analysis Set (Study JNJ28431754-DIA3018)

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N[a]	LS Mean (SE)	N[a]	LS Mean (SE)	LS Mean (SE)	CI[b]	p-value[b]
Week 26 (LOCF)	82	15.3 (6.68)	76	-11.5 (6.86)	-26.9 (8.84)	(-44.3, -9.4)	0.003
Week 52 (LOCF)	83	19.2 (6.90)	79	-16.4 (6.98)	-35.6 (9.05)	(-53.5, -17.8)	<0.001

a: Number of subjects with non-missing value of change from baseline.
b: CI (confidence interval) and p-value are based on ANCOVA model with treatment and the stratification factors (AHA background and age group) as fixed effects and baseline FPG value as a covariate.

Proportion of Participants with HbA1c <7.5%, <7.0%, and <6.5%

HbA1c <6.5 %:

- *Week 26:* 11.3% on placebo and 41.6% on canagliflozin achieved an HbA1c <6.5% (OR [cana vs plc] = 4.81; [95% CI: 1.59, 14.62]; p=0.006).

- *Week 52:* 12 % on placebo and 36.6% on canagliflozin achieved an HbA1c <6.5% (OR = 2.46 [cana vs plc; 95% CI: 0.91, 6.65]; p=0.077).

HbA1c <7 %:

- *Week 26:* slightly more than a quarter of the participants on placebo and more than half of the participants on canagliflozin achieved an HbA1c of <7% (OR = 2.22; [95% CI: 0.74, 6.66]; p=0.153).
- *Week 52:* slightly less than a quarter of participants on placebo and more than half on canagliflozin achieved <7% HbA1c (OR = 3.04 [95% CI: 1.07, 8.60]; p=0.037).

HbA1c < 7.5 %:

- *Week 26:* about 40% of participants on placebo and 65% on canagliflozin achieved an HbA1c reduction of <7.5% (OR = 2.26 [95% CI: 0.86, 5.96] p=0.099).
- *Week 52:* about 29.3% of participants on placebo and 69% on canagliflozin achieved an HbA1c reduction of <7.5% (OR = 4.96 [95% C1: 1.65, 14.86]; p=0.004).

See also Table 13 below.

Table 13: Proportion of subjects with HbA1c (%) <7.5%, <7% or <6.5% at Week 52; FAS (Study JNJ28431754-DIA3018)

Category	Placebo (N=87)		Cana (N=84)		Cana vs Placebo		
	N	%	N	%	Odds Ratio	95% CI	p-value
Week 26							
<7.5%	32	40.0	50	64.9			
≥7.5%	48	60.0	27	35.1			
Total	80	100	77	100	2.26	(0.86, 5.96)	0.099
<7%	22	27.5	40	51.9			
≥7%	58	72.5	37	48.1			
Total	80	100	77	100	2.22	(0.74, 6.66)	0.153
<6.5%	9	11.3	32	41.6			
≥6.5%	71	88.8	45	58.4			
Total	80	100	77	100	4.81	(1.59, 14.62)	0.006
Week 52							
<7.5%	22	29.3	49	69.0			
≥7.5%	53	70.7	22	31.0			
Total	75	100	71	100	4.96	(1.65, 14.86)	0.004
<7%	17	22.7	39	54.9			
≥7%	58	77.3	32	45.1			
Total	75	100	71	100	3.04	(1.07, 8.60)	0.037
<6.5%	9	12.0	26	36.6			
≥6.5%	66	88.0	45	63.4			
Total	75	100	71	100	2.46	(0.91, 6.65)	0.077

Note: Odds ratios are based on the generalized linear mixed model for repeated measures including the fixed categorical effects of treatment, stratification factors (ie, background AHA and age group), visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction, and subject as a random effect. A compound symmetry covariance was used since the model did not converge using the unstructured covariance.

Time to Rescue and Proportion of Participants Receiving Rescue Therapy

Fewer participants on canagliflozin (10/84 [11.9%]) received rescue medications as compared to placebo (40/87 [46.0%]). Participants treated with canagliflozin had a longer time to rescue and a smaller proportion of participants received rescue therapy compared to placebo – see Figure 2 below:

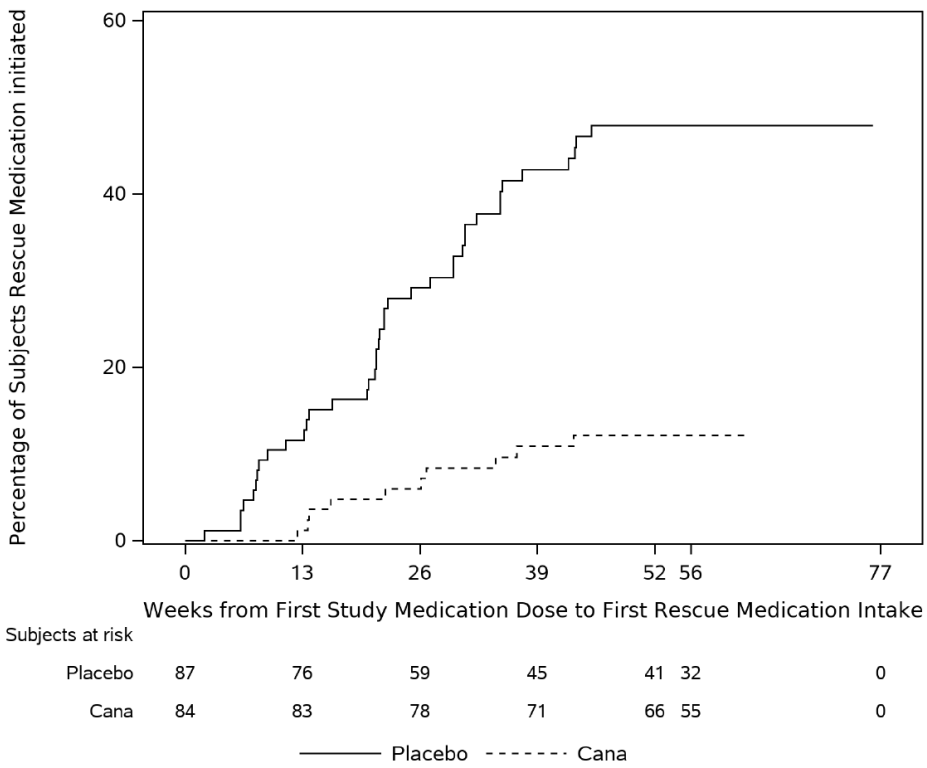

Figure 2: Time to Rescue Medication Initiated; Full Analysis Set (Study JNJ28431754-DIA3018)

Percent Change from Baseline in Body Weight (LOCF)

At Week 26, body weight decreased with canagliflozin (LS mean: –1.6 [SE: 0.51]), but did not change with placebo (LS mean: 0.0, [SE: 0.51]). The difference in LS means was statistically significant (difference in LS means: -1.6 [SE: 0.66; 95% CI: -2.9, -0.3]; p=0.019).

At Week 52, body weight also decreased with canagliflozin, when compared to placebo (LS mean: -0.5 [SE: 0.69], but the difference in LS means was not statistically significant (difference in LS means: -0.9 [SE: 0.90; 95% CI: -2.7, 0.8]; p=0.293) – see Table 14 below.

Table 14: % Change from Baseline in Body Weight at Week 26 and 52 - LOCF; Full Analysis Set (Study JNJ28431754-DIA3018)

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N[a]	LS Mean (SE)	N[a]	LS Mean (SE)	LS Mean (SE)	CI[b]	p-value[b]
Week 26 (LOCF)	85	-0.0 (0.51)	84	-1.6 (0.51)	-1.6 (0.66)	(-2.9, -0.3)	0.019
Week 52 (LOCF)	85	0.4 (0.69)	84	-0.5 (0.69)	-0.9 (0.90)	(-2.7, 0.8)	0.293

a: Number of subjects with non-missing value of change from baseline.
b: CI (confidence interval) and p-value are based on ANCOVA model with treatment and the stratification factors (AHA background and age group) as fixed effects and baseline body weight value as a covariate.

An analysis of weight loss over time (data not shown here) indicates that the weight loss in the canagliflozin group was observed from Week 6 and continued gradually to Week 26, after which the weight loss was attenuated until Week 52 (-0.5 kg in the canagliflozin group in weeks 34, 42 and 52). The differences in change in weight at each time point between canagliflozin and placebo were statistically significant up to Week 26. In the placebo group, the weight gain continued over time throughout the study.

Change from Baseline in BMI at Week 26 and Week 52 (LOCF approach)

At week 26, a reduction from baseline in BMI was observed both on placebo (LS mean -0.4 [SE=0.15]) and on canagliflozin (LS mean -0.8 [SE: 0.15]). Although the drop in BMI was more pronounced with canagliflozin, the difference in LS means was not statistically significant (difference in LS means: -0.4 [SE: 0.20; 95% CI: -0.8, 0.0]; p=0.068). Comparable results were observed at Week 52 - see Table 15 below.

Table 15: Change from baseline in BMI (kg/m^2) at Week 26 - LOCF; FAS (Study JNJ28431754-DIA3018)

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N[a]	LS Mean (SE)	N[a]	LS Mean (SE)	LS Mean (SE)	CI[b]	p-value[b]
Week 26 (LOCF)	85	-0.4 (0.15)	84	-0.8 (0.15)	-0.4 (0.20)	(-0.8, 0.0)	0.068
Week 52 (LOCF)	85	-0.5 (0.19)	84	-0.7 (0.19)	-0.2 (0.25)	(-0.7, 0.3)	0.352
a: Number of subjects with non-missing value of change from baseline. b: CI (confidence interval) and p-value are based on ANCOVA model with treatment and the stratification factors (AHA background and age group) as fixed effects and baseline body mass index value as a covariate.							

Percent Change from Baseline Fasting Plasma Lipids (LOCF)

Week 26:
Analysis of the percent change from baseline showed an increase in HDL-C, total cholesterol, LDL-C, and non-HDL-C in the patients treated with canagliflozin. The changes from baseline in LDL-C/HDL-C and non-HDL-C/LDL-C ratios were slightly higher on canagliflozin as compared to the placebo group.

Week 52:
LS mean in HDL-C increased clinically significantly on canagliflozin as compared to the placebo group (LS mean difference of 6.9 (SE=3.33), p=0.039). No difference or only minimal difference in LS mean change from baseline was observed in total cholesterol, LDL-C, non-HDL-C at Week 52.
The change from baseline in the LDL-C/HDL-C ratio was lower at week 52 in the canagliflozin group (LS mean=4.2 [SE=4.95] as compared to placebo (LS mean=10.4 [SE=5.07]), but the difference was not statistically significant.

Mean and median triglyceride levels at baseline were higher in the canagliflozin group as compared to placebo. At week 26 and 52, the mean and median decreased on canagliflozin while it increased in the placebo group.

To keep the assessment report short, Table 16 only shows results for week 26 and 52, calculated with LOCF approach.

Table 16: Percent change from baseline for various lipid parameters at Week 26 and 52 - LOCF; Full Analysis Set (Study JNJ28431754-DIA3018)

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N[a]	LS Mean (SE)	N[a]	LS Mean (SE)	LS Mean (SE)	CI[b]	p-value[b]
Total cholesterol							
Week 26	76	1.2 (2.22)	72	8.2 (2.22)	6.9 (2.88)	(1.2, 12.6)	0.017
Week 52	78	5.6 (2.16)	76	5.1 (2.13)	-0.6 (2.77)	(-6.0, 4.9)	0.838
LDL-C							
Week 26	67	3.3 (3.73)	67	12.4 (3.58)	9.1 (4.77)	(-0.3, 18.6)	0.057
Week 52	72	7.5 (3.57)	74	8.3 (3.44)	0.8 (4.54)	(-8.2, 9.8)	0.864
HDL-C							
Week 26	68	1.5 (2.40)	68	6.4 (2.33)	4.9 (3.10)	(-1.3, 11.0)	0.120
Week 52	73	1.0 (2.58)	74	7.9 (2.52)	6.9 (3.33)	(0.3, 13.5)	0.039
Non-HDL-C							
Week 26	66	1.7 (2.69)	66	6.8 (2.62)	5.2 (3.46)	(-1.7, 12.0)	0.139
Week 52	71	7.7 (3.02)	74	5.0 (2.95)	-2.7 (3.87)	(-10.4, 4.9)	0.484
LDL-C/HDL-C							

Week 26	66	6.0 (4.77)	66	8.3 (4.66)	2.3 (6.14)	(-9.9, 14.4)	0.710
Week 52	71	10.4 (5.07)	74	4.2 (4.95)	-6.1 (6.49)	(-19.0, 6.7)	0.347
non-HDL-C/LDL-C							
Week 26	63	0.5 (4.05)	60	2.4 (4.03)	1.8 (5.31)	(-8.7, 12.3)	0.732
Week 52	68	-1.5 (3.20)	69	4.0 (3.13)	5.5 (4.16)	(-2.7, 13.7)	0.189
Triglycerides							
Week 26	76	8.6 (6.32)	72	4.5 (6.28)	-4.1 (8.23)	(-20.4, 12.1)	0.617
Week 52	78	18.2 (7.17)	76	3.4 (7.05)	-14.9 (9.23)	(-33.1, 3.3)	0.109
a: Number of subjects with non-missing value of change from baseline. b: CI (confidence interval) and p-value are based on ANCOVA model with treatment and the stratification factors (AHA background and age group) as fixed effects and corresponding baseline lipid parameter value as a covariate.							

Change from Baseline in SBP and DBP

There were no meaningful changes in SBP or DBP with canagliflozin compared to placebo at week 26 or week 52. Please see tabular results for SBP and DBP below. For the sake of brevity, only the LS mean differences with CIs and p-values are shown in Table 17 below but not mean/median change from baseline and range.

Table 17: Change from Baseline in Systolic and Diastolic Blood Pressure at Week 26 and 52 - LOCF; Full Analysis Set (Study JNJ28431754-DIA3018)

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N[a]	LS Mean (SE)	N[a]	LS Mean (SE)	LS Mean (SE)	CI[b]	p-value[b]
SBP							
Week 26	81	1.3 (1.09)	80	0.6 (1.08)	-0.7 (1.40)	(-3.4, 2.1)	0.632
Week 52	75	1.3 (1.12)	74	0.2 (1.12)	-1.1 (1.45)	(-4.0, 1.8)	0.449
DBP							
Week 26	81	-0.4 (0.83)	80	-0.3 (0.83)	0.2 (1.08)	(-2.0, 2.3)	0.878
Week 52	75	0.6 (0.88)	74	0.2 (0.89)	-0.5 (1.15)	(-2.7, 1.8)	0.685
a: Number of subjects with non-missing value of change from baseline. b: CI (confidence interval) and p-value are based on ANCOVA model with treatment and the stratification factors (AHA background and age group) as fixed effects and baseline systolic or diastolic blood pressure value as a covariate.							

Change from Baseline in HbA1c at Week 12 and Week 52

At week 12, canagliflozin caused a statistically significant HbA1c reduction from baseline compared to placebo, which was sustained through Week 52 – see Table 18 below, grey shaded lines.

Table 18: Mean and LS mean change from baseline in HbA1c (%) over time (up to Week 12) using mixed model for repeated measures (MMRM) - all subjects; FAS (Study JNJ28431754-DIA3018)

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N[a]	LS Mean (SE)	N[a]	LS Mean (SE)	LS Mean (SE)	CI[b]	p-value[b]
Week 6	83	-0.08 (0.098)	84	-0.67 (0.098)	-0.59 (0.129)	(-0.85, -0.34)	<0.001
Week 12	83	0.09 (0.137)	84	-0.58 (0.137)	-0.67 (0.187)	(-1.05, -0.30)	<0.001
Week 20	78	0.26 (0.158)	76	-0.43 (0.159)	-0.69 (0.220)	(-1.13, -0.26)	0.002
Week 26	80	0.32 (0.168)	77	-0.41 (0.169)	-0.73 (0.234)	(-1.20, -0.27)	0.002
Week 34	73	0.28 (0.171)	76	-0.15 (0.170)	-0.43 (0.238)	(-0.90, 0.04)	0.072
Week 42	73	0.41 (0.165)	75	-0.23 (0.164)	-0.65 (0.229)	(-1.10, -0.19)	0.005
Week 52	75	0.70 (0.182)	71	-0.32 (0.184)	-1.02 (0.256)	(-1.52, -0.51)	<0.001
a: Number of subjects with non-missing value of change from baseline. b: CIs (confidence interval) and p-values are based on a mixed model for repeated measures including the fixed effects of treatment, stratification factors (i.e., background AHA and age group), visit, and treatment-by-visit interaction, as well as the fixed, continuous covariates of baseline and baseline-by-visit interaction. An unstructured covariance is used to model the within-patient errors.							

Other efficacy analyses

Change from baseline in HbA1c at week 26 between canagliflozin 100 mg and placebo.

Participants on 100 mg of canagliflozin who remained at the same dose at week 12 re-randomization showed a statistically significant improvement in HbA1c at Week 26 compared to placebo (LS means difference of-0.58 [SE: 0.250; 95% CI -1.08, -0.09]; p=0.02; see Table 19 below).

Table 19: Change from Baseline in HbA1c (%) at Week 26 between canagliflozin 100 mg and placebo using MMRM; FAS (Study JNJ28431754- DIA3018)

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N[a]	LS Mean (SE)	N[a]	LS Mean (SE)	LS Mean (SE)	CI[b]	p-value[b]
Week 6	83	-0.05 (0.099)	84	-0.62 (0.097)	-0.57 (0.129)	(-0.83, -0.32)	<.001
Week 12	83	0.12 (0.138)	84	-0.52 (0.135)	-0.64 (0.187)	(-1.01, -0.27)	<.001
Week 20	78	0.29 (0.161)	76	-0.29 (0.151)	-0.58 (0.216)	(-1.01, -0.15)	0.008
Week 26	80	0.34 (0.184)	77	-0.25 (0.173)	-0.58 (0.250)	(-1.08, -0.09)	0.020

[a]: Number of subjects with non-missing value of change from baseline.
[b]: CIs (confidence interval) and p-values are based on a mixed model for repeated measures including the fixed effects of treatment, stratification factors (i.e., background AHA and age group), visit, and treatment-by-visit interaction, as well as the fixed, continuous covariates of baseline and baseline-by-visit interaction. An unstructured covariance is used to model the within-patient errors.
Comparison of canagliflozin (100 mg with no dose increase after week12) to placebo is made by using the weights in the analysis as follows: All subjects start with a weight of 1. After Week 12, subjects who are re-randomized to continue canagliflozin 100 mg will have a weight of 2. The subjects who are re-randomized to up-titrate to canagliflozin 300 mg will have a weight of 0.

Change from baseline in HbA1c at week 26 between canagliflozin 100 mg followed by a dose increase to 300 mg and placebo.

Participants who started on 100 mg and were re-randomized at Week 12 to 300 mg of canagliflozin showed a statistically significant improvement in HbA1c at Week 26 compared to placebo (LS means difference of-0.74, [SE: 0.237; 95% CI: -1.21, -0.28]; p=0.002; see Table 20 below).

Table 20: Change from baseline in HbA1c (%) at Week 26 between canagliflozin 100 mg followed by a dose increase to 300 mg and placebo using MMRM; FAS (Study JNJ28431754-DIA3018)

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N[a]	LS Mean (SE)	N[a]	LS Mean (SE)	LS Mean (SE)	CI[b]	p-value[b]
Week 6	83	-0.07 (0.099)	84	-0.65 (0.098)	-0.59 (0.129)	(-0.84, -0.33)	<.001
Week 12	83	0.10 (0.137)	84	-0.55 (0.135)	-0.65 (0.186)	(-1.02, -0.28)	<.001
Week 20	78	0.29 (0.184)	76	-0.33 (0.171)	-0.62 (0.246)	(-1.11, -0.14)	0.012
Week 26	80	0.33 (0.175)	77	-0.41 (0.167)	-0.74 (0.237)	(-1.21, -0.28)	0.002

[a]: Number of subjects with non-missing value of change from baseline.
[b]: CIs (confidence interval) and p-values are based on a mixed model for repeated measures including the fixed effects of treatment, stratification factors (i.e., background AHA and age group), visit, and treatment-by-visit interaction, as well as the fixed, continuous covariates of baseline and baseline-by-visit interaction. An unstructured covariance is used to model the within-patient errors.
Comparison of canagliflozin (100 mg up-titrate to 300 mg after week 12) to placebo is made by using the weights in the analysis as follows: All subjects start with a weight of 1. After Week 12, subjects who are re-randomized to continue canagliflozin 100 mg will have a weight of 0 and those who are re-randomized to up-titrate to canagliflozin 300 mg will have a weight of 2.

Ancillary analyses

Subgroup analyses for the primary efficacy endpoint

In order to assess the interaction of the treatment effect with each of the subgroups, the p-value for the interaction was also assessed based on the same PMM (pattern mixture model) methodology used for the primary analysis of the primary efficacy endpoint. Additionally, treatment effects for each level (category) within each of the subgroups were estimated using the same ANCOVA model containing the treatment by subgroup interaction term. The results of PMM-based analyses for each of subgroup are described below.

Treatment by Background AHA

The treatment by background AHA interaction effect was not significant (p-value=0.29). The change from baseline in HbA1c for canagliflozin was consistently better as compared to placebo, as indicated by differences in LS means (-0.46, -0.96, -0.88, and -0.65 for the diet and exercise only, insulin monotherapy, metformin and insulin, and metformin monotherapy subgroups, respectively), although not statistically significant due to increased standard error/smaller sample size. For the sake of brevity, the detailed tabular representation is omitted in this AR.

Treatment by Age Group

The p-value for the treatment by age group interaction was not statistically significant (p-value=0.463). While there was an improvement in HbA1c as observed by the change from baseline with canagliflozin when compared to placebo in both categories of the age group, the improvement in the ≥15 to <18-year-old age group was statistically significant (LS means difference = -1.05 [SE: 0.351], p-value=0.003) (see Table 21 below).

Table 21: Change from baseline in HbA1c(%) at Week 26 – age subgroup analysis based on pattern mixture model; FAS (Study JNJ28431754-DIA3018)

	Placebo (N=87)	Cana (N=84)
Treatment-by-Age group interaction p-value applying Rubin's Rule[a]		0.463
Summary of results for each subgroup level of Age group at Week 26 applying Rubin's Rule[a]		
>=10 TO <15 YEARS OLD		
Observed Value at Baseline		
N	42	39
Mean (SD)	8.1 (1.45)	7.8 (1.18)
Change from Baseline at Week 26		
LS Mean (SE)	0.23 (0.257)	-0.21 (0.252)
Diff. (Cana - Placebo) of LS Means (SE)		-0.45 (0.360)
p-value[a]		0.212
95% CI[a]		(-1.16, 0.26)
>=15 TO <18 YEARS OLD		
Observed Value at Baseline		
N	45	45
Mean (SD)	8.5 (1.23)	7.8 (1.42)
Change from Baseline at Week 26		
LS Mean (SE)	0.49 (0.242)	-0.56 (0.245)
Diff. (Cana - Placebo) of LS Means (SE)		-1.05 (0.351)
p-value[a]		0.003
95% CI[a]		(-1.74, -0.36)

Treatment by Sex

The treatment by sex interaction effect was not statistically significant (p-value=0.944). There was an improvement in HbA1c (change from baseline cana vs. placebo) in both females and males, but only the effect in females was statistically significant (difference in LS means= -0.90 [SE: 0.308], p-value=0.004) (see Table 22 below).

Table 22: Change from baseline in HbA1c (%) at Week 26 – sex subgroup analysis based on pattern mixture model; FAS (Study JNJ28431754-DIA3018)

	Placebo (N=87)	Cana (N=84)
Treatment-by-Sex interaction p-value applying Rubin's Rule[a]		0.944
Summary of results for each subgroup level of Sex at Week 26 applying Rubin's Rule[a]		
Female		
Observed Value at Baseline		
N	60	57
Mean (SD)	8.4 (1.41)	7.8 (1.23)
Change from Baseline at Week 26		
LS Mean (SE)	0.43 (0.212)	-0.47 (0.219)
Diff. (Cana - Placebo) of LS Means (SE)		-0.90 (0.308)
p-value[a]		0.004
95% CI[a]		(-1.50, -0.30)
Male		
Observed Value at Baseline		
N	27	27
Mean (SD)	8.1 (1.22)	7.8 (1.49)
Change from Baseline at Week 26		
LS Mean (SE)	0.28 (0.321)	-0.28 (0.301)
Diff. (Cana - Placebo) of LS Means (SE)		-0.56 (0.440)
p-value[a]		0.205
95% CI[a]		(-1.42, 0.30)

Results using the MMRM analysis are not shown in this AR. However, these results were consistent with the above-shown results based on the PMM methodology. Specifically, there was no treatment by subgroup interaction for any of the subgroups. In addition, the respective treatment effects for each category within a subgroup were mostly similar for each subgroup.

Sensitivity analyses of the primary endpoint

Additional sensitivity analyses were conducted for the primary analysis of the primary efficacy endpoint for all participants as well as for those on background metformin (with or without insulin) in the FAS. For the sake of brevity, only the summary of results for the total randomized population are presented in the following (for the population on background metformin with or without insulin, see clinical study report):

Copy reference multiple imputation model

Based on this method of analysis, canagliflozin showed a statistically significant improvement with respect to change from baseline in HbA1c at Week 26 compared to placebo in all participants (Table 23 below) and in participants on background metformin with or without insulin (data not shown in this AR).

Table 23: Summary of results at Week 26 applying Rubin's rules to combine the ANCOVA results across the imputed datasets based on pattern mixture model (Table shortened)[a]

	Placebo (N=87)	Cana (N=84)
LS Mean (SE)	0.38 (0.180)	-0.33 (0.182)
Difference [Cana-Placebo] in LS Means (SE)		-0.71 (0.236)
95% CI		(-1.17, -0.25)
p-value		0.003
[a]: Imputed datasets are analyzed using analysis ofcovariance (ANCOVA) with terms for treatment, stratification factors (AHA background and age group), and baseline HbA1c.		

A subject is considered to have received rescue medication prior to Week 26 if the day of initiation of the medication is prior to the lower limit of Week 26 Analysis Visit window (Day 163 to 211). Same rule applies for subjects who discontinued treatment prior to Week 26.

Mixed Model for Repeated Measures (MMRM)

Canagliflozin showed a statistically significant improvement with respect to change from baseline in HbA1c at Week 26 compared to placebo in all participants. The improvement in HbA1c change from baseline was observed as early as Week 6 with gradual improvement to Week 26. The difference in LS means (relative to placebo) was statistically significant at each time point starting at Week 6 in all participants – see Table 23 below.

Table 23: LS Mean Change from Baseline in HbA1c (%) Over Time (Up to Week 26)

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N[a]	LS Mean (SE)	N[a]	LS Mean (SE)	LS Mean (SE)	CI[b]	p-value[b]
WEEK 6	83	-0.07 (0.099)	84	-0.66 (0.098)	-0.59 (0.129)	(-0.85, -0.34)	<.001
WEEK 12	83	0.10 (0.137)	84	-0.57 (0.137)	-0.68 (0.187)	(-1.05, -0.31)	<.001
WEEK 20	78	0.29 (0.159)	76	-0.41 (0.160)	-0.70 (0.221)	(-1.14, -0.26)	0.002
WEEK 26	80	0.33 (0.168)	77	-0.40 (0.169)	-0.73 (0.234)	(-1.19, -0.27)	0.002

a: Number of subjects with non-missing value of change from baseline.
b: CIs (confidence interval) and p-values are based on a mixed model for repeated measures including the fixed effects of treatment, stratification factors (i.e., background AHA and age group), visit, and treatment-by-visit interaction, as well as the fixed, continuous covariates ofbaseline and baseline-by-visit interaction. An unstructured covariance is used to model the within-patient errors.

Tipping point analyses

Tipping point analyses were performed to assess the impact of the missing at random (MAR) assumption in the multiple imputation. For all participants, the tipping point of results changing from statistical significance to non-significance corresponds to a delta of 2.6 (see Table 24 below). The scenarios, where imputed values in canagliflozin are worse by a magnitude of 2.6 to reach the tipping point would not be considered plausible values, and the results under MAR assumption (analysis based on MMRM) would be supported.

Table 24: Tipping point analysis of primary efficacy endpoint (primary estimand, treatment policy strategy): change from baseline in HbA1c (%) at Week 26 using Delta adjustment applied to missing at random MI - all subjects; FAS (Study JNJ28431754-DIA3018)

Delta	Change from Baseline						
	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	LS Mean	SE	LS Mean	SE	LS Mean	SE	p-value[a]
2.1000	0.38	0.186	-0.16	0.188	-0.53	0.245	0.029 *
2.2000	0.38	0.187	-0.15	0.189	-0.52	0.246	0.033 *
2.3000	0.38	0.188	-0.14	0.190	-0.52	0.247	0.037 *
2.4000	0.38	0.188	-0.13	0.190	-0.51	0.248	0.041 *
2.5000	0.37	0.189	-0.12	0.191	-0.50	0.249	0.046 *
2.6000	0.37	0.190	-0.11	0.192	-0.49	0.250	0.051
2.7000	0.37	0.191	-0.11	0.193	-0.48	0.251	0.056
2.8000	0.37	0.191	-0.10	0.193	-0.47	0.252	0.062
2.9000	0.37	0.192	-0.09	0.194	-0.46	0.253	0.069
3.0000	0.37	0.193	-0.08	0.195	-0.45	0.254	0.076

Note: Last 10 observations are displayed.
a: Imputed datasets are analyzed using analysis of covariance (ANCOVA) with terms for treatment, stratification factors (AHA background and age group), and baseline HbA1c.
* indicates significance (p<0.05).

For the subset of participants on background metformin (with or without insulin), the tipping point corresponds to a delta of 1.6 (data not shown in this AR).

Last Observation Carried Forward (LOCF)
Canagliflozin showed a statistically significant improvement with respect to change from baseline in HbA1c at Week 26 compared to placebo in all participants. All participants-LS means difference = -0.79% (SE: 0.233; 95% CI: -1.25, -0.33; p = <0.001; Table 25 below).

Table 25: Analysis of the primary efficacy endpoint - change from baseline in HbA1c (%) at Week 26 - LOCF - all subjects; FAS (Study JNJ28431754-DIA3018)

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N[a]	LS Mean (SE)	N[a]	LS Mean (SE)	LS Mean (SE)	CI[b]	p-value[b]
Week 26 (LOCF)	85	0.42 (0.178)	84	-0.37 (0.178)	-0.79 (0.233)	(-1.25, -0.33)	<0.001

a: Number of subjects with non-missing value of change from baseline.
b: CI (confidence interval) and p-value are based on ANCOVA model with treatment and the stratification factors (AHA background and age group) as fixed effects and baseline HbA1c value as a covariate.

Supportive Analyses of the Primary Efficacy Endpoint
Re-randomization Test
Since dynamic randomization using minimization algorithm was employed, a re-randomization test was performed to determine the p-value for the treatment comparison of the primary efficacy endpoint. One thousand iterations of the re-randomization were performed using the same minimization algorithm. For each iteration, the test statistic for the treatment comparison was determined using the MMRM method. The p-value corresponding to the re-randomization test for all participants is 0.001 (see Table 26).

Table 26: Change from Baseline in HbA1c (%) at Week 26 by Using Re-Randomization Test – All Subjects; Full Analysis Set (Study JNJ28431754-DIA3018)

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N	LS Mean (SE)	N	LS Mean (SE)	LS Mean (SE)	CIa	p-valuea
Week 26 (observed results)	80	0.33 (0.168)	77	-0.40 (0.169)	-0.73 (0.234)	(-1.19, -0.27)	0.002
Re-randomization Test[b]							
Number of iterations	1000						
p-values based on re-randomization test[c]	0.001						

a: CIs and p-values are based on a mixed model for repeated measures including the fixed effects of treatment, stratification factors (i.e., background AHA and age group), visit, and treatment-by-visit interaction, as well as the fixed, continuous covariates of baseline and baseline-by-visit interaction. An unstructured covariance was used to model the within-patient errors.
b: The re-randomization test would fix the observed HbA1c data, regenerate treatment assignments for the entire study using the same minimization algorithm employed in the study and compute the test statistics corresponding to the primary efficacy comparison using MMRM method.
c: The p-value for the primary efficacy comparison is defined as the proportion of re-randomized studies whose test statistic (difference in LS means) for that comparison is at least as extreme as that of the test statistic based on the original treatment assignment.

2.5.1. Discussion on clinical efficacy

JNJ-28431754DIA3018 (DIA3018)

Design and conduct of clinical study

This was a randomized, double blind, placebo-controlled, 2-arm, parallel group, multi-center study that evaluated canagliflozin in male or female participants ≥10 to<18 years of age with T2DM. The 52-week treatment phase consisted of a 26-week core double-blind treatment period (relevant for primary endpoint), followed by a 26-week double-blind treatment extension. Patients on canagliflozin with HbA_{1c} ≥7.0% at Week 12 (i.e. non responders) and an eGFR ≥60 mL/min/1.73m^2 were re-randomized 1:1 at week 13 to either remain on double-blind canagliflozin 100 mg (or matching placebo) or to up-titrate to double-blind canagliflozin 300 mg (or matching placebo). The primary objective was to demonstrate the superiority of canagliflozin 100 mg and 300 mg against placebo regarding HbA1c reduction from baseline at week 26.

The study design is adequate and in line with the recommendations of the EU guideline on medicinal products for treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev.2). Given the challenges regarding recruitment in this population, the re-randomization design is considered appropriate to obtain the maximum amount of information with a limited number of patients. However, due to the up-titration step after week 12, the estimated effect is a mixture of two different treatment strategies: (1) increasing the dose to 300 mg or (2) remaining on 100 mg in case of insufficient glycaemic control. Thus, it is important that the applicant has individually assessed each treatment strategy (see effects table section 5.6).

Studied population

In total, 171 patients were randomised to once daily treatment with canagliflozin (n=84) or placebo (n=87), with stratified randomization according to diet and exercise only as well as diet and exercise plus either metformin monotherapy, or insulin monotherapy or a combination of metformin and insulin. Moreover, strata were generated for age group (≥10 to <15 years; ≥15 to <18 years). This approach is endorsed, as it ensures sufficient coverage of the entire target age range, and the background therapies largely reflect the therapies recommended in the 2022 ISPAD guideline (*Pediatr Diabetes.* 2022; 23:872–902). The distribution of anti-diabetic background treatments was balanced across the treatment groups. The majority of patients took metformin with or without insulin.

As pre-specified by the study protocol, ≥30% of participants between ≥10 and <15 years of age were randomized (n=81 [47.4%]). The pre-planned upper limit of 65% of female participants per age group was slightly exceeded (67.9% for ≥10 to <15 years and 68.9% for ≥15 to <18 years), which, however, is still considered acceptable. A larger proportion of female in comparison to male participants reflects the distribution of paediatric T2DM patients reported in the literature (see e.g., Pinhas-Hamiel O (2023), https://www.ncbi.nlm.nih.gov/books/NBK597439/).

The study was conducted in North America, South America, Europe and Asia, but only 3.4% of the participants were from Europe (Poland). If the patients from the United States are considered to have a "European-like" lifestyle, the pre-defined criterion to reach 30% of participants with ethnicity and lifestyle comparable to Europe may have been met (Participants from US and Europe: 28.7%).

Demographic and baseline characteristics were largely comparable across treatment groups. About half of the patients had baseline HbA1c values <8% (n=92 [53.8]); for the remaining patients, approximately similar proportions had either HbA1c values of 8.0% to <9.0% (n=31 [18.1%]) or 9.0 to ≤10.0% (n=32 [18.7%]). It is noted that 16 patients (9.4%) had a baseline HbA1c of >10%. Mean baseline HbA1c was lower in the canagliflozin arm (7.8%) as compared to placebo-treated patients (8.3%), which went along with a slightly shorter mean duration of disease, a higher baseline eGFR and higher fasting serum triglycerides in comparison to the placebo arm. As the effect size of HbA1c reduction depends on the baseline HbA1c, this imbalance favoured the placebo arm.

Although body weight was relatively high in a large proportion of the included population (mean BMI of 30.8 ± 7.43 kg/m^2; obesity in 46.2%), 24.0 % of the patients had normal weight. Exposure was 4- to 5-fold higher with the 300 mg as compared to the 100 mg dose (AUC_T [h*ng/mL]: 28,392 vs. 6,190) in

the overall population of the PK/PD study DIA1055. Further data provided by the MAH indicated that in lower-weight paediatric patients (<50 kg), exposure with the 300 mg dose may exceed levels observed in adults at the same dose. For example, in the 30–40 kg subgroup, the AUC 50th percentile approached the adult 95th percentile, and Cmax values in this subgroup were even higher, with the 25th percentile already exceeding the adult 95th percentile (see also Section 2.6.1).

Due to its small size (only n=17), the baseline characteristics of the canagliflozin 300 mg up-titration group (i.e., non-responders at week 12) differed from the characteristics of the other treatment groups in several aspects. The percentage of overweight or obese individuals was higher than in the other treatment groups, which may reflect higher disease severity. This is supported by the observation that the highest baseline HbA1c and FPG values were reported for the up-titration group. Only 6 patients (35.3%) aged <15 years were up-titrated to 300 mg, while all other patients in the 300 mg group were older than 15 years (n=11; 64.7%). Thus, the evidence for efficacy of 300 mg of canagliflozin in the younger age group is rather limited.

Statistical methods
The statistical methods are generally considered adequate. However, the estimand currently used for the primary endpoint does not fully correspond to the recommendations of the EMA Guideline CPMP/EWP/1080/00 Rev. 2, which recommends targeting the effect regardless of treatment discontinuation (treatment policy strategy) and had rescue medication not been introduced (hypothetical strategy). Nonetheless, the chosen estimand was considered acceptable, as the number of patients experiencing intercurrent events was limited, particularly in the active treatment arm, and the majority of patients maintained available HbA1c data at the key timepoints. Additional analyses aligned with alternative estimands were conducted and consistently supported the efficacy conclusions. Thus, despite some deviation from the guideline-recommended strategies, the overall evidence base and robustness of results justify the acceptability of the current estimand.

Conduct
The majority of patients remained on treatment with trial drug up to Week 26 (n=149 [87.1%]) and up to Week 52 (n=142 [83.0%]). The frequency of premature treatment discontinuations was generally comparable across treatment groups.

Results
Primary endpoint
The LS mean difference of the HbA1c change from baseline at week 26 was –0.76 % (SE: 0.249) for pooled canagliflozin *vs.* placebo (95% CI -1.25 to –0.27; p=0.002), which indicated clinically relevant anti-hyperglycaemic efficacy. The secondary analysis of the primary efficacy endpoint in the subgroup on background metformin (with or without insulin) yielded almost identical results.

Primary endpoint in subgroups
Although the treatment by background AHA effect did not reach significance, there was a tendency towards increased treatment effect of canagliflozin in the patients receiving background medication as compared to those being on diet and exercise only, i.e., canagliflozin seems to become more effective with increasing disease severity. This is confirmed by the data on the requirement of rescue therapy in the different AHA background treatment subgroups. Regarding age group, the improvement in HbA1c (change from baseline with canagliflozin *vs.* placebo at week 26) was only significant in the ≥15 to <18-year-old age group (-1.05%; 95% CI -1.74, -0.36) but not in the patients aged <15 years (-0.45%; 95% CI -1.16, 0.26). Nevertheless, the difference with regard to age group was not significant, and efficacy was still clinically relevant in patients aged < 15 years, and thus, no concern regarding efficacy

in the younger age group is warranted. Canagliflozin seemed to be more effective in female than in male patients, but this difference was not significant.

Main secondary and exploratory endpoints and other efficacy analyses
The blood glucose-related main secondary endpoints confirmed superiority of canagliflozin over placebo. The changes in HbA1c over time demonstrate early onset of the treatment effect as well as maintenance of HbA1c reduction through 52 weeks. Compared to the 26-week analysis, the effect is further enhanced after 52 weeks. Likewise, the reduction in FPG from baseline was significantly higher with canagliflozin than with placebo at week 26 (-26.9 mg/dL) and further enhanced at week 52 (-35.6 mg/dL).

In the HbA1c responder analysis, the lowest category of HbA1c <6.5 was achieved by ~42% of canagliflozin-treated patients, but by only 11.3% of the placebo-treated subjects. Fewer participants on canagliflozin received rescue medications as compared to placebo.

Canagliflozin caused significant body weight loss/ BMI reduction in comparison to placebo at week 26 (possibly due to the caloric deficit caused by increased urinary glucose excretion), which was, however, attenuated at week 52. No relevant effect of canagliflozin on systolic and diastolic blood pressure was observed.

Regarding plasma lipids, canagliflozin caused an increase in HDL-, LDL-, and total cholesterol at week 26 in comparison to placebo, while plasma triglycerides were reduced. This is in accordance with previous findings from the adult study programme. It is reassuring that the dyslipidaemia did not get more pronounced at week 52 and that the LDL-C/HDL-C ratio even showed a reduction from baseline in the canagliflozin-treated group.

HbA1c change from baseline at week 26 in the non-responder population up-titrated to canagliflozin 300 mg was -0.74 (SE: 0.237) in comparison to placebo (95% C, -1.21 to -0.28; p=0.002). The corresponding HbA1c change from baseline in those who remained on 100 mg of canagliflozin was -0.58% (SD: 0.250); 95% Cl -1.08 to -0.09; p=0.020). This supports the notion that up-titration to 300 mg may provide additional benefit, although the evidence is rather limited for the participants aged <15 years (only n=6). Moreover, this analysis complements the primary endpoint, which is difficult to interpret, since it represents a mixture of both approaches (remaining on 100 mg and up-titrating to 300 mg).

2.5.2. Conclusions on the clinical efficacy

In children from 10 to ≤18 years of age, canagliflozin (100 mg and 300 mg) causes a significant and clinically relevant decrease in HbA1c compared to placebo. This effect was confirmed by various blood glucose-related secondary endpoints. Up-titration of non-responders from 100 mg to 300 mg of canagliflozin seems to provide additional benefit, although the evidence is somewhat limited in the younger age group of ≥10 to <15 years (small group size of n=6). Subgroup analyses did not show significant differences with regard to background medication, age and sex. There seems to be a tendency towards reduced efficacy in participants aged ≥10 to <15 years, but the treatment effect is still clinically relevant.

In summary, canagliflozin 100 mg and 300 mg is efficacious at improving blood glucose control in the paediatric population with T2DM, and the intended extension of indication to the paediatric population aged ≥10 to <18 years is considered sufficiently justified from the efficacy perspective.

2.6. Clinical safety

Introduction

This application to extend the indication for Invokana to the paediatric patients ≥10 to <18 years of age with T2DM is based on the final results from the following two clinical trials:

- Study JNJ-28431754DIA3018 (hereafter referred to as Study DIA3018) was a randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicenter Phase 3 study in participants with T2DM ≥10 and <18 years of age who had inadequate glycaemic control (i.e. HbA1c of ≥6.5% to ≤11.0%). The total duration of the study was approximately 59 weeks.
- Study JNJ-28431754DIA1055 (hereafter referred to as Study DIA1055), was an open-label, sequential, multiple-dose (14 days of dosing), multicenter Phase 1 study of canagliflozin in 2 treatment groups in children and adolescents (≥10 to <18 years of age) who were diagnosed with T2DM and on a stable regimen of metformin (at a dose of at least 1,000 mg per day) for at least 8 weeks before screening.

Table 1: Overview of the Completed Studies with T2DM in the Pediatric Population

Study Number (Phase)	Study Population	Treatment Groups (Numbers of Treated Participants)
JNJ-28431754DIA3018 (Phase 3)	Male or female participants ranging in age from ≥10 to <18 years, with diagnosis of T2DM, who were on a stable regimen of metformin or injectable insulin within 8 weeks of the first dose of study drug. All participants had to have HbA_{1c} of ≥6.5% to ≤11.0% and who were either: a. on diet and exercise for 4 weeks or, b. on diet and exercise and a stable dose of metformin monotherapy or, c. on diet and exercise and a stable insulin monotherapy or, d. on diet and exercise and a stable combination therapy with metformin and insulin for at least 8 weeks prior to screening, as described above.	Participants were randomly assigned in a 1:1 ratio (n=171) to once daily administration of canagliflozin 100 mg, or placebo and entered a 52-week double-blind placebo-controlled treatment phase consisting of a 26-week core double-blind treatment period, followed by a 26-week double-blind extension treatment period. Randomization was stratified by AHA background and age group (10 to <15 years old; 15 to <18 years old). Participants who at Week 12 had an HbA_{1c} of ≥7.0% and an eGFR ≥60 mL/min/1.73m^2 were re-randomized at Week 13 in a 1:1 ratio to either remain on double-blind canagliflozin 100 mg (or matching placebo) or to up-titrate to double-blind canagliflozin 300 mg (or matching placebo).
JNJ-28431754DIA1055 (Phase 1)	Male or female participants ranging in age from ≥10 to <18 years, with diagnosis of T2DM according to ADA criteria for at least 3 months before screening, without pancreatic autoimmunity and who were on a stable regimen of metformin IR monotherapy of at least 1,000 mg/day for at least 8 weeks before screening were enrolled in the study. Participants had to have normal renal function (eGFR ≥90 ml/min/1.73 m^2 as assessed by Schwartz formula), ALT or AST ≤2.0×ULN, a hemoglobin A1c (HbA1c) of ≥6.1% to ≤10% and a fasting C-peptide of >0.6 ng/mL at screening.	• Canagliflozin, 100 mg (as 1×100 mg tablet) daily for 14 days (n=8). • Canagliflozin, 300 mg (as 1×300 mg tablet) daily for 14 days (n=9).

In addition, the comprehensive Phase 3 studies conducted in adults with T2DM (date of first authorisation: 15 November 2013) offer substantial confirmatory evidence for the safety of canagliflozin.

Patient exposure

Patient exposure in Phase 3 study (DIA3018)

A total of 84 participants received canagliflozin with a mean treatment duration of 337.8 (SD=79.01) days. The mean duration of exposure was comparable for the 87 participants receiving placebo (335 [SD=85.79] days) and participants receiving canagliflozin 100 mg and canagliflozin 300 mg (333.4 [SD=85.34] and 355.2 [SD=44.03] days, respectively). 9 participants receiving placebo (10.3%) and 5 participants (6.0%) receiving canagliflozin had less than 26 weeks of exposure. 50 participants (57.5%) receiving placebo and 57 participants (67.9%) receiving canagliflozin had at least 52 weeks of exposure.

Patient exposure in Phase 1 study (DIA1055)

A total of 17 participants were enrolled: 8 participants received canagliflozin 100 mg/d for 14 days and 9 participants received canagliflozin 300 mg/d for 14 days. All 17 participants enrolled completed the study.

Adverse events

Treatment-Emergent Adverse Events (TEAEs) during the Phase 3 study DIA3018

Table 4 provides an overall summary of TEAEs (regardless of rescue medication) for participants in the safety analysis set. The proportion of participants reporting 1 or more TEAEs, TEAEs that were considered by the investigator to be related to study drug, SAEs, and AEs leading to discontinuation was comparable between participants receiving placebo and participants receiving canagliflozin.

Table 4: Overall Summary of Treatment-emergent Adverse Events Regardless of Rescue Medication; Safety Analysis Set (Study JNJ-28431754-DIA3018)

		Canagliflozin		
	Placebo	100 mg	300 mg	Combined
Analysis set: Safety	87	67	17	84
Subjects with 1 or more:				
AEs	65 (74.7%)	51 (76.1%)	14 (82.4%)	65 (77.4%)
Related AEs [a]	14 (16.1%)	6 (9.0%)	3 (17.6%)	9 (10.7%)
AEs leading to death [b]	0	0	0	0
Related AEs leading to death [a,b]	0	0	0	0
Serious AEs	5 (5.7%)	7 (10.4%)	1 (5.9%)	8 (9.5%)
Related serious AEs	1 (1.1%)	0	0	0
AEs leading to discontinuation of study agent	1 (1.1%)	1 (1.5%)	0	1 (1.2%)
Related AEs leading to discontinuation of study agent	0	0	0	0

Key: AE = adverse event

[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.

[b] AEs leading to death are based on AE outcome of Fatal.

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Table 5 shows that in the Phase 3 study (DIA3018) more commonly (≥2%) reported TEAEs in participants receiving canagliflozin versus placebo included headache (10.7% vs. 3.4%), dizziness (3.6% vs. 1.1%), nasopharyngitis (9.5% vs. 5.7%), rhinitis (4.8% vs. 2.3%), urinary tract infection

(7.1% vs. 4.6%), vomiting (6.0% vs. 2.3%), nausea (4.8% vs. 1.1%) and abdominal pain (3.6% vs. 0%).

In addition, various TEAEs of genital mycotic or bacterial infections were reported in paediatric patients receiving canagliflozin and none with placebo: balanitis candida (2.4% vs. 0%), vulvovaginal candidiasis (2.4% vs. 0%), bacterial vaginosis (1.2% vs. 0%) and genital infection fungal (1.2% vs. 0%).

Hypoglycemia as a TEAE was reported more frequently in participants receiving placebo (9.2%) as compared with participants receiving canagliflozin (3.6%). All 3 hypoglycemia TEAEs were reported by participants who received canagliflozin 100 mg. None of the hypoglycemia TEAEs were serious.

Table 5: Number of Subjects with Treatment-emergent Adverse Events with Frequency of at Least 2% in Any Treatment Group by System Organ Class and Preferred Term Regardless of Rescue Medication; Safety Analysis Set (Study JNJ-28431754DIA3018)

		Canagliflozin		
	Placebo	100 mg	300 mg	Combined
Analysis set: Safety	87	67	17	84
Subjects with 1 or more AEs	65 (74.7%)	51 (76.1%)	14 (82.4%)	65 (77.4%)
System organ class Preferred term				
Infections and infestations	35 (40.2%)	27 (40.3%)	12 (70.6%)	39 (46.4%)
Nasopharyngitis	5 (5.7%)	8 (11.9%)	0	8 (9.5%)
Urinary tract infection	4 (4.6%)	1 (1.5%)	5 (29.4%)	6 (7.1%)
Rhinitis	2 (2.3%)	3 (4.5%)	1 (5.9%)	4 (4.8%)
Upper respiratory tract infection	11 (12.6%)	3 (4.5%)	1 (5.9%)	4 (4.8%)
Influenza	4 (4.6%)	2 (3.0%)	1 (5.9%)	3 (3.6%)
Viral upper respiratory tract infection	1 (1.1%)	2 (3.0%)	1 (5.9%)	3 (3.6%)
Balanitis candida	0	1 (1.5%)	1 (5.9%)	2 (2.4%)
COVID-19	2 (2.3%)	1 (1.5%)	1 (5.9%)	2 (2.4%)
Pharyngotonsillitis	1 (1.1%)	1 (1.5%)	1 (5.9%)	2 (2.4%)
Vulvovaginal candidiasis	0	1 (1.5%)	1 (5.9%)	2 (2.4%)
Bacterial vaginosis	0	0	1 (5.9%)	1 (1.2%)
External ear cellulitis	0	0	1 (5.9%)	1 (1.2%)
Gastroenteritis viral	0	0	1 (5.9%)	1 (1.2%)
Genital herpes	0	0	1 (5.9%)	1 (1.2%)
Genital herpes simplex	0	0	1 (5.9%)	1 (1.2%)
Genital infection fungal	0	0	1 (5.9%)	1 (1.2%)
Pharyngitis streptococcal	0	0	1 (5.9%)	1 (1.2%)
Urinary tract infection bacterial	0	0	1 (5.9%)	1 (1.2%)
Viral infection	2 (2.3%)	0	1 (5.9%)	1 (1.2%)
Impetigo	2 (2.3%)	0	0	0
Otitis media acute	2 (2.3%)	0	0	0
Tonsillitis	2 (2.3%)	0	0	0
Gastrointestinal disorders	13 (14.9%)	12 (17.9%)	5 (29.4%)	17 (20.2%)
Vomiting	2 (2.3%)	3 (4.5%)	2 (11.8%)	5 (6.0%)
Diarrhoea	5 (5.7%)	3 (4.5%)	1 (5.9%)	4 (4.8%)
Nausea	1 (1.1%)	2 (3.0%)	2 (11.8%)	4 (4.8%)
Abdominal pain	0	2 (3.0%)	1 (5.9%)	3 (3.6%)
Gastritis	2 (2.3%)	2 (3.0%)	0	2 (2.4%)
Pancreatitis acute	0	0	1 (5.9%)	1 (1.2%)
Metabolism and nutrition disorders	26 (29.9%)	13 (19.4%)	4 (23.5%)	17 (20.2%)
Vitamin D deficiency	6 (6.9%)	3 (4.5%)	1 (5.9%)	4 (4.8%)
Hyperglycaemia	5 (5.7%)	2 (3.0%)	1 (5.9%)	3 (3.6%)
Hypoglycaemia	8 (9.2%)	3 (4.5%)	0	3 (3.6%)
Ketosis	1 (1.1%)	2 (3.0%)	0	2 (2.4%)

Table 5: Number of Subjects with Treatment-emergent Adverse Events with Frequency of at Least 2% in Any Treatment Group by System Organ Class and Preferred Term Regardless of Rescue Medication; Safety Analysis Set (Study JNJ-28431754DIA3018)

		Canagliflozin		
	Placebo	100 mg	300 mg	Combined
Dehydration	1 (1.1%)	0	1 (5.9%)	1 (1.2%)
Diabetes mellitus inadequate control	1 (1.1%)	0	1 (5.9%)	1 (1.2%)
Hypertriglyceridaemia	2 (2.3%)	0	1 (5.9%)	1 (1.2%)
Acetonaemia	4 (4.6%)	0	0	0
Hyperlipidaemia	2 (2.3%)	0	0	0
Hyperuricaemia	2 (2.3%)	0	0	0
Nervous system disorders	3 (3.4%)	14 (20.9%)	2 (11.8%)	16 (19.0%)
Headache	3 (3.4%)	8 (11.9%)	1 (5.9%)	9 (10.7%)
Dizziness	1 (1.1%)	2 (3.0%)	1 (5.9%)	3 (3.6%)
Investigations	10 (11.5%)	5 (7.5%)	3 (17.6%)	8 (9.5%)
Blood ketone body increased	2 (2.3%)	1 (1.5%)	1 (5.9%)	2 (2.4%)
Blood glucose increased	0	0	1 (5.9%)	1 (1.2%)
High density lipoprotein decreased	0	0	1 (5.9%)	1 (1.2%)
Respiratory, thoracic and mediastinal disorders	7 (8.0%)	7 (10.4%)	1 (5.9%)	8 (9.5%)
Epistaxis	0	2 (3.0%)	0	2 (2.4%)
Cough	4 (4.6%)	1 (1.5%)	0	1 (1.2%)
Rhinorrhoea	2 (2.3%)	0	1 (5.9%)	1 (1.2%)
Skin and subcutaneous tissue disorders	4 (4.6%)	6 (9.0%)	2 (11.8%)	8 (9.5%)
Skin lesion	0	0	1 (5.9%)	1 (1.2%)
Urticaria	0	0	1 (5.9%)	1 (1.2%)
General disorders and administration site conditions	4 (4.6%)	6 (9.0%)	1 (5.9%)	7 (8.3%)
Pyrexia	3 (3.4%)	4 (6.0%)	0	4 (4.8%)
Malaise	0	2 (3.0%)	0	2 (2.4%)
Fatigue	0	0	1 (5.9%)	1 (1.2%)
Thirst	0	0	1 (5.9%)	1 (1.2%)
Musculoskeletal and connective tissue disorders	2 (2.3%)	5 (7.5%)	2 (11.8%)	7 (8.3%)
Pain in extremity	0	3 (4.5%)	0	3 (3.6%)
Myalgia	1 (1.1%)	1 (1.5%)	1 (5.9%)	2 (2.4%)
Musculoskeletal pain	0	0	1 (5.9%)	1 (1.2%)
Injury, poisoning and procedural complications	4 (4.6%)	4 (6.0%)	1 (5.9%)	5 (6.0%)
Skin abrasion	1 (1.1%)	0	1 (5.9%)	1 (1.2%)
Skin laceration	0	0	1 (5.9%)	1 (1.2%)
Psychiatric disorders	6 (6.9%)	3 (4.5%)	1 (5.9%)	4 (4.8%)
Anxiety	2 (2.3%)	2 (3.0%)	0	2 (2.4%)
Autism spectrum disorder	0	0	1 (5.9%)	1 (1.2%)
Renal and urinary disorders	4 (4.6%)	3 (4.5%)	1 (5.9%)	4 (4.8%)
Ketonuria	0	0	1 (5.9%)	1 (1.2%)
Pollakiuria	2 (2.3%)	0	0	0
Reproductive system and breast disorders	2 (2.3%)	3 (4.5%)	1 (5.9%)	4 (4.8%)
Balanoposthitis	0	0	1 (5.9%)	1 (1.2%)
Vulvovaginal pruritus	2 (2.3%)	0	0	0
Endocrine disorders	0	3 (4.5%)	0	3 (3.6%)

Table 5:	Number of Subjects with Treatment-emergent Adverse Events with Frequency of at Least 2% in Any Treatment Group by System Organ Class and Preferred Term Regardless of Rescue Medication; Safety Analysis Set (Study JNJ-28431754DIA3018)			
			Canagliflozin	
	Placebo	100 mg	300 mg	Combined
Ear and labyrinth disorders	1 (1.1%)	1 (1.5%)	1 (5.9%)	2 (2.4%)
Vertigo	1 (1.1%)	0	1 (5.9%)	1 (1.2%)
Hepatobiliary disorders	1 (1.1%)	2 (3.0%)	0	2 (2.4%)
Immune system disorders	0	1 (1.5%)	1 (5.9%)	2 (2.4%)
Seasonal allergy	0	0	1 (5.9%)	1 (1.2%)
Vascular disorders	1 (1.1%)	2 (3.0%)	0	2 (2.4%)
Blood and lymphatic system disorders	2 (2.3%)	1 (1.5%)	0	1 (1.2%)
Eye disorders	2 (2.3%)	1 (1.5%)	0	1 (1.2%)

Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 26.0.

Hypoglycemia

Table 6 shows the number of participants with treatment-emergent hypoglycemia that was documented by blood glucose measurements, whether symptomatic or not.

Table 6:	Treatment-Emergent Biochemically Documented Hypoglycemia Prior to Rescue Medication; Safety Analysis Set (Study JNJ-28431754DIA3018)			
			Canagliflozin	
	Placebo	100 mg	300 mg	Combined
Analysis set: Safety	87	67	17	84
Subjects with episodes*	14 (16.1%)	14 (20.9%)	1 (5.9%)	15 (17.9%)
<=70 mg/dL (3.9 mmol/L)	14 (16.1%)	14 (20.9%)	1 (5.9%)	15 (17.9%)

Table 6:	Treatment-Emergent Biochemically Documented Hypoglycemia Prior to Rescue Medication; Safety Analysis Set (Study JNJ-28431754DIA3018)			
			Canagliflozin	
	Placebo	100 mg	300 mg	Combined
< 56 mg/dL (3.1 mmol/L)	7 (8.0%)	6 (9.0%)	0	6 (7.1%)
< 36 mg/dL (2.0 mmol/L)	2 (2.3%)	0	0	0
Total number of episodes	74	57	1	58
Subjects with numbers of biochemically documented hypoglycemia	14 (16.1%)	14 (20.9%)	1 (5.9%)	15 (17.9%)
1 episode	4 (4.6%)	5 (7.5%)	1 (5.9%)	6 (7.1%)
2 episodes	6 (6.9%)	3 (4.5%)	0	3 (3.6%)
>= 3 episodes	4 (4.6%)	6 (9.0%)	0	6 (7.1%)
Event rate per subject-year exposure	1.24	0.98	0.07	0.8

Note: Count (%) is based on Number of Subjects, Not Number of Episodes.
*Subjects with any treatment-emergent biochemically documented hypoglycemia episodes;
A subject may be counted in each of the 3 glucose categories listed below;
Results of LOW is included in all the 3 glucose categories (i.e., ≤ 70, <56, and/or <36 mg/dL).
Glucose data could be reported in either mg/dL or mmol/L units. No conversion between the 2 units was made. The comparison between the reported glucose values and the cutoffs was based on the units in which the glucose values were reported.
[TSFAE15.RTF] [JNJ-28431754B/DIA3018/DBR_FINAL_RE2/RE_CSR/PROD/TSFAE15.SAS] 28DEC2023, 17:43

The number of hypoglycemic episodes per participant prior to rescue medications were comparable between participants receiving placebo and those receiving canagliflozin.

Urinary albumin-creatinine ratio (ACR)

As indicated in the table below, urine ACR results over time were generally comparable across the treatment groups. There was a trend towards increased ACR geometric mean in the Cana 300 mg group as compared to Cana 100 mg and placebo.

Table 65: ACR Over Time; Safety Analysis Set (Study JNJ28431754-DIA3018)

	Placebo				Cana 100 mg				Cana 300 mg			
	N	Median	GM(a)	(95% CI)	N	Median	GM(a)	(95% CI)	N	Median	GM(a)	(95% CI)
Parameter: Urine Albumin/Creatinine (mg/g)												
Baseline	72	8.15	11.87	(8.84; 15.94)	55	8.57	13.83	(9.84; 19.45)	13	14.06	17.05	(8.79; 33.07)
Week 26	64	9.90	15.62	(11.24; 21.71)	48	11.01	14.41	(9.85; 21.07)	12	9.82	24.84	(11.81; 52.26)
Week 52	65	11.49	14.98	(10.97; 20.46)	47	10.61	15.45	(10.75; 22.22)	11	10.96	21.27	(10.42; 43.45)

Note: [a] GM=Geometric mean estimated from the mixed model for repeated measures including the fixed effects of treatment, stratification factors (ie, background AHA and age group), visit, treatment-by-visit interaction.
ACR is log transformed.

[tsfacr01.rtf] [PROD/jnj-28431754b/dia3018/dbr_final_re2/re_csr/tsfacr01.sas] 28DEC2023, 17:43

Adverse events regarding growth and development

Tanner staging

Girls (breast development):

At Week 26, compared to baseline,
- Placebo: 6 girls increased by 1 stage
- Canagliflozin 100 mg: 13 girls increased by 1 stage; 1 girl increasing by ≥2 stages

At Week 52, compared to baseline,
- Placebo: 12 girls increased by 1 stage; 1 girl increased by ≥2 stages
- Canagliflozin 100 mg: 14 girls increased by 1 stage

Canagliflozin 300 mg: 2 girls increased by 1 stage at both Week 26 and 52.

Boys (genital development)

At Week 26, compared to baseline,
- Placebo: 3 boys increased by 1 stage; 1 boy increased by ≥2 stages.
- Canagliflozin 100 mg: 4 boys increased by 1 stage; 1 boy increased by ≥2 stages.

At Week 52, compared to baseline,
- Placebo: 8 boys increased by 1 stage; 3 boys increased by ≥2 stages
- Canagliflozin 100 mg: 5 boys increased by 1 stage; 2 increased by ≥2 stages.

Canagliflozin 300 mg: 1 boy increased by 1 stage at both Week 26 and 52.

Growth velocity

At week 26, growth velocity was 1.99, 2.00 and 1.00 cm/year for placebo, canagliflozin 100 mg and 300 mg, respectively.

At week 52, growth velocity was 1.63, 1.57 and 1.76 cm/year for placebo, canagliflozin 100 mg and 300 mg, respectively.

Biomarkers

Bone turnover markers
The data on bone turnover markers suggest no apparent clinically meaningful differences from placebo, given the wide standard deviations on osteocalcin, and noting the relatively low numbers on the Type 1 collagen C-telopeptides.

Markers of calcium and phosphate homeostasis:
The following results pertain to the median changes from baseline at week 26 and 52 and within 2 days after last study agent:

- For calcium, calcitonin, phosphate and parathyroid hormone, no relevant difference in median change from baseline seemed to occur at week 26 and 52 for canagliflozin vs. placebo.
- Regarding urine calcium and phosphate, the excretion appeared to be reduced at week 26 and 52 in the canagliflozin-treated patients as compared to placebo (median change from baseline):
  - Urine calcium: week 26: +1.4 mg/dL with placebo; 0.00 mg/dL with canagliflozin
    week 52: +1.5 mg/dL with placebo; +0.10 mg/dL with canagliflozin
  - Urine phosphate: week 26: +8.5 mg/dL with placebo; - 7.60 mg/dL with canagliflozin
    week 52: +6.6 mg/dL with placebo; -10.20 mg/dL with canagliflozin
- 25-hydroxy vitamin D showed a more pronounced reduction from baseline in the canagliflozin-treated patients as compared to the placebo-treated arm at both week 26 and 52:
  - week 26: -3.0 nmol/l and -4 nmol/l with canagliflozin 100 mg and 300 mg, respectively, vs. +1.5 nmol/l with placebo
  - week 52: -1.0 nmol/l and -3 nmol/l with canagliflozin 100 mg and 300 mg, respectively, vs. +1.0 nmol/l with placebo
- Magnesium appeared to be slightly increased from baseline with canagliflozin as compared to placebo (0.0 mg/dL with placebo vs. +0.1 mg/dL with canagliflozin at both week 26 and 52).

Treatment-Emergent Adverse Events (TEAEs) during the Phase 1 study DIA1055

The most frequently reported TEAE (≥2 participants) by preferred term was nausea (n=3); all other TEAEs were reported as single incident. Overall, the incidence of TEAEs was balanced between both treatment groups (Table 8).

Table 8: Treatment-Emergent Adverse Events by Body System or Organ Class and Dictionary-derived Term Safety Analysis Set (Study JNJ-28431754DIA1055)

Body System Or Organ Class Dictionary-Derived Term	Canagliflozin 100 mg (N=8) n (%)	Canagliflozin 300 mg (N=9) n (%)	Total (N=17) n (%)
Total no. participants with adverse events	4 (50.0)	5 (55.6)	9 (52.9)
GASTROINTESTINAL DISORDERS	2 (25.0)	3 (33.3)	5 (29.4)
Nausea	1 (12.5)	2 (22.2)	3 (17.6)
Abdominal pain	1 (12.5)	0	1 (5.9)
Vomiting	0	1 (11.1)	1 (5.9)
METABOLISM AND NUTRITION DISORDERS	1 (12.5)	1 (11.1)	2 (11.8)
Hypoglycemia	0	1 (11.1)	1 (5.9)
Metabolic acidosis	1 (12.5)	0	1 (5.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (12.5)	1 (11.1)	2 (11.8)
Onycholysis	1 (12.5)	0	1 (5.9)
Rash	0	1 (11.1)	1 (5.9)
INFECTIONS AND INFESTATIONS	1 (12.5)	0	1 (5.9)
Upper respiratory tract infection	1 (12.5)	0	1 (5.9)
NERVOUS SYSTEM DISORDERS	0	1 (11.1)	1 (5.9)
Headache	0	1 (11.1)	1 (5.9)

Reported dictionary version: MedDRA 18.1
Note: Incidence is based on the number of participants, not the number of events.

Serious adverse event/deaths/other significant events

Deaths

There were no deaths reported in either of the two paediatric studies (DIA3018 and DIA1055).

Serious Adverse Events (SAEs) during the Phase 3 study DIA3018

A summary of participants in the safety analysis set with serious TEAEs by SOC and PT regardless of rescue medication is provided in Table 9. Eight participants receiving canagliflozin (9.5%) and 5 participants receiving placebo (5.7%) reported serious TEAEs. Seven of these 8 events occurred in participants receiving canagliflozin 100 mg and 1 in canagliflozin 300 mg. The events were balanced across several SOCs. None of the serious TEAEs were considered by the investigator to be related to canagliflozin.

Table 9: Number of Participants with Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term Regardless of Rescue Medication; Safety Analysis Set (Study JNJ-28431754DIA3018)

		Canagliflozin		
	Placebo	100 mg	300 mg	Combined
Analysis set: Safety	87	67	17	84
Participants with 1 or more SAEs	5 (5.7%)	7 (10.4%)	1 (5.9%)	8 (9.5%)

Table 9:	Number of Participants with Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term Regardless of Rescue Medication; Safety Analysis Set (Study JNJ-28431754DIA3018)			
	Placebo	Canagliflozin 100 mg	Canagliflozin 300 mg	Combined
System organ class Preferred term				
Infections and infestations	0	2 (3.0%)	0	2 (2.4%)
Erysipelas	0	1 (1.5%)	0	1 (1.2%)
Pneumonia	0	1 (1.5%)	0	1 (1.2%)
Metabolism and nutrition disorders	2 (2.3%)	2 (3.0%)	0	2 (2.4%)
Diabetic ketoacidosis	1 (1.1%)	1 (1.5%)	0	1 (1.2%)
Hyperglycaemia	0	1 (1.5%)	0	1 (1.2%)
Diabetes mellitus inadequate control	1 (1.1%)	0	0	0
Gastrointestinal disorders	0	0	1 (5.9%)	1 (1.2%)
Pancreatitis acute	0	0	1 (5.9%)	1 (1.2%)
Hepatobiliary disorders	0	1 (1.5%)	0	1 (1.2%)
Cholelithiasis	0	1 (1.5%)	0	1 (1.2%)
Immune system disorders	0	1 (1.5%)	0	1 (1.2%)
Anaphylactic reaction	0	1 (1.5%)	0	1 (1.2%)
Psychiatric disorders	0	1 (1.5%)	0	1 (1.2%)
Suicide attempt	0	1 (1.5%)	0	1 (1.2%)
Injury, poisoning and procedural complications	1 (1.1%)	0	0	0
Ankle fracture	1 (1.1%)	0	0	0
Pregnancy, puerperium and perinatal conditions	1 (1.1%)	0	0	0
Abortion spontaneous	1 (1.1%)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (1.1%)	0	0	0
Tonsillar hypertrophy	1 (1.1%)	0	0	0

Key: SAE = serious adverse event
Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 26.0.

Serious Adverse Events during the Phase 1 study (DIA1055)

There were no serious adverse events reported during the Phase 1 study (DIA1055). None of the participants discontinued the study drug due to an adverse event.

Adverse Events of Special Interest during the Phase 3 study (DIA3018)

Diabetic Ketoacidosis

The incidence of ketosis/acidosis-related adverse events was balanced in the canagliflozin and placebo groups (Table 10). Two of these events were serious, 1 was reported in a participant receiving placebo and the second, in a participant receiving canagliflozin 100 mg.

Table 10: Treatment-Emergent Ketosis/Acidosis by Preferred Term Regardless of Rescue Medication; Safety Analysis Set (Study JNJ-28431754DIA3018)

		Canagliflozin		
	Placebo	100 mg	300 mg	Combined
Analysis set: Safety	87	67	17	84
Participants with 1 or more ketosis/acidosis-related AEs	5 (5.7%)	4 (6.0%)	1 (5.9%)	5 (6.0%)
System organ class Preferred term				
Metabolism and nutrition disorders	3 (3.4%)	3 (4.5%)	0	3 (3.6%)
Ketosis	1 (1.1%)	2 (3.0%)	0	2 (2.4%)
Diabetic ketoacidosis	1 (1.1%)	1 (1.5%)	0	1 (1.2%)
Metabolic acidosis	1 (1.1%)	0	0	0
Investigations	2 (2.3%)	1 (1.5%)	1 (5.9%)	2 (2.4%)
Blood ketone body increased	2 (2.3%)	1 (1.5%)	1 (5.9%)	2 (2.4%)
Renal and urinary disorders	0	0	1 (5.9%)	1 (1.2%)
Ketonuria	0	0	1 (5.9%)	1 (1.2%)

Note: Percentages Calculated with The Number of Participants In Each treatment group As Denominator.
Note: Incidence Is Based On The Number of Participants Experiencing At Least One Adverse Event, Not The Number of Events.

Fractures

Three participants experienced bone fractures during the study. Two of these participants received placebo and one received canagliflozin 100 mg. The subject on canagliflozin 100 mg reported a thumb fracture which could not be confirmed by an external adjudication. The event was non-serious, mild in severity, and not considered by the investigator to be related to canagliflozin.

Pancreatitis

One participant who had a history of acute pancreatitis prior to enrolment experienced another episode of pancreatitis during the study, when the participant was receiving 100 mg canagliflozin, and was hospitalized. The acute pancreatitis was resolved on temporary withdrawal of study drug and did not re-occur after re-initiation of the study drug. The AE was moderate in severity and was considered by the investigator to be doubtfully related to the study drug. The endpoint adjudication committee confirmed the event to be pancreatitis. The participant resumed study drug and was later re-randomized to canagliflozin 300 mg and completed the study without any recurrence.

Adverse Events of Special Interest during the Phase 1 study (DIA1055)

There were no pre-defined AESIs for the study. A few AEs of clinical interest were reported which included asymptomatic hypoglycemia, metabolic acidosis, and rash.

One participant who was receiving canagliflozin 300 mg experienced 4 episodes of asymptomatic hypoglycemia based on fingerstick blood glucose measurements on Day 3 (3.88 mmol/L [70 mg/dL]), Day 11 (3.61 mmol/L [65 mg/dL]), Day 15 (3.55 mmol/L [64 mg/dL]), and Day 23 (3.83 mmol/L [69

mg/dL]) with resolution of each episode within less than 3.5 hours. These events were considered to be mild in intensity and doubtfully related to the study drug by the investigator.

One participant who was receiving canagliflozin 100 mg experienced an episode of metabolic acidosis on Day 14. At that time, the participant was asymptomatic, had normal glucose levels, and no ketones present in the urinalysis. The subject's bicarbonate level was within the normal range at the follow-up visit (i.e. 10 days after Day 14). The adverse event of metabolic acidosis was considered to be moderate in intensity and very likely related to the study drug by the investigator.

One participant who was receiving canagliflozin 300 mg experienced a rash on Day 9. The rash was described as a slightly pruritic, papular lesion localized to the right anterior wrist and forearm. The investigator judged this event as contact dermatitis or eczema, mild in intensity, and doubtfully related to study drug. The rash was treated with a topical hydrocortisone cream and had resolved by the follow-up visit.

Laboratory findings

There were no clinically important differences between canagliflozin and placebo regarding changes over time in laboratory parameters.

Safety in special populations

Elderly

Renal function and risk of volume depletion should be taken into account. This is already included in the SmPC (see SmPC section 4.4).

Renal impairment

For treatment of diabetic kidney disease as add on to standard of care (e.g. ACE-inhibitors or ARBs), a dose of 100 mg canagliflozin once daily should be used (see Table 1). Because the glycaemic lowering efficacy of canagliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe renal impairment, if further glycaemic control is needed, the addition of other anti-hyperglycaemic agents should be considered. For dose adjustment recommendations according to eGFR refer to Table 1.

Table 1: Dose adjustment recommendations in adults and children aged 10 years and older [a]

eGFR (mL/min/1.73 m²) or CrCl (mL/min)	Total daily dose of canagliflozin
≥ 60	Initiate with 100 mg. In patients tolerating 100 mg and requiring additional glycaemic control, the dose can be increased to 300 mg.
30 to < 60[b]	Use 100 mg.
< 30[b, c]	Continue 100 mg for patients already taking Invokana[d]. Invokana should not be initiated.

[a] See sections 4.4, 4.8, 5.1, and 5.2.
[b] If further glycaemic control is needed, the addition of other anti hyperglycaemic agents should be considered
[c] With urinary albumin/creatinine ratio > 300 mg/g
[d] Continue dosing until dialysis or renal transplantation.

Hepatic impairment

For patients with mild or moderate hepatic impairment, no dose adjustment is required. Canagliflozin has not been studied in patients with severe hepatic impairment and is not recommended

for use in these patients. This is reflected accordingly in the SmPC (see SmPC sections 4.2 and 5.2).

Paediatric population
No dose adjustment is required for the treatment of type 2 diabetes mellitus in children aged 10 years and above. This is reflected accordingly in the SmPC. (see SmPC sections 4.2 5.1 and 5.2).
Clinical efficacy and safety of Invokana have not been established in children below 10 years of age.

Safety related to drug-drug interactions and other interactions

Interaction studies have only been performed in adults.

Discontinuation due to adverse events

In the Phase 3 study (DIA3018), of 87 participants receiving placebo and 84 receiving canagliflozin 1 in each treatment group (1.1% vs 1.2%) reported 1 or more TEAEs leading to discontinuation.

The participant on placebo reported MedDRA PT Mood swings while the participant on canagliflozin reported MedDRA PT Generalized tonic-clonic seizures; the participant with the seizure event had a history of epilepsy and the event was considered by the investigator not to be related to canagliflozin.

In the Phase 1 study (DIA1055), none of the participants discontinued the study drug due to an adverse event.

Post-marketing experience

A cumulative search of the MAH's global safety database retrieved 20 cases involving the use of canagliflozin in paediatric patients aged ≥10 years and <18 years old or where age group is reported as adolescent/child. None of the post-marketing cases retrieved in this search reported any new significant safety information on the paediatric age group.

2.6.1. Discussion on clinical safety

Results from the Phase 1 study (DIA1055) showed that PK/PD profiles in the paediatric population were consistent with those observed in adults.

In the Phase 3 study (DIA3018) more commonly (≥2%) reported TEAEs in participants receiving canagliflozin versus placebo included headache (10.7% vs. 3.4%), dizziness (3.6% vs. 1.1%), nasopharyngitis (9.5% vs. 5.7%), rhinitis (4.8% vs. 2.3%), urinary tract infection (7.1% vs. 4.6%), vomiting (6.0% vs. 2.3%), nausea (4.8% vs. 1.1%) and abdominal pain (3.6% vs. 0%).

In addition, various TEAEs of genital mycotic or bacterial infections were reported in paediatric patients receiving canagliflozin and none with placebo: balanitis candida (2.4% vs. 0%), vulvovaginal candidiasis (2.4% vs. 0%), bacterial vaginosis (1.2% vs. 0%) and genital infection fungal (1.2% vs. 0%).

Vitamin D levels seemed to be slightly reduced in canagliflozin-treated subjects. Indeed, in Study DIA3018, a modest reduction in 25-hydroxy Vitamin D was observed at Week 26 in the canagliflozin group compared to placebo. However, this laboratory finding did not translate into a higher incidence of TEAEs related to Vitamin D deficiency. On the contrary, the incidence of Vitamin D deficiency reported as a TEAE was slightly lower in the canagliflozin group (4 participants, 4.8%) than in the placebo group (6 participants, 6.9%). Moreover, Vitamin D deficiency is a known comorbidity in

paediatric patients with T2DM, and supplementation is recommended for this population regardless of antidiabetic treatment. Therefore, the observed reduction is not considered clinically meaningful, and no update to the product information was deemed necessary.

Adverse events of special interest (AESI) across both studies (DIA3018 and DIA1055) included:

- Hypoglycemia that was documented by blood glucose measurements occurred in both groups (17.9% in canagliflozin vs. 16.1% in placebo) in study DIA3018 and in 1 participant on 300 mg canagliflozin in study DIA1055.

- Ketosis/acidosis-related AEs were comparable in the canagliflozin and placebo groups. Three DKA events were confirmed by external adjudication in study DIA3018. Two of the DKA events were serious, 1 was reported in a participant receiving placebo and 1 in a participant receiving canagliflozin 100 mg. In study DIA1055 one participant receiving canagliflozin 100 mg experienced an episode of metabolic acidosis. A DKA warning including information on how to manage this condition is already part of SmPC section 4.4. Moreover, in response to the observed events and based on pharmacokinetic considerations, a warning was added to Section 4.4 of the SmPC indicating that the risk of DKA may be increased in children with low body weight when receiving the 300 mg dose of canagliflozin.

- One SAE of pancreatitis was reported in Study DIA3018 in a participant receiving canagliflozin 100 mg. There were no reports of pancreatitis in Study DIA1055.

No deaths, amputations, or malignancies were reported in Study DIA3018 and Study DIA1055.

Overall, the results of the two paediatric studies show that the safety profile for canagliflozin in children and adolescents aged 10 to less than 18 years with T2DM is similar to the established safety profile in adults with T2DM, with no new adverse drug reactions (ADRs) or new safety signals identified.

Once approved canagliflozin would be the third SGLT-2 inhibitor besides dapagliflozin and empagliflozin which are already marketed in the EU for the treatment of children and adolescents with type 2 diabetes aged 10 to less than 18 years.

2.6.2. Conclusions on clinical safety

Study DIA3018 and Study DIA1055 confirm that the safety profile of Invokana in children and adolescents (≥10 to <18 years) with T2DM is consistent with the known safety profile in adults with T2DM.

Available post-marketing data suggest intended off-label treatment in paediatric patients who were mostly treated for T2DM (where reported). No clinically important new risks were identified from the review of the post-marketing cases in children and adolescents (≥10 to <18 years) with T2DM.

Except for the potential effect of canagliflozin on vitamin D levels, there were no clinically important differences between canagliflozin and placebo regarding changes over time in laboratory parameters, vital signs, developmental parameters or other observations related to safety in the two paediatric studies DIA3018 and DIA1055.

In conclusion, based on the review of available data presented in this application, Invokana (canagliflozin 100 mg and 300 mg once daily) is considered to have an acceptable safety profile in children and adolescents (≥10 to <18 years) with T2DM.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Risk management plan

The MAH submitted an RMP version 13.1 and an updated RMP version 13.2 during the assessment.

3.1. Safety Specification

Summary of the safety concerns

Not changed

3.2. Pharmacovigilance plan

Not changed

3.3. Risk minimisation measures

Routine risk minimisation measures

Not changed

Additional risk minimisation measures

Not changed

3.4. Overall conclusion on the RMP

The CHMP endorsed the Risk Management Plan version 13.2 (Date of sign-off 14 January 2025).

4. Changes to the Product Information

As a result of this type 2 variation, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. In addition, the MAH took the opportunity to update the information of local representative in the package leaflet.

4.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- Full user testing in compliance with the legislative requirements was successfully completed in January 2013, on the original INVOKANA patient leaflet (100 mg and 300 mg tablets).

- A supplementary Focus Test was also successfully completed in May 2013 following revisions to the INVOKANA patient leaflet at D120.
- The package leaflet in the current application has the same format as previously tested.
- No additional safety issues have been identified.
- No new route of administration is proposed.
- With the proposed variation application, only minor changes were introduced in the patient leaflet to list the new indication.
- The proposed changes to the package leaflet reflect language that is consistent with the currently approved leaflet.

4.2. Significance of paediatric studies

NA

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

Current approved clinical indication in adults:
INVOKANA (canagliflozin) is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see SmPC sections 4.4, 4.5 and 5.1.

Proposed new paediatric indication (**in bold**)
*INVOKANA (canagliflozin) is indicated for the treatment of adults **and children aged 10 years and older** with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:*

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see SmPC sections 4.4, 4.5 and 5.1.

The applicant does not propose any changes to the dosage form, route of administration, or dosing regimen via this application.

5.1.2. Available therapies and unmet medical need

The recommended treatment for paediatric T2DM is similar to that on for the adults population, with emphasis on a step-wise approach starting with lifestyle modifications, particularly diet and exercise,

followed by the use of a single medical therapy and later by two therapies in combination. The aim is that the patient achieves and maintains low levels of glucose in the blood in order to prevent long-term complications.

For a long time, the only two approved treatment options for paediatric patients with T2DM in most countries were metformin and insulin. Recently, additional treatment options have become available in the EU for children and adolescents aged 10 to less than 18 years, e.g. the GLP-1 receptor agonists Liraglutide (Victoza), Exenatide extended-release once-weekly injection (Bydureon), Dulaglutide (Trulicity) and the SGLT-2 inhibitors Dapagliflozin (Forxiga) and Empagliflozin (Jardiance).

5.1.3. Main clinical studies

Thought this variation application, the MAH is seeking to extend the indication for Invokana (canagliflozin 100 mg and 300 mg once daily) to the paediatric patients ≥10 to <18 years of age with T2DM based on the final results from the following two clinical trials:

- Study JNJ-28431754DIA3018 (Study DIA3018), that was a randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicenter Phase 3 study in participants with T2DM ≥10 and <18 years of age who had inadequate glycaemic control (i.e. HbA1c of ≥6.5% to ≤11.0%). The total duration of the study was approximately 59 weeks.
- Study JNJ-28431754DIA1055 (Study DIA1055), that was an open-label, sequential, multiple-dose (14 days of dosing), multicenter Phase 1 study of canagliflozin in 2 treatment groups in children and adolescents (≥10 to <18 years of age) who were diagnosed with T2DM and on a stable regimen of metformin (at a dose of at least 1,000 mg per day) for at least 8 weeks before screening.

  The studies were part of the completed PIP.

5.2. Favourable effects

The primary endpoint results and the secondary endpoint analyses from the phase 3 study DIA3018 clearly show that canagliflozin is effective at reducing HbA1c and plasma glucose levels in paediatric T2DM patients between 10 and 18 years of age. In case no sufficient anti-hyperglycaemic effect is achieved with the 100 mg dose, the DIA3018 data suggest that up-titration to 300 mg is beneficial to further improve blood glucose control. Treatment with canagliflozin was also associated with a slight reduction in body weight, which is considered a favourable effect in overweight/obese paediatric T2DM patients. Moreover, plasma triglycerides were reduced in canagliflozin-treated patients.

5.3. Uncertainties and limitations about favourable effects

The patient group that was up-titrated from 100 mg to 300 mg was relatively small (n=17), specifically the subgroup of patients aged ≥10 to <15 years (n=6). Thus, evidence for a benefit of the 300 mg dose in the younger age group is only limited.

While about 75% of the included population were overweight or obese, 24.0 % of the patients had normal weight (one patient even with underweight). It is uncertain whether the currently proposed doses (that are identical with the adult doses) can be transferred to the normal weight paediatric population without safety concerns or whether a dose of ≤100 mg might be warranted in normal weight paediatric T2DM patients. A statement in the SmPC section 4.2 is added to indicate that in children (specifically those weighing <50 kg), caution is advised when up-titrating to the 300 mg dose, since safety data is limited for the resulting exposure levels. Statements in the SmPC sections 4.4 and 5.2 are also included.

5.4. Unfavourable effects

Results from the Phase 1 study (DIA1055) showed that the safety profile in the paediatric population was consistent with the corresponding information available for the adult populations.

In the Phase 3 study (DIA3018) more commonly (≥2%) reported TEAEs in participants receiving canagliflozin versus placebo included headache (10.7% vs. 3.4%), dizziness (3.6% vs. 1.1%), nasopharyngitis (9.5% vs. 5.7%), rhinitis (4.8% vs. 2.3%), urinary tract infection (7.1% vs. 4.6%), vomiting (6.0% vs. 2.3%), nausea (4.8% vs. 1.1%) and abdominal pain (3.6% vs. 0%).

In addition, various TEAEs of genital mycotic or bacterial infections were reported in paediatric patients receiving canagliflozin and none with placebo: balanitis candida (2.4% vs. 0%), vulvovaginal candidiasis (2.4% vs. 0%), bacterial vaginosis (1.2% vs. 0%) and genital infection fungal (1.2% vs. 0%).

Canagliflozin seemed to slightly reduce Vitamin D levels at week 26 and 52 as compared to placebo.

Adverse events of special interest (AESI) across both studies (DIA3018 and DIA1055) included:

- Hypoglycemia that was documented by blood glucose measurements occurred in both groups (17.9% in canagliflozin vs. 16.1% in placebo) in Study DIA3018 and in 1 participant on 300 mg canagliflozin in Study DIA1055.
- Ketosis/acidosis-related AEs were comparable in the canagliflozin and placebo groups. Three DKA events were confirmed by external adjudication in study DIA3018. Two of the DKA events were serious, 1 was reported in a participant receiving placebo and 1 in a participant receiving canagliflozin 100 mg. In study DIA1055 one participant receiving canagliflozin 100 mg experienced an episode of metabolic acidosis. A DKA warning including information on how to manage this condition is already part of SmPC section 4.4. In response to the observed events and based on pharmacokinetic considerations, a warning was also added to Section 4.4 of the SmPC indicating that the risk of DKA may be increased in children with low body weight when receiving the 300 mg dose of canagliflozin.
- One SAE of pancreatitis was reported in Study DIA3018 in a participant receiving canagliflozin 100 mg. There were no reports of pancreatitis in Study DIA1055.
- No deaths, amputations, or malignancies were reported in either study.

Overall, the results of the two paediatric studies show that the safety profile for canagliflozin in children and adolescents aged 10 to less than 18 years with T2DM is similar to the established safety profile in adults with T2DM, with no new adverse drug reactions (ADRs) or new safety signals identified.

5.5. Uncertainties and limitations about unfavourable effects

No uncertainties and limitations about unfavourable effects have been identified.

5.6. Effects Table

Table 1. Effects Table for Invokana (canagliflozin) for the treatment of T2DM in children and adolescents (≥10 to <18 years)

Table 2.

Effect	Short description	Unit	Canagliflozin N=84	Placebo N=87	Uncertainties Strength of evidence	References
Favourable Effects						
at 26 weeks						
Change in HbA1c from baseline at week 26	**Primary endpoint**	% mean (SD)	-0.4 (1.44)	+0.3 (1.56)	Phase 3 data; p = 0.002	Study DIA 3018
Change in HbA1c from baseline at week 26 in participants taking metformin (with or without insulin)	Major secondary endpoint	% mean (SD)	-0.4 (1.50)	+0.3 (1.63)	Phase 3 data; p = 0.012	Study DIA 3018
Effect on fasting plasma glucose (FPG) after 26 weeks	Major secondary endpoint	mg/dL mean (SE)	-11.5 (6.86)	15.3 (6.68)	Phase 3 data; (LOCF) p = 0.003	Study DIA 3018
Proportion of participants with HbA1c <7.5%, <7.0% and <6.5% after 26 weeks	Major secondary endpoint	%	<7.5%: 64.9% <7.0%: 51.9% <6.5%: 41.6%	<7.5%: 40.0% <7.0%: 27.5% <6.5%: 11.3%	Phase 3 data	Study DIA 3018
Proportion of participants receiving rescue therapy after 26 weeks	Major secondary endpoint	%	6.0%	27.6%	Phase 3 data	Study DIA 3018
% change from baseline in body weight after 26 weeks	Major secondary endpoint	% (SD)	-1.6 (0.51)	-0.0 (0.51)	Phase 3 data (LOCF) p = 0.019	Study DIA 3018
% change from baseline in body weight after 26 weeks, **cana 100 mg vs. placebo**	Other efficacy analysis	% (SD)	-0.25 (0.173)	+0.34 (0.184)	Phase 3 data (MMRM) p = 0.020	Study DIA 3018
% change from baseline in body weight after 26 weeks, **up-titrated to cana 300 mg vs. placebo**	Other efficacy analysis	% (SD)	-0.41 (0.167)	+0.33 (0.175)	Phase 3 data (MMRM) p = 0.002	Study DIA 3018
at 52 weeks						
Change in HbA1c from baseline at week 52	Major secondary endpoint	% (SE)	-0.32 (0.184)	+0.70 (0.182)	Phase 3 data (MMRM) p < 0.001	Study DIA 3018
Effect on FPG after 52 weeks	Major secondary endpoint	mg/dL	-16.4 (6.98)	19.2 (6.90)	Phase 3 data; (LOCF) p <0.001	Study DIA 3018
Proportion of participants with HbA1c <7.5%, <7.0% and <6.5% after 52 weeks	Major secondary endpoint	%	<7.5%: 69.0% <7.0%: 54.9% <6.5%: 36.6%	<7.5%: 29.3% <7.0%: 22.7% <6.5%: 12.0%	Phase 3 data	Study DIA 3018
Proportion of participants receiving rescue therapy after 52 weeks	Major secondary endpoint	%	11.9%	46.0%	Phase 3 data	Study DIA 3018
% change from baseline in body weight after 52 weeks	Major secondary endpoint	% (SD)	-0.5 (0.69)	0.4 (0.69)	Phase 3 data (LOCF) p = 0.293	Study DIA 3018
Unfavourable Effects						
Hypoglycemia (documented by blood glucose measurements)	Treatment-emergent AE	n (%)	15 (17.9%)	14 (16.1%)	Phase 3 data	Phase 3 study (DIA3018)
Headache	Treatment-emergent AE	n (%)	9 (10.7%)	3 (3.4%)	Phase 3 data	Phase 3 study (DIA3018)
Dizziness	Treatment-	n (%)	3 (3.6%)	1 (1.1%)	Phase 3 data	Phase 3 study

Effect	Short description	Unit	Canagliflozin N=84	Placebo N=87	Uncertainties Strength of evidence	References
	emergent AE					(DIA3018)
Nasopharyngitis	Treatment-emergent AE	n (%)	8 (9.5%)	5 (5.7%)	Phase 3 data	Phase 3 study (DIA3018)
Rhinitis	Treatment-emergent AE	n (%)	4 (4.8%)	2 (2.3%)	Phase 3 data	Phase 3 study (DIA3018)
Urinary tract infection	Treatment-emergent AE	n (%)	6 (7.1%)	4 (4.6%)	Phase 3 data	Phase 3 study (DIA3018)
Balanitis candida	Treatment-emergent AE	n (%)	2 (2.4%)	0 (0%)	Phase 3 data	Phase 3 study (DIA3018)
Vulvovaginal candidiasis	Treatment-emergent AE	n (%)	2 (2.4%)	0 (0%)	Phase 3 data	Phase 3 study (DIA3018)
Vomiting	Treatment-emergent AE	n (%)	5 (6.0%)	2 (2.3%)	Phase 3 data	Phase 3 study (DIA3018)
Nausea	Treatment-emergent AE	n (%)	4 (4.8%)	1 (1.1%)	Phase 3 data	Phase 3 study (DIA3018)
Abdominal pain	Treatment-emergent AE	n (%)	3 (3.6%)	0 (0%)	Phase 3 data	Phase 3 study (DIA3018)
Ketosis/ diabetic ketoacidosis	Treatment-emergent AE	n (%)	2 (2.4%)	1 (1.1%)	Phase 3 data	Phase 3 study (DIA3018)
Pancreatitis acute	Treatment-emergent AE	n (%)	1 (1.2%)	0 (0%)	Phase 3 data	Phase 3 study (DIA3018)
Reduction of 25-hydroxy Vitamin D	Median change from baseline at week 26	nmol/l	-3.0	+1.5	Phase 3 data	Phase 3 study (DIA3018)

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

The key favourable effect is a clinically relevant and significant reduction in HbA_{1C} after 26 weeks of treatment with 100 mg or 300 mg of canagliflozin (difference canagliflozin vs. placebo: -0.76%). Improvement of blood glucose control by canagliflozin is further confirmed by reduction in fasting plasma glucose, by shifts towards lower HbA_{1c} categories in the responder analysis as well as by a considerable reduction of the proportion of participants requiring rescue medication. Additional favourable effects are a reduction in plasma triglycerides and, specifically in the overweight/obese population, a slight reduction in body weight.

Importance of unfavourable effects

The most important unfavourable effect would be diabetic ketoacidosis (DKA), which, however, occurred at comparable frequency in placebo- and canagliflozin-treated patients. A DKA warning including information on how to manage this condition is already part of SmPC section 4.4. In addition, a warning

has been added in 4.4 of the SmPC in relation to children with low body weight when they receive the 300 mg dose of canagliflozin, since the exposure may exceed the levels observed in adults with the 300 mg dose.

The second most important unfavourable effect is an increase in genital and urinary tract infections, which was more pronounced with canagliflozin than with placebo, probably due to increased urinary glucose excretion. Although most of these adverse events are considered to be temporary and can be treated with antibiotic/antimycotic medications, it cannot be excluded that severe complications may occur in individual cases.

The slight reduction of vitamin D levels by canagliflozin was discussed, since it may be important for individuals with low vitamin D at baseline. Although the effects of reduced Vitamin D levels may not immediately become visible in terms of fractures in the paediatric population, the build-up of bone mass may be slowed down, leading to a lower peak bone mass, which potentially favours bone-related complications in later adulthood. However, this laboratory finding did not translate into a higher incidence of TEAEs related to Vitamin D deficiency. Moreover, Vitamin D deficiency is a known comorbidity in paediatric patients with T2DM, and supplementation is recommended for this population regardless of antidiabetic treatment. Therefore, the observed reduction is not considered clinically meaningful, and no update to the product information was deemed necessary.

Hypoglycaemia (documented by blood glucose measurements) occurred at comparable frequency in canagliflozin- and placebo-treated participants; no severe events occurred, and moderate hypoglycaemia can be quickly managed without serious long-term consequences. Of note, hypoglycaemia is rather unlikely under canagliflozin monotherapy.

The other adverse events detected with a frequency of ≥2% (i.e., headache, dizziness, nasopharyngitis, rhinitis, vomiting, nausea and abdominal pain) are mostly temporary, can be easily managed and do not lead to negative long-term consequences.

Except for the slight reduction of vitamin D levels, no new safety signals were identified in the paediatric population and the observed important unfavourable effects are already adequately addressed in the SmPC.

5.7.2. Balance of benefits and risks

Study DIA3018 showed superior efficacy of Invokana for the treatment of T2DM in children and adolescents (≥10 to <18 years) when compared to placebo. Treatment with canagliflozin resulted in a statistically significant improvement with respect to change from baseline in HbA1c at Week 26 compared to placebo in the overall study population.

A clinically meaningful reduction in HbA1c was observed as early as Week 12 and was sustained up to the end of the trial at Week 52. These results were supported by statistically significant improvements in key secondary efficacy endpoints and were consistent with the efficacy outcomes in adults with T2DM.

The outcomes of these clinical studies support the efficacy of Invokana for the treatment of T2DM in children and adolescents (≥10 to <18 years).

Results from the Phase 1 study DIA1055 showed that PK/PD profiles in the paediatric population were largely consistent with those observed in the adult population.

The results from the Phase 3 study DIA3018 confirmed that at the recommended dose, the safety profile of Invokana (canagliflozin 100 mg and 300 mg once daily) in children and adolescents (≥10 to <18 years) with T2DM is consistent with the known safety profile in adults with T2DM.

Except for a reduction of vitamin D levels, no new risks or new safety signals were identified in children and adolescents aged 10 to less than 18 years with T2DM.

In conclusion, based on the review of the provided efficacy and safety data from the two additionally conducted paediatric studies, Invokana is considered to have a positive benefit-risk profile in children and adolescents (≥10 to <18 years) with T2DM.

5.8. Conclusions

The overall benefit-risk profile of Invokana for the treatment of children and adolescents (≥10 to <18 years) with insufficiently controlled T2DM is positive.

6. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of paediatric patients with type 2 diabetes mellitus aged 10 years old and older for INVOKANA, based on final results from study JNJ-28431754DIA3018 as well as study JNJ-28431754DIA1055. Study JNJ-28431754DIA3018 is a double-blind, placebo-controlled, 2-arm, parallel-group, multicenter Phase 3 study in participants with T2DM >10 and <18 years of age who had inadequate glycemic control (i.e, HbA1c of >6.5% to <11.0%). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 13.2 of the RMP has also been agreed.

In addition, the Marketing authorisation holder (MAH) took the opportunity to the update the list of local representatives in the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP) are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0208/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

7. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Invokana - EMEA/H/C/002649/II/0069