28 May 2020
EMA/306073/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invokana

International non-proprietary name: canagliflozin

Procedure No. EMEA/H/C/002649/II/0046

Note

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

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List of abbreviations

Abbreviation or special term	Explanation
AHA	Antihyperglycemic agent
ACEi	Angiotensin converting enzyme inhibitor
ACM	All-cause mortality
ACR	Albumin-to-creatinine ratio
AE	Adverse event
AHA	Antihyperglycemic agent
AKI	Acute kidney injury
ARB	Angiotensin receptor blocker
BL	Baseline
BMI	Body mass index
B/R	Benefit/Risk
Cana	Canagliflozin
CEC	Clinical Endpoint Committee
CHMP	Committee for medicinal products for human use
CI	Confidence interval
CKD	Chronic diabetic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CV	Cardiovascular
DBP	Diastolic blood pressure
D/C	Discontinuation
DKA	Diabetic ketoacidosis
DKD	Diabetic kidney disease
DN	Diabetic nephropathy
DPP-4	Dipeptidylpeptidase 4
DRI	Direct renin inhibitor
EAC	Endpoint adjudication committee
ECG	Electrocardiogram
eCRF	Electronic case report form

Abbreviation or special term	Explanation
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESKD	End-Stage kidney disease
EU	European Union
EVRT	Event rate
FAS	Full analysis set
FPG	Fasting plasma glucose
GCP	Good clinical practice
GFR	Glomerular filtration rate
GMI	Genital mycotic infection
GTED	Global trial end date
HbA1c	Glycated haemoglobin
HDL	high-density lipoprotein
HHF	Hospitalized heart failure
HUSA	Hospitalized unstable angina
HR	Hazard ratio
IDMC	Independent Data Monitoring Committee
IEAC	Independent endpoint adjudication committee
IRD	Incidence rate difference
ISS	Integrated summary of safety
ITT	Intention to treat
IWRS	Interactive web response system
KDOQI	Kidney Disease Outcomes Quality Inititative
LDL	low-density lipoprotein
LS	Least squares
MAA	Marketing authorization application
MACE	Major adverse CV events
MAH	Marketing authorization holder
MI	Myocardial infarction
MO	Major objection
MoA	Mechanism of action

Abbreviation or special term	Explanation
MRA	Mineralocorticoid receptor antagonists
NDKD	Non-diabetic kidney disease
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PEP	Primary endpoint
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PL	Package leaflet
Plc	Placebo
PT	Preferred term
Pts.	Patients
PVD	Peripheral vascular disease
RAS	Renin angiotensin system
RMP	Risk management plan
RSI	Request for supplementary information
SA	Scientific advice
SAS	Safety analysis set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SCS	Summary of Clinical Safety
SD	Standard deviation
SE	Standard error
SGLT2	Sodium glucose transporter 2
SmPC	Summary of Product Characteristics
SoC	Standard of Care
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TGF	Tubuloglomerular feedback
UACR	Urine albumin-to-creatinine ratio
UTI	Urinary tract infection

Abbreviation or special term	Explanation
VTE	Venous thromboembolic events

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 NV submitted to the European Medicines Agency on 30 July 2019 an application for a variation.

The following variation was **requested** (at initial submission of the variation):

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 and IIIB

Update of sections 4.1 , 4.2, 4.8 and 5.1of the Summary of Product Characteristics to add a new therapeutic indication for INVOKANA (canagliflozin) for the treatment of stage 2 or 3 chronic kidney disease and albuminuria, as an adjunct to standard of care, in adults with type 2 diabetes mellitus. The proposed new indication is based upon new clinical efficacy and safety data from the Phase 3 study: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial (CREDENCE) (DNE3001).
The Package Leaflet is updated in accordance. The RMP version 8.1 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0205/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001030-PIP01-M07 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

This claim was withdrawn by the applicant during the procedure.

Scientific advice

The MAH received Scientific Advice from the CHMP on 19 July 2013 (EMEA/H/SA/1252/3/2013/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise Co-Rapporteur: Kristina Dunder

Timetable	Actual dates
Submission date	30 July 2019
Start of procedure:	17 August 2019
CHMP Co-Rapporteur Assessment Report	14 October 2019
CHMP Rapporteur Assessment Report	15 October 2019
PRAC Rapporteur Assessment Report	22 October 2019
PRAC members comments	23 October 2019
PRAC Outcome	31 October 2019
CHMP members comments	4 November 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 November 2019
Request for supplementary information (RSI)	14 November 2019
CHMP Rapporteur and Co-Rapporteur Assessment Reports	29 January 2020
PRAC Rapporteur Assessment Report	31 January 2020
PRAC members comments	5 February 2020
Updated PRAC Rapporteur Assessment Report	7 February 2020
PRAC Outcome	13 February 2020
CHMP members comments	17 February 2020
Updated CHMP Rapporteur Assessment Report	20 February 2020
2nd Request for supplementary information (RSI)	27 February 2020
PRAC Rapporteur Assessment Report	6 April 2020
PRAC members comments	7 April 2020
Updated PRAC Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	15 April 2020
PRAC Outcome	17 April 2020

Timetable	Actual dates
CHMP members comments	20 April 2020
Updated CHMP Rapporteur Assessment Report	24 April 2020
Oral Explanation	29 April 2020
3rd Request for supplementary information	30 April 2020
PRAC Rapporteur Assessment Report	13 May 2020
CHMP Rapporteur Assessment Report	13 May 2020
CHMP/PRAC comments	18 May 2020
Updated CHMP Rapporteur Assessment Report	20 May 2020
Updated PRAC Rapporteur Assessment Report	20 May 2020
Opinion	28 May 2020

2. Scientific discussion

2.1. Introduction

Canagliflozin is an orally administered sodium-glucose cotransporter 2 (SGLT2) inhibitor. It is approved in the European Union (EU) since November 15th 2013 (Invokana: EMEA/H/C/002649). Canagliflozin can be given as monotherapy or in combination with other medicinal products indicated for the treatment of T2DM.

The current application is based on the recently completed Phase 3 study DNE3001 (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial) (hereafter referred to as 'CREDENCE').

In the CREDENCE study, canagliflozin was compared to placebo in subjects with T2DM and stage 2 or 3 chronic diabetic kidney disease (CKD) and macroalbuminuria.

Based on the results of the CREDENCE study, the MAH sought to extend section 4.1 of the SmPC for Invokana in adults with T2DM with the following new indication:

For the treatment of stage 2 or 3 chronic kidney disease and albuminuria, as an adjunct to standard of care, in adults with type 2 diabetes mellitus.

Updates are proposed to the Summary of Product Characteristics (SmPC), the package leaflet (PIL) and the Risk Management Plan (RMP) based on the assessment of CREDENCE data.

2.2. Non-clinical aspects

No new non-clinical data, other than an updated ERA, have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The applicant has submitted an updated ERA based on the EMEA/CHMP/SWP/4447/00 guideline and the EMA Q&A document on ERA which also includes an assessment for Metformin. This ERA was submitted in 2013 during the first registration of Vokanamet, a related fixed combination drug which additionally includes

Metformin. The update consists mainly in a recalculation of the $PEC_{Surfacewater}$ and all connected values including the risk quotients. The applicant did not identify any risk associated with the extension.

The original ERA was assessed in 2013/2014. As it included the identical tests, no detailed assessment was necessary at this time only some entries in the 'summary of main study results tables' had to be slightly updated. The updated table is presented at the end of this assessment.

The CHMP did not agree with the PEC refinement. First of all the maximal dose of Canagliflozin is 300 mg/d not 100 mg/d on which basis the assessment was conducted. Second the adjustment of the Fpen with sales forecast is not possible in Phase I. But since Phase IIA is reached an adjustment is possible at that stage. Therefore, the Fpen recalculation was assessed anyway.
The applicant was asked to further clarify and, in case the Fpen has to be changed, to recalculate the $PEC_{Surfacewater}$ and all connected values, including the risk quotients.
Furthermore, an experimental logK_{ow} and a BCF study for Canagliflozin were submitted in the course of the first registration, the applicant was asked to include these in the updated ERA.
As NOEC for the Activated Sludge Respiration Inhibition Test (OECD 209) of Canagliflozin the lowest test concentration (100 mg/L) should be used instead of the EC_{15} (368 mg/L).
Moreover, as the summarized results of the test according to OECD TG 308 are not consistent with the results of the first assessment, the applicant was asked to update these.

In May 2014 the EMA safety working party (SWP) decided that a disposal advice should be included in SmPC and package leaflet independent of the conclusions on the ERA. Therefore, the applicant was asked to include the following disposal advice as per EMA template: "*Any unused medicinal product or waste material should be disposed of in accordance with local requirements*."

Summary of main study results on Canagliflozin

Substance (INN/Invented Name): Canagliflozin			
CAS-number (if available):928672-86-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	3.42	Potentially B study on bioaccumulation required
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.42	
	BCF	11 L/kg	Not B
Persistence	DT50	38.5 d in sediment	not P
Toxicity	NOEC or CMR	NOEC = 0.56 mg/L (Daphnia, 21 d)	not T
PBT-statement :	The compound is not considered as PBT nor vPvB following the given parameters.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surface water	1.5 µg/l	µg/L	≥ 0.01 threshold Y
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 121	K_{oc} = 5.9	
Ready Biodegradability Test	OECD 301	Not readily biodegradable	
Aerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50\ water}$: 2.2/6.4 d $DT_{50\ whole\ system}$: 30/39 d $DT_{50\ sediment}$: 25.1/38.5 d	

		Mineralisation: 11.4/4.0 % Bound residues: 34.2/29.4 % Sediment shifting: 65.2/58.1 % (14 d) Transformation Products: 4 TP > 10%			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOErC	⩾ 8	mg/L	mean measured
Daphnia sp. Reproduction Test/ *Daphnia magna*	OECD 211	NOEC	0.56	mg/L	mean measured
Fish, Early Life Stage Toxicity Test/*Species* / *Pimephales promelas*	OECD 210	NOEC	4.8	mg/L	mean measured
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	100	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	11	L/kg	5 % lipidnormalised, no risk of bioaccumulation
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC	⩾ 100	mg/kg dry weight	nominal

2.2.2. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, an increase in environmental exposure is possible.

Nevertheless, no risk for the environment was identified. A disposal advice was included in Section 6.6 of the SmPC. No outstanding issues remained.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacokinetics

No new PK data were submitted.

2.3.3. Pharmacodynamics

No new PD data were submitted.

2.4. Clinical efficacy

2.4.1. Main study

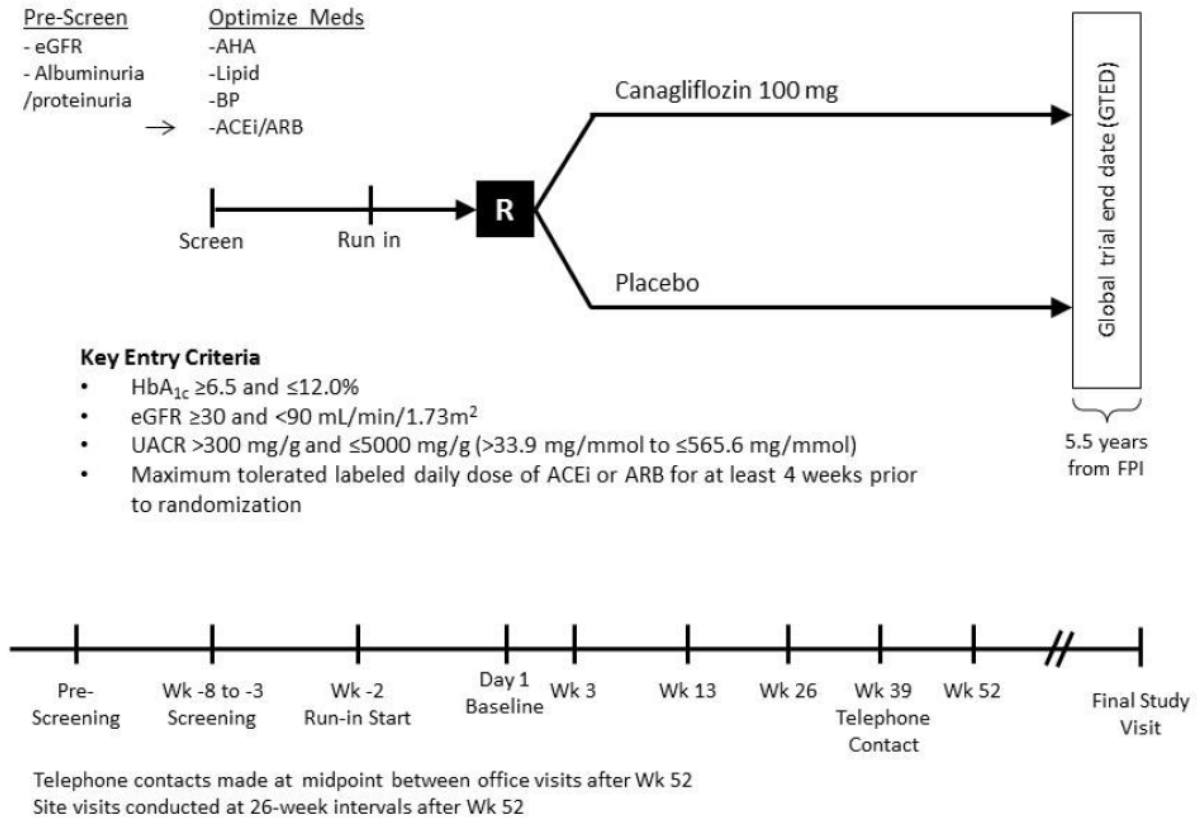
A Randomized, Double-blind, Event-driven, Placebo-controlled, Multicenter Study of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Subjects With Type 2 Diabetes Mellitus and Diabetic Nephropathy (CREDENCE)

Methods

The CREDENCE study was a multicenter, randomised, double-blind, placebo-controlled event-driven phase III study to evaluate the effect of canagliflozin on renal and CV outcomes in patients with T2DM with established nephropathy.

CREDENCE was an event-driven study with a planned duration of 5 to 5.5 years and a target of approximately 844 primary efficacy endpoint events (doubling of serum creatinine, ESKD, renal or CV death.

Figure 1: Study design Diagram



According to the study protocol, the randomized subjects will return to the clinic at Week 3, Week 13, Week 26, and every 26 weeks for laboratory assessments, concomitant medication review, adverse event

collection and determination of clinical endpoints. An interim analysis was planned, when approximately 405 subjects had an adjudicated event within the primary composite endpoint.

Study participants

The original protocol was dated 10 December 2013. The first patient was screened on 21 February 2014 and the first subject was randomized on 24 March 2014.

Key inclusion criteria

In order to be enrolled in this study, the subjects had to meet the following key inclusion criteria:

- male or female ≥30 years-old with a clinical T2DM diagnosis
- HbA1c ≥6.5% to ≤12.0%
- eGFR ≥30 to <90 mL/min/1.73 m^2 (as determined using the Chronic Kidney Disease-Epidemiology Collaboration [CKD-EPI] equation). An overall global target ratio for randomized cohort of approximately 60% : 40% for CKD Stage 3 : CKD Stage 2 was monitored centrally and entry of subjects with stage 2 CKD could be restricted on a regional and/or site basis to keep this CKD Stage 2 vs 3 ratio.
- urinary ACR >300 mg/g to ≤5,000 mg/g (>33.9 mg/mmol to ≤565.6 mg/mmol)
  For the pre-screening assessment where UACR is not routinely measured as per standard of care, it may be substituted by one of the following measures: albumin excretion rate >300 mg/24 hours, urine protein-to-creatinine ratio (PCR) >500 mg/g (>56.5 mg/mmol), or protein excretion rate >500 mg/24 hours.
- All subjects must have been on a stable maximum tolerated labelled daily dose of ACEi or ARB for at least 4 weeks prior to randomization

Key exclusion criteria

Subjects were excluded from study participation, if they met any of the following exclusion criteria:

Diabetes-Related/Metabolic

- History of diabetic ketoacidosis or type 1 diabetes mellitus (T1DM)
- History of hereditary glucose-galactose malabsorption or primary renal glucosuria

Renal/Cardiovascular

- Known medical history or clinical evidence suggesting nondiabetic renal disease
- Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant (Note: Subjects with a history of treated childhood renal disease, without sequelae, could participate).
- Uncontrolled hypertension (systolic blood pressure [SBP] ≥180 and/or diastolic blood pressure [DBP] ≥100 mmHg) by Week -2
- Blood potassium level >5.5 mmol/L during screening
- Myocardial infarction, unstable angina, revascularization procedure (e.g., stent or bypass graft surgery), or cerebrovascular accident within 12 weeks before randomization, or a revascularization procedure was planned during the study
- Current or history of heart failure of New York Heart Association (NYHA) Class IV cardiac disease (The Criteria Committee of the New York Heart Association)
- ECG findings within 12 weeks before randomization that would require urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance)

- History of atraumatic amputation within past 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening. (Note: introduced in protocol Amendment INT-5.)

Other Conditions

- History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix *in situ*, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence)

Medications/Therapies

- Combination use of ACEi and ARB
- Use of MRA or a direct renin inhibitor (DRI) (Note, post-randomization use of MRAs was prohibited until INT-4. Thereafter, treatment with an MRA was allowed if determined medically necessary over the course of the double-blind treatment period, while continuing on study drug.)

  Note: If deemed clinically appropriate at the discretion of the investigator, subjects may be removed from therapy with MRA or DRI during screening. Subjects who are off therapy with MRA or DRI for at least 8 weeks prior to randomization may be considered eligible for enrolment.

Treatments

After completion of initial screening, the potentially eligible subjects entered a 2-week run-in period, during which single-blind placebo capsules were administered once daily to assess compliance.

During the double-blind treatment period, the doses and treatment regimens were:

- Canagliflozin 100 mg tablets, administered orally once daily until the end of the study
- Placebo administered orally once daily until the end of the study

The study drug was administered at the study site on day 1. After day 1, the study participants were instructed to take 1 capsule of canagliflozin 100 mg or matching placebo once daily before the first meal of the day during the study period. The projected study duration was 5 to 5.5 years (adjusted from 5.5 years to 5 – 5.5 years in amendment INT-4).

Background therapies:

Concomitant therapies:

- Medications are optimized during screening period as required by local standard guidelines (including antihyperglycemic, lipid-lowering, and anti-hypertensive therapy).
- ACEi or ARB should remain stable after the maximum tolerated dose is achieved.
- Medication doses should be kept stable for approximately 4 weeks prior to randomization.
- Medications with impact on serum creatinine levels (e.g., NSAIDs, trimethoprim, cimetidine, probenecid, aminoglycosides, amphotericin, ketoconazole, and clofibrate) should be kept stable during the screening period.

Prohibited therapies (see also exclusion criteria above):

- other SGLT2 inhibitors
- combinations of ACEi and ARB
- direct renin inhibitors (DRI)
- mineralocorticoid receptor antagonists (MRA) (after amendment INT-4, however, MRA treatment was allowed during the double-blind treatment period if deemed medically necessary).

Objectives

Primary objective

In subjects with T2DM, Stage 2 or 3 CKD and macroalbuminuria who are receiving standard of care, to assess the efficacy of canagliflozin relative to placebo in reducing

- the composite endpoint of ESKD, doubling of serum creatinine, and renal or CV death

For secondary and exploratory objectives, please refer to section "Outcomes/endpoints" below.

Safety Objective: To assess the overall safety and tolerability of canagliflozin.

Outcomes/endpoints

Primary efficacy outcome:

composite endpoint of

- the first occurrence of ESKD (defined as initiation of maintenance dialysis for at least 1 month, or renal transplantation, or a sustained eGFR of <15 mL/min/1.73m^2 determined by CKD-EPI formula and confirmed by repeat central laboratory measure ≥30 days and preferably within 60 days)
- doubling of serum creatinine (from baseline average; sustained and confirmed by repeat central laboratory measure ≥30 days and preferably within 60 days)
- renal death (death in subjects with ESKD, without initiating renal replacement therapy, no other cause of death determined via adjudication)
- or CV death: death due to MI, stroke, heart failure, sudden death, death during a CV procedure or as a result of procedure-related complications, presumed sudden CV death, death of unknown cause, or death resulting from a documented CV cause other than those listed above (e.g., aneurysm, peripheral vascular disease [PVD]).

An independent endpoint adjudication committee (IEAC) adjudicates all components of this composite endpoint.

Secondary efficacy outcome:

- composite endpoint of CV death and hospitalized heart failure
- the composite endpoint of CV death, non-fatal myocardial infarction (MI), and non-fatal stroke (ie, 3-point MACE)
- hospitalized heart failure
- the renal composite endpoint of ESKD, doubling of serum creatinine, and renal death
- CV death
- all-cause death
- the CV composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalized heart failure, and hospitalized unstable angina

Exploratory efficacy variables:

- composite endpoint of ESKD, renal or CV death
- individual components of the renal and cardiovascular composite endpoints (ESKD, doubling of serum creatinine, renal death, CV death, fatal or non-fatal MI, fatal or nonfatal stroke, hospitalized heart failure, hospitalized unstable angina)
- estimated glomerular filtration rate (eGFR)
- eGFR slope (total, acute, chronic)
- changes in albuminuria over time (ACR, albumin-to-creatinine ratio)

Other (metabolic) efficacy assessments:

- Changes in HbA1c
- Changes in fasting plasma glucose (FPG)
- Body weight
- Blood pressure
- Fasting plasma lipids

Sample size

The study was planned to include ~ 4200 subjects with the aim to observe occurrence of primary efficacy events in 844 unique randomized subjects until the global trial end date. The study was designed to have a power of 90% to detect a 20% relative risk reduction (effect of treatment discontinuation on the primary endpoint) at a 2-sided significance level of 5%.

Additionally, it was assumed that the composite endpoint occurs in the placebo arm at an event rate of 6.5% per year. Moreover, a premature treatment discontinuation rate of 6% and an overall lost-to-follow-up were considered in sample size determination. The duration of enrolment was expected to be 27 months, and the study duration (from first randomization of a subject to last end-of-study visit) was estimated to be 60 months.

It is noted that the sample size was originally planned to be 3,700 subjects but was increased to 4,200 subjects with amendment INT-4 from January 19th 2016 to increase the likelihood of accruing endpoints within the primary composite.

Additionally, amendment INT-4 removed the global cap limiting enrollment of subjects with eGFR ≥60 to <90 mL/min/1.73 m^2 to ~25%. Instead, a ratio of 60%:40% regional and/or site level CKD Stage 3 (eGFR ≥30 to <60 mL/min/1.73 m2; first category): CKD Stage 2 (eGFR ≥60 to <90 mL/min/1.73 m2; second category) was allowed. Moreover, text was revised to list post-baseline use of MRAs as restricted rather than strictly prohibited.

Randomisation

To assess compliance, the study included a 2-week placebo run-in period (+ 14 days) starting at Visit 1. Randomization number, medication numbers, and treatment code, which is linked to the randomization schedule, are assigned at baseline (day 1) via central randomization using an interactive web response system (IWRS). Subjects will be randomly assigned to treatment groups according to on a computer-generated randomization schedule prepared under sponsor supervision. The randomization was

balanced by using randomly permuted blocks and was stratified by pre-treatment eGFR (≥30 to <45, ≥45 to <60, ≥60 to <90 mL/min/1.73m^2).

Blinding (masking)

Blinding at study site level
The run-in period was performed in a single-blinded, the randomised treatment period in a double-blinded manner.

The canagliflozin 100 mg dose was administered as a gray-colored hard, gelatine capsule containing a tablet embedded in microcrystalline cellulose. The matching placebo capsules consisted of microcrystalline cellulose within a gray-colored, hard, gelatine capsule. The study drug was packaged as individual bottles.

Unblinding to the study site was only possible in case of emergencies requiring knowledge of treatment status for further treatment/course of action. Breaking the blinding had to be reported to the sponsor as soon as possible (telephone contact available 24/7). The treatment assignment revealed after unblinding was retained with the subject's source documents in a secure manner (e.g., sealed envelope) to avoid unblinding to the study site or sponsor personnel. No site level emergency unblinding of any subjects took place during the study.

Urine glucose results were not reported by the central laboratory. Investigators were counselled to avoid performing local urinalysis with dipstick unless required for urgent medical management.

Blinding at sponsor level
All randomization codes were released to the sponsor after completion of the study at the time of database lock. For the purpose of the planned interim analysis, the randomization codes were disclosed only to those authorized to have access in order to carry out the analysis.

Monitoring and adjudication committees
Suspected endpoint events (ESKD, doubling of serum creatinine, death, MI, stroke, hospitalized unstable angina, hospitalized congestive heart failure) were to be verified and confirmed by an Endpoint Adjudication Committee (CEC) that remains blinded to treatment assignment.

An Independent Data Monitoring Committee (IDMC) was responsible for monitoring unblinded safety and endpoint data by treatment group throughout the course of the trial. Based upon this monitoring, the IDMC recommends changes to the conduct of the trial to the chairpersons of the CREDENCE steering committee. Moreover, the IDMC reviews and evaluates unblinded safety and efficacy results from the pre-specified interim analysis.

Statistical methods

Data from CREDENCE were analyzed using the following 3 analysis sets:

- Intent-to-treat (ITT): all randomized subjects, including data from Day 1 to the last study contact date up to the global trial end date (GTED)
- On-study: all subjects who received at least 1 dose of study drug, including data from Day 1 to the last study contact date up to the GTED
- On-treatment: all subjects who received at least 1 dose of study drug, including data from Day 1 to the last dose date plus X days, or the last study contact date, whichever occurred earlier; X was 2

days for laboratory and vital sign measurements and 30 days for adverse event, CV, renal, and mortality endpoints.

Analyses of the primary and secondary endpoints were based on the ITT analysis set. Premature discontinuation of study treatment did not comprise study completion and was not a criterion for withdrawal from the study. All subjects who prematurely discontinued study treatment were to continue subsequent study visits and post-treatment follow-up evaluations. An On-treatment analysis (which includes primary composite endpoints with an onset after the initiation of double-blind study medication and before the last study medication date plus 30 days) was performed to assess the consistency of the primary efficacy analysis.

The comparison of canagliflozin versus placebo for the primary efficacy endpoint was analyzed using a stratified Cox proportional hazard model including treatment as the explanatory variable, with stratification of the baseline hazard by screening eGFR (⩾30 to <45, ⩾45 to <60, ⩾60 to <90 mL/min/1.73 m2). To assess the robustness of the primary efficacy analysis, sensitivity analysis of the primary composite endpoint using a log-rank test stratified by screening eGFR was also performed. The estimated treatment effect was expressed as the relative risk reduction (1 minus HR), HR, and 95% CI. Ratios of cause-specific hazards between the treatment groups were obtained for each component of the primary efficacy composite endpoint, using similar methods as for the primary efficacy composite endpoint.

The cumulative incidence of the primary composite endpoint over time was presented using Kaplan-Meier curves for each of the 2 treatment groups. Cumulative incidence curves were also presented for each of the components of the primary composite (doubling of serum creatinine, ESKD, renal death, and CV death) in order to assess competing risks, depending on the event counts of the individual components.

An interim analysis was planned after approximately 405 subjects experienced an adjudicated primary composite endpoint, as confirmed by the EAC. At the interim analysis, the primary efficacy endpoint was tested with alpha of 0.01 as determined by the alpha spending function taking form of $\alpha\tau^{\varphi}$ with τ as the information fraction and $\varphi = 2.19$. After review of the interim results, the IDMC recommended stopping the study for efficacy based on the pre-specified stopping rules (2-sided p-value for comparison of the primary composite endpoint of <0.01, and 2-sided p-value of the composite endpoint of ESKD, renal death, and CV death comparison of <0.025, both in favor of canagliflozin 100 mg). Based on the IDMC recommendation, the decision was taken to conclude the study and the GTED was announced on 16 July 2018 and final visits were subsequently conducted. A total of 585 subjects were confirmed by the EAC to have experienced a primary composite endpoint through the end of the GTED period on 30 October 2018. The test of the primary composite endpoint was based on the data accrued through the final clinic visit where the significance level was determined by the alpha spending function (two-sided alpha=0.022).

The consistency of the treatment effect on the primary composite endpoint was assessed across different baseline demographic variables (eg, age, race, sex) as well as other important baseline disease characteristics (eg, history of prior CV disease, duration of diabetes, baseline HbA1c, baseline eGFR, baseline ACR).

A pre-specified multiple imputation analysis was performed to assess the impact, if any, of missing follow-up for either clinical outcomes or laboratory assessments on the robustness of the primary efficacy analysis. As described in the supplemental SAP (Appendix 9), event imputation for the clinical outcomes (ie, dialysis, renal transplantation and CV/renal death) proceeded via a retrieved dropout approach, whereas missing laboratory data was imputed assuming the data were missing at random for the on-treatment period and assumed to follow a copy control pattern for the off-treatment period. This process was repeated 1,000 times. The imputed data were integrated with the observed data to generate 1,000 replicates of the primary composite endpoint data and the data were combined into a single inferential summary using Rubin's rule.

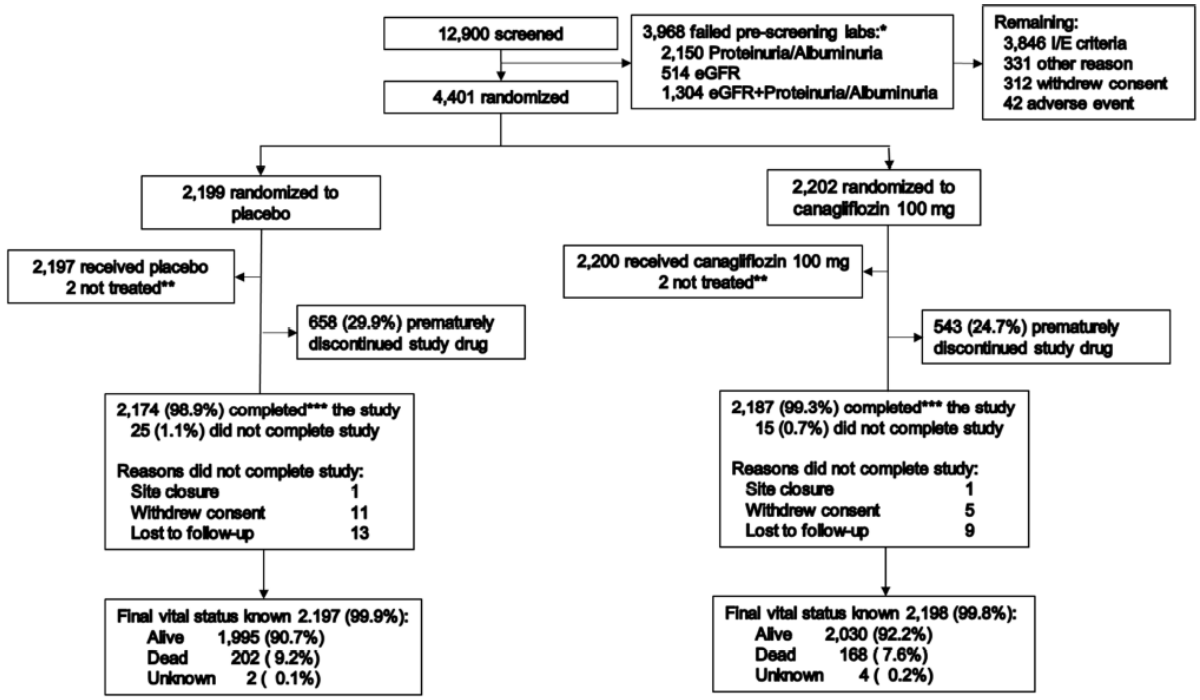
The secondary outcomes were analyzed using methods similar to those described for the primary composite endpoint analysis.

Testing of the secondary efficacy endpoints was based on the data accrued through the final clinic visit (which was planned regardless of the study stopping after the interim analysis or proceeding to the planned completion of 844 primary composite events) using a two-sided alpha of 0.038. A closed testing procedure was implemented to control the family-wise type I error rate at 5% for the primary and secondary endpoints. The hypothesis of superiority on primary and major secondary efficacy endpoints of canagliflozin versus placebo was tested in a hierarchical order. If an individual test during any step was not statistically significant, later tests were considered nominal.

Results

Participant flow

Figure 2 Patient disposition and study participation



* Includes failed prescreening of eGFR and/or proteinuria/albuminuria
** Subjects did not receive study drug and were therefore excluded from the On-treatment and On-study analysis sets
*** Completed was defined as a subject who was followed until a time point after the notification of the GTED or until the time of death for subjects who died prior to the GTED notification

Of the 12,900 screened subjects, 8,499 subjects were not eligible for study participation due to the following reasons:

- 3,968 failed pre-screening assessments (2,150: proteinuria/albuminuria; 514: eGFR; 1,304: eGFR+proteinuria/albuminuria)
- 3,846 failed because of inclusion/exclusion criteria
- 331: other reasons
- 312: withdrew consent
- 42: adverse events

4,401 subjects were randomized (2,199 to placebo and 2,202 to canagliflozin 100 mg).

Duration of follow-up

The study had a mean follow-up time of 2.6 years (136.23 weeks) with comparable study durations between the canagliflozin (137.93 weeks) and the placebo (135.71 weeks) group.

Completion of the study on study drug

There were 4 randomised patients (2 in each group) who did not receive study drug (Figure 2).

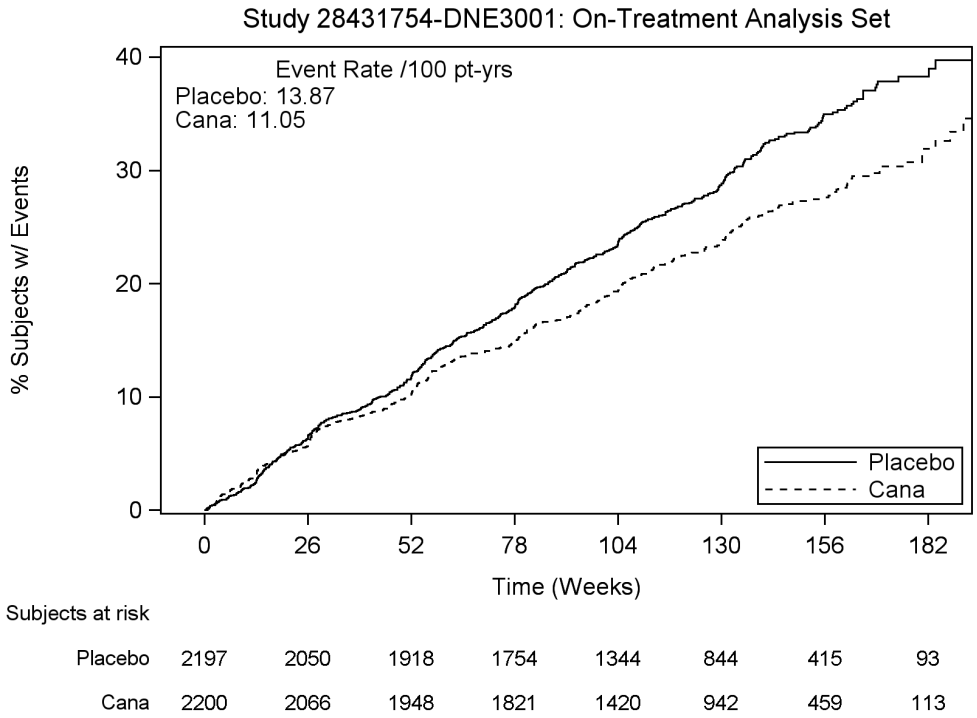
A subject was considered having completed the study, regardless of whether the subject was on or off study drug, if the subject was followed from randomization until a time point after the notification of the global trial end date (GTED) or until the time of death (for subjects who died prior to GTED notification). On placebo, the study was completed by 2,174 (98.9%) patients, while 2187 (99.3%) patients completed the study on canagliflozin.

More patients discontinued the study drug prematurely in the placebo group (658; 29.9%) as compared to the canagliflozin group (543; 24.7%). 11 patients in the placebo group and 5 patients in the canagliflozin group withdrew consent. 13 placebo-treated subjects and 9 canagliflozin-treated subjects were lost to follow up. One patient in each group discontinued the study due to site closure.

At the end of the study, the vital status was unknown for 2 placebo and 4 canagliflozin subjects.

The Kaplan-Meier plot of time to discontinuation from study medication (on treatment analysis set) in Figure 3 shows that the rate of study drug discontinuation was higher in the placebo group (13.87/100 subject years) as compared to the canagliflozin group (11.05/100 patient years). The most common reasons for discontinuation were adverse events (12.5%) and personal reasons (8.5 %).

Figure 3 Kaplan-Meier plot of time to discontinuation from study medication (on treatment analysis set)



The interim analysis was conducted on July 9th 2018, when 413 subjects had experienced the primary composite endpoint (adjudicated by the EAC). The IDMC recommended stopping the study early, because the efficacy objectives specified in the IDMC charter were met. The GTED period was announced on July 16th 2018, and 585 primary composite endpoints were accrued through the end of the GTED on October 30th 2018.

Recruitment

The study was conducted at 690 centers in 34 countries. 26.9% of the subjects (n=1,182) were enrolled in North America, 19.6% (n=864) in Europe, 21.4% (n=941) in Central/South America, and 32.1 % (n=1414) in the rest of the world.

The study lasted from February 21st 2014 (Date first subject signed informed consent) to October 30th 2018 (Date of last observation for last subject recorded as part of the database).

Conduct of the study

Changes in the conduct of the study

The study was completed on 30 October 2018.

The protocol underwent 6 substantial global amendments. The most important changes are listed in the following:

INT-1 (12 June 2014): The amendment included mainly clarifications. In addition, an assessment of stroke disability was introduced to evaluate stroke outcomes.

INT-2 (03 February 2015): The amendment included e.g. several clarifications, additional instructions on eligibility of subjects for study enrolment, a widening of the range of pre-screening albuminuria/proteinuria measures. Moreover, other changes regarding to the pre-screening phase were included, e.g. subjects who failed local laboratory pre-screening assessments were allowed to repeat the laboratory tests.

Most importantly, however, the inclusion criteria were revised to allow subjects with higher baseline HbA1c. The upper HbA1c limit was changed from "≤10.5%" to "≤12.0%". It is noted, however, that this change was not accepted by DE, which resulted in the country-specific amendment DEU-1 (see below).

INT-3 (29 September 2015): This amendment intended to inform investigators of additional safety reporting requirements associated with DKA. Moreover, the event time frame for the exclusion criteria #7 (myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident), #14 (major surgery) and #18 (current use of SGLT2 inhibitor) was changed from "prior to screening" to "prior to randomization". Finally, background information, pre-clinical and clinical data related to bone fracture and decrease in bone mineral density were added.

INT-4 (19 January 2016): Two secondary endpoints were added and the hierarchical order of testing of the secondary endpoints was adjusted. Moreover, the sample size was expanded from 3,700 to 4,200 subjects to increase the likelihood of accruing endpoints within the primary composite. Finally, the global cap that limited enrolment of subjects with eGFR ≥60 to <90 mL/min/1.73 m^2 to ~25% was removed to allow more of these subjects to participate in the study. Text was added to allow a ratio of 60%:40% regional and/or site level CKD Stage 3 (eGFR ≥30 to <60 mL/min/1.73 m2; first category): CKD Stage 2 (eGFR ≥60 to <90 mL/min/1.73 m2; second category).
Moreover, text was revised to list post-baseline use of MRAs as restricted rather than strictly prohibited (in connection with a hyperkalemia warning).

INT-5 (06 May 2016): The amendment added several clarifications, e.g. that all potential sustained doublings of serum creatinine values are derived from a baseline average determination rather than a single baseline value. Moreover, exclusion criterion #16 was added to exclude patients with a history of atraumatic amputation within past 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower limb extremity within 6 months of screening.

Addition of new safety information and guidance regarding subject management surrounding the event of lower-extremity amputation. A statement was added that study drug should be interrupted for subjects developing conditions associated with amputation. The Italian health authority did not agree with some of the changes made in INT-5 regarding subjects with a history of amputation, resulting in the country-specific amendment ITA-1 (see below).

INT-6 (06 September 2017):
Two new secondary endpoints were added and the order of hierarchical testing of the endpoints was adjusted. Moreover, the number of events (number of subjects meeting the primary composite endpoint) required for interim analysis was reduced from 540 to 405. Furthermore, occurrences of pancreatitis were designated as adverse events of special interest. Finally, several clarifications were added.

Moreover, 4 country-specific amendments (Japan, Germany, India, Italy) were added to the study protocol. The changes influencing selection of study participants are detailed in the following:

Japan (JPN-1: 24 October 2014; JPN-2: 23 February 2018): JPN-1was based on INT-1 and intended to clarify that all potential sustained doublings of serum creatinine values are derived from a baseline average determination rather than a single baseline value. Moreover, guidance was added regarding foot care and reducing risk of amputation and an exclusion criterion was added to exclude individuals at a higher risk for lower-extremity amputation. Additional safety reporting requirements associated with DKA where also clarified by JPN-1.

JPN-2 was based on INT-6 and corrected 3 collection time-points for fasting plasma glucose to match the global protocol.

Germany (DEU-1: 05 October 2015): The German health authority did not approve the increase in the upper inclusionary threshold of HbA1c that was changed in the global Amendment INT-2 from ≤10.5% to ≤12.0%. Therefore, the upper limit was kept at ≤10.5% in Germany.

India (IND-1: 05 February 2016): based on global Amendment INT-4, an archive sample collection at week 13 should be added (or week 26 if missed at week 13).

Italy (ITA-1: 20 September 2016): The primary reason for the country-specific amendment in Italy (based on global Amendment INT-5) was that the Italian health authority did not agree with some of the changes made in INT-5 regarding subjects with a history of amputation. Specifically, they did not agree with: (1) the exclusion of subjects with atraumatic amputation within the past 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene or critical ischemia of the lower extremity within 6 months of screening; instead, the Italian healthy authority required that subjects with any history of these events (regardless of duration) be excluded and (2) the requirement that subjects who experienced a lower-extremity amputation or developed a condition that led to an amputation would be temporarily discontinued from study drug; instead, the Italian healthy authority required that such subjects be permanently discontinued from study drug. All other global changes in INT-5 were incorporated.

Protocol deviations
Overall, there were 1,356 patients with protocol deviations. There were numerically more disallowed concomitant treatments in the placebo group as compared to the canagliflozin group. The other deviations were balanced between the treatment groups. The most common deviations assigned to the largest group of "other" deviations were related to delays in signing of updated versions of the Informed Consent Form following randomization.

Table 1: Protocol Deviations in Study 28431754-DNE3001 (ITT analysis set)

TSIDV02: Protocol Deviations (Study 28431754-DNE3001: Intent-To-Treat Analysis Set)

Protocol Deviation Coded Term	Placebo (N=2199) n (%)	Cana (N=2202) n (%)	Total (N=4401) n (%)
Total no. subjects with Protocol Deviations	679 (30.9)	677 (30.7)	1356 (30.8)
Developed withdrawal criteria but not withdrawn	1 (<0.1)	2 (0.1)	3 (0.1)
Entered but did not satisfy criteria	143 (6.5)	147 (6.7)	290 (6.6)
Received a disallowed concomitant treatment	52 (2.4)	23 (1.0)	75 (1.7)
Received wrong treatment or incorrect dose	23 (1.0)	19 (0.9)	42 (1.0)
Other	539 (24.5)	557 (25.3)	1096 (24.9)

Note: Percentages calculated with the number of subjects in each group as the denominator.
Note: Subjects may be included in more than one category.
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Baseline data

The following tables provide an overview over the baseline characteristics:

Table 4: Baseline Demographic Characteristics (Study 28431754-DNE3001: Intent-To-Treat Analysis Set)

	----- Placebo ---- (N=2199)	------ Cana ------ (N=2202)	------ Total ----- (N=4401)
Sex, n (%)			
N	2199	2202	4401
Male	1467 (66.7)	1440 (65.4)	2907 (66.1)
Female	732 (33.3)	762 (34.6)	1494 (33.9)
Age (Years)			
N	2199	2202	4401
Category, n (%)			
< 65	1151 (52.3)	1193 (54.2)	2344 (53.3)
≥ 65	1048 (47.7)	1009 (45.8)	2057 (46.7)
Mean (SD)	63.2 (9.23)	62.9 (9.17)	63.0 (9.20)
Median	64.0	64.0	64.0
Range	(34;89)	(30;86)	(30;89)
Age (Years)			
N	2199	2202	4401
Category, n (%)			
< 75	1971 (89.6)	1986 (90.2)	3957 (89.9)
≥ 75	228 (10.4)	216 (9.8)	444 (10.1)
Mean (SD)	63.2 (9.23)	62.9 (9.17)	63.0 (9.20)
Median	64.0	64.0	64.0
Range	(34;89)	(30;86)	(30;89)
Age (Years)			
N	2199	2202	4401
Category, n (%)			
< 55	384 (17.5)	400 (18.2)	784 (17.8)
55 - < 65	767 (34.9)	793 (36.0)	1560 (35.4)
65 - < 75	820 (37.3)	793 (36.0)	1613 (36.7)
≥ 75	228 (10.4)	216 (9.8)	444 (10.1)
Mean (SD)	63.2 (9.23)	62.9 (9.17)	63.0 (9.20)
Median	64.0	64.0	64.0
Range	(34;89)	(30;86)	(30;89)
Race, n (%)			
N	2199	2202	4401
White	1444 (65.7)	1487 (67.5)	2931 (66.6)
Black or African American	112 (5.1)	112 (5.1)	224 (5.1)
Asian	452 (20.6)	425 (19.3)	877 (19.9)
American Indian or Alaska Native	42 (1.9)	36 (1.6)	78 (1.8)
Native Hawaiian or Other Pacific Islander	16 (0.7)	9 (0.4)	25 (0.6)
Multiple	32 (1.5)	32 (1.5)	64 (1.5)
Other	91 (4.1)	95 (4.3)	186 (4.2)
Unknown	6 (0.3)	1 (<0.1)	7 (0.2)
Not Reported	4 (0.2)	5 (0.2)	9 (0.2)
Ethnicity, n (%)			
N	2199	2202	4401
Hispanic or Latino	706 (32.1)	717 (32.6)	1423 (32.3)
Not Hispanic or Latino	1457 (66.3)	1436 (65.2)	2893 (65.7)
Not Reported	20 (0.9)	24 (1.1)	44 (1.0)
Unknown	16 (0.7)	25 (1.1)	41 (0.9)

	----- Placebo ---- (N=2199)	------ Cana ------ (N=2202)	------ Total ----- (N=4401)
Region, n (%)			
N	2199	2202	4401
North America	608 (27.6)	574 (26.1)	1182 (26.9)
Central/South America	465 (21.1)	476 (21.6)	941 (21.4)
Europe	410 (18.6)	454 (20.6)	864 (19.6)
Rest of the World	716 (32.6)	698 (31.7)	1414 (32.1)

Note: Percentages calculated with the number of subjects with non-missing values in each group as the denominator.
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Table 5: Baseline Anthropometric Characteristics (Study 28431754-DNE3001: Intent-To-Treat Analysis Set)

	----- Placebo ---- (N=2199)	------ Cana ------ (N=2202)	------ Total ----- (N=4401)
Baseline Weight (kg)			
N	2198	2202	4400
Mean (SD)	86.9 (20.66)	87.2 (20.80)	87.1 (20.73)
Median	84.5	84.5	84.5
Range	(40;196)	(38;199)	(38;199)
Baseline BMI (kg/m2)			
N	2196	2196	4392
Category, n (%)			
< 30	1028 (46.8)	998 (45.4)	2026 (46.1)
≥ 30	1168 (53.2)	1198 (54.6)	2366 (53.9)
Mean (SD)	31.3 (6.18)	31.4 (6.17)	31.3 (6.18)
Median	30.4	30.6	30.5
Range	(15;63)	(15;71)	(15;71)

Note: Percentages calculated with the number of subjects with non-missing values in each group as the denominator.
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Demographic characteristics (intent-to-treat analysis set)

The mean age of the overall patient population was 63.0 years. 46.7% of patients were ≥65 years and 10.1% were ≥75 years. 66.1% of patients were male and 33.9% were female.

Randomisation occurred worldwide (Europe: 19.6%; North America: 26.9%; Central/South America: 21.4%; "rest of the world": 32.1%). 66.6% of patients were white, 19.9% were Asian and 5.1% black or African American.

Baseline anthropometric Characteristics (intent-to-treat analysis set)

The mean body weight of the overall population was 87.1 kg, corresponding to a mean BMI of 31.3 kg/m^2. Overall, 53.9% of the population had a BMI ≥ 30 kg/m^2.

Baseline diabetes characteristics (intent-to-treat analysis set; see also Table 2)

Overall, the mean diabetes duration was 15.78 years with 74.7% of patients having T2DM since ≥ 10 years. The mean HbA1c for all subjects was 8.27%, which is consistent with mild to moderate hyperglycemia. In 53.2% of patients, the baseline HbA1c was ≥8.0%. An HbA1c > 10 (n = 450) was measured in 10.2% of patients. It is noted that with amendment INT-2 (03 February 2015), the upper HbA1c limit for inclusion was changed from "≤10.5%" to "≤12.0%".

The subjects showed a mean baseline eGFR of 56.2 mL/min/1.73 m^2, reflecting the inclusion criteria of eGFR ≥30 to <90 mL/min/1.73 m^2. The baseline eGFR was <60.0 mL/min/1.73 m^2 in ~60% of the population. The eGFR strata of 30 to <45, 45 to <60, and 60 to <90 mL/min/1.73 m^2 comprised 27.1%, 28.8%, and 35.4%

of all subjects. The proportion of patients in the highest eGFR stratum reflects amendment INT-4 that permitted up to 40% of patients to be randomized with an eGFR ≥60 to <90 mL/min/1.73 m^2. 56 patients had been stratified into the incorrect eGFR stratum, including 2 subjects without a screening eGFR measurement. Impaired kidney function of the study subjects was also reflected by a urinary albumin-to-creatinine ratio (ACR) of 1,381 mg/g at baseline (> 1,000 mg/g in 46.6% of subjects). Normo- or microalbuminuria was reported in 12.0% of all subjects at baseline, although all patients were required to have macroalbuminuria (ACR > 300 mg/g) at screening.

Table 2 Baseline diabetes characteristics (intent-to-treat analysis set)

	------- Placebo ------- (N=2199)	--------- Cana -------- (N=2202)	-------- Total -------- (N=4401)
Baseline Hemoglobin A1c (%)			
N	2198	2201	4399
Category, n (%)			
< 7	327 (14.9)	323 (14.7)	650 (14.8)
7 - < 8	702 (31.9)	704 (32.0)	1406 (32.0)
8 - < 9	589 (26.8)	555 (25.2)	1144 (26.0)
9 - ≤ 10	344 (15.7)	405 (18.4)	749 (17.0)
> 10	236 (10.7)	214 (9.7)	450 (10.2)
Mean (SD)	8.26 (1.322)	8.27 (1.305)	8.27 (1.313)
Median	8.10	8.10	8.10
Range	(5.3;14.7)	(5.2;14.3)	(5.2;14.7)
Subjects in Randomization Strata, n (%)			
N	2199	2202	4401
Screening eGFR 30 to <45 mL/min/1.73m2	656 (29.8)	657 (29.8)	1313 (29.8)
Screening eGFR 45 to <60 mL/min/1.73m2	639 (29.1)	640 (29.1)	1279 (29.1)
Screening eGFR 60 to <90 mL/min/1.73m2	904 (41.1)	905 (41.1)	1809 (41.1)
Duration of Diabetes (Years)			
N	2199	2202	4401
Category, n (%)			
<10	550 (25.0)	563 (25.6)	1113 (25.3)
≥ 10	1649 (75.0)	1639 (74.4)	3288 (74.7)
Mean (SD)	16.02 (8.577)	15.55 (8.676)	15.78 (8.629)
Median	15.00	15.00	15.00
Range	(0.1;57.7)	(0.0;55.0)	(0.0;57.7)
Subjects with microvascular complications of diabetes, n (%)			
N	2199	2202	4401
Any	2199 (100)	2202 (100)	4401 (100)
Autonomic Neuropathy	121 (5.5)	112 (5.1)	233 (5.3)
Other Diabetic Neuropathy	327 (14.9)	327 (14.9)	654 (14.9)
Peripheral Diabetic Neuropathy	894 (40.7)	890 (40.4)	1784 (40.5)
Diabetic Retinopathy	947 (43.1)	935 (42.5)	1882 (42.8)
Diabetic Nephropathy	2199 (100)	2202 (100)	4401 (100)
Subjects with number of microvascular complications of diabetes, n (%)			
N	2199	2202	4401
≥ 1	2199 (100)	2202 (100)	4401 (100)
1	794 (36.1)	779 (35.4)	1573 (35.7)
2	793 (36.1)	834 (37.9)	1627 (37.0)
3	612 (27.8)	589 (26.7)	1201 (27.3)
≥ 2	1405 (63.9)	1423 (64.6)	2828 (64.3)
Baseline eGFR (mL/min/1.73m2)			
N	2199	2201	4400
Category, n (%)			
< 15	1 (<0.1)	1 (<0.1)	2 (<0.1)
15 - < 30	89 (4.0)	83 (3.8)	172 (3.9)
30 - < 45	597 (27.1)	594 (27.0)	1191 (27.1)
45 - < 60	636 (28.9)	630 (28.6)	1266 (28.8)
60 - < 90	770 (35.0)	788 (35.8)	1558 (35.4)
≥ 90	106 (4.8)	105 (4.8)	211 (4.8)
Mean (SD)	56.0 (18.33)	56.3 (18.16)	56.2 (18.24)
Median	54.0	55.0	54.0
Range	(12;113)	(11;124)	(11;124)
Baseline ACR(mg/g)			
N	2199	2202	4401
Mean (SD)	1396.5 (1322.15)	1365.3 (1370.18)	1380.9 (1346.34)
Median	931.0	923.0	927.0
Range	(3;11437)	(4;14435)	(3;14435)

Table 2 continued: Baseline diabetes characteristics (intent-to-treat analysis set)

	------- Placebo ------- (N=2199)	--------- Cana -------- (N=2202)	-------- Total -------- (N=4401)
Baseline ACR(mg/mmol)			
N	2199	2202	4401
Mean (SD)	157.93 (149.537)	154.41 (154.959)	156.17 (152.267)
Median	105.30	104.40	104.75
Range	(0.3;1293.8)	(0.4;1632.6)	(0.3;1632.6)
Baseline ACR Group (mg/g), n (%)			
N	2199	2202	4401
≤ 1000	1163 (52.9)	1185 (53.8)	2348 (53.4)
> 1000	1036 (47.1)	1017 (46.2)	2053 (46.6)
Baseline Albuminuria, n (%)			
N	2199	2202	4401
Normo-albuminuria	15 (0.7)	16 (0.7)	31 (0.7)
Micro-albuminuria	245 (11.1)	251 (11.4)	496 (11.3)
Non-nephrotic range macroalbuminuria	1669 (75.9)	1702 (77.3)	3371 (76.6)
Nephrotic range macroalbuminuria	270 (12.3)	233 (10.6)	503 (11.4)
Baseline Systolic Blood Pressure (mmHg)			
N	2199	2202	4401
Category, n (%)			
≤ 140	1189 (54.1)	1205 (54.7)	2394 (54.4)
>140	1010 (45.9)	997 (45.3)	2007 (45.6)
Mean (SD)	140.2 (15.63)	139.8 (15.59)	140.0 (15.61)
Median	140.0	139.0	140.0
Range	(90;199)	(89;198)	(89;199)
Baseline Diastolic Blood Pressure (mmHg)			
N	2199	2202	4401
Category, n (%)			
≤ 90	2025 (92.1)	2017 (91.6)	4042 (91.8)
>90	174 (7.9)	185 (8.4)	359 (8.2)
Mean (SD)	78.4 (9.38)	78.2 (9.36)	78.3 (9.37)
Median	80.0	79.0	79.0
Range	(46;118)	(43;110)	(43;118)
Baseline Serum HDL Cholesterol (mmol/L) - Fasting			
N	2188	2186	4374
Category, n (%)			
< 1.01	791 (36.2)	823 (37.6)	1614 (36.9)
≥ 1.01	1397 (63.8)	1363 (62.4)	2760 (63.1)
Mean (SD)	1.150 (0.3377)	1.150 (0.3553)	1.150 (0.3466)
Median	1.090	1.090	1.090
Range	(0.28;3.05)	(0.26;4.35)	(0.26;4.35)
Baseline Serum HDL Cholesterol (mg/dL) - Fasting			
N	2188	2186	4374
Mean (SD)	44.5 (13.06)	44.5 (13.75)	44.5 (13.41)
Median	42.0	42.0	42.0
Range	(11;118)	(10;168)	(10;168)

Table 2 continued: Baseline diabetes characteristics (intent-to-treat analysis set)

	------- Placebo ------- (N=2199)	--------- Cana -------- (N=2202)	-------- Total -------- (N=4401)
Baseline Serum LDL Cholesterol (mmol/L) - Fasting			
N	2188	2186	4374
Category, n (%)			
≤ 1.81	617 (28.2)	646 (29.6)	1263 (28.9)
>1.81	1571 (71.8)	1540 (70.4)	3111 (71.1)
Mean (SD)	2.481 (1.0321)	2.507 (1.1035)	2.494 (1.0683)
Median	2.330	2.310	2.320
Range	(0.25;9.35)	(0.17;8.59)	(0.17;9.35)
Baseline Serum LDL Cholesterol (mg/dL) - Fasting			
N	2188	2186	4374
Mean (SD)	95.9 (39.92)	97.0 (42.68)	96.4 (41.32)
Median	90.0	89.0	90.0
Range	(10;362)	(7;332)	(7;362)
Baseline Triglycerides (mmol/L)			
N	2188	2186	4374
Mean (SD)	2.225 (1.6722)	2.244 (1.5868)	2.234 (1.6300)
Median	1.790	1.840	1.810
Range	(0.35;23.41)	(0.34;22.11)	(0.34;23.41)
Baseline Triglycerides (mg/dL)			
N	2188	2186	4374
Mean (SD)	197.0 (148.11)	198.8 (140.54)	197.9 (144.37)
Median	159.0	163.0	160.0
Range	(31;2073)	(30;1958)	(30;2073)
History of Amputation, n (%)			
N	2199	2202	4401
Yes	115 (5.2)	119 (5.4)	234 (5.3)
No	2084 (94.8)	2083 (94.6)	4167 (94.7)

Note: Percentages calculated with the number of subjects with non-missing values in each group as the denominator.
Note: Non-nephrotic range macroalbuminuria is defined as ACR >300 mg/g and ≤ 3000 mg/g.
Note: Nephrotic range macroalbuminuria is defined as ACR > 3000 mg/g.
Note: ACR = Urine albumin/creatinine
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Baseline characteristics with regard to cardiovascular history (intent-to-treat analysis set)

50.4% of patients had a history of CV disease at baseline. 96.8% of the patients had a history of hypertension and 14.8% of heart failure.

Table 3: Baseline characteristics – cardiovascular history

Table 7: Baseline Characteristics - Cardiovascular History (Study 28431754-DNE3001: Intent-To-Treat Analysis Set)

	-------- Placebo -------- (N=2199)	---------- Cana --------- (N=2202)	--------- Total --------- (N=4401)
History of CV Disease, n (%)			
Yes	1107 (50.3)	1113 (50.5)	2220 (50.4)
Atherosclerotic vascular disease history(a), n (%)			
History of Coronary	660 (30.0)	653 (29.7)	1313 (29.8)
History of Cerebrovascular	358 (16.3)	342 (15.5)	700 (15.9)
History of Peripheral Vascular Disease	515 (23.4)	531 (24.1)	1046 (23.8)
Any	1107 (50.3)	1113 (50.5)	2220 (50.4)
History of hypertension, n (%)			
Yes	2129 (96.8)	2131 (96.8)	4260 (96.8)
History of Heart Failure, n (%)			
Yes	323 (14.7)	329 (14.9)	652 (14.8)

Note: (a) Some participants had ≥ 1 type of atherosclerotic disease.
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Use of concomitant medication and treatment compliance

Medications at randomisation

ACEi and ARBs:
For at least 4 weeks prior to randomization, all subjects had to be on a stable maximum tolerated labelled daily dose of ACEi or ARB. Five subjects had entered the study without being treated with ACEi or ARB. All other patients were on a maximum tolerated labeled dose of an ACEi or ARB. The maximum-labelled dose was reached by 72% of the subjects with balanced distribution over the treatment groups. In 27.9% of subjects, the maximum labelled dose was not reached. This was mostly due to hypotension, acute renal failure, or hyperkalemia (reasons similar across treatment groups).

Other CV therapies:
At randomization, 92.1% of all subjects were on at least 1 CV therapy, with no difference between treatment groups. Most common CV therapies: statins (69.0%), anti-thrombotics (including aspirin) (59.6%), calcium channel blockers (48.4%), beta-blockers (40.2%), loop (21.7%) and non-loop (28.9%) diuretics. No subject was taking both types of diuretics concomitantly. Only 0.5 % of all subjects used MRAs at baseline.

Antihyperglycemic agents (AHAs):
At randomization, 99.5% of subjects received AHA therapy. Most common medications were insulin (65.5%), biguanides (57.8%), sulphonyl ureas (28.8%) and dipeptidyl peptidase 4 (DPP-4) inhibitors (17.1%).

Table 12: AHA Medication at Baseline (Study 28431754-DNE3001: On-Treatment Analysis Set)

Concomitant Medication	Placebo (N=2197) n (%)	Cana (N=2200) n (%)	Total (N=4397) n (%)
Total no. subjects with therapy	2184 (99.4)	2189 (99.5)	4373 (99.5)
Alpha glucosidase inhibitors	73 (3.3)	66 (3.0)	139 (3.2)
Biguanides	1268 (57.7)	1275 (58.0)	2543 (57.8)
Dipeptidyl peptidase 4 (DPP-4) inhibitors	373 (17.0)	378 (17.2)	751 (17.1)
GLP-1 agonist	94 (4.3)	89 (4.0)	183 (4.2)
Insulin	1431 (65.1)	1451 (66.0)	2882 (65.5)
Sulfonylurea	656 (29.9)	611 (27.8)	1267 (28.8)
Thiazolidinediones (PPARγ)	65 (3.0)	71 (3.2)	136 (3.1)
Other AHA agents	81 (3.7)	79 (3.6)	160 (3.6)

Note: Percentages calculated with the number of subjects in each group as the denominator.
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Changes in concomitant medications during study

ACEi and ARBs:
At the end of the study, 10.1% of all subjects (canagliflozin group: 9.0%; placebo: 11.2%) in the Intent-to-treat analysis set had discontinued their ACEi or ARB.

Table 9: Concomitant RAAS Medication Discontinued at the End of the Study for Subjects on ACEi/ARB at baseline (Study 28431754-DNE3001: Intent-To-Treat Analysis Set)

	Placebo (N=2194) n (%)	Cana (N=2200) n (%)	Total (N=4394) n (%)
No. of subjects discontinued RAAS inhibitor	246 (11.2)	199 (9.0)	445 (10.1)

Note: Percentages calculated with the number of subjects in each group as denominator.
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Nearly all subjects entered the study on ACEi/ ARB (99.9%). At week 52 97.1% of subjects were still on ACEi/ ARB therapy, at week 104 94.6% and at week 208 93.5%.

Other CV therapies:
A greater proportion of subjects in the placebo group (40.3%) initiated a CV therapy compared with the canagliflozin group (31.1%). The most common newly initiated CV therapies were loop diuretics (12.0%) and calcium channel blockers (10.1%). The percentage of patients initiating a CV therapy was numerically higher in the placebo as compared to the canagliflozin group for all types of medications. MRAs were newly initiated by 3.8 % of all subjects. This had become possible through amendment INT-4, which changed the instructions regarding post-baseline use of MRAs from "strictly prohibited" to "restricted" (in connection with a hyperkalemia warning).

Antihyperglycemic agents (AHAs):
A greater proportion of subjects in the placebo group (19.8%) as compared to the canagliflozin group (14.9%) initiated a new AHA therapy, most commonly insulin (5.2%) and DPP-4 inhibitors (4.5%). The percentage of patients initiating an AHA therapy was numerically higher in the placebo as compared to the canagliflozin group for all types of medications.

Overall, 1.3 % of subjects received a prohibited therapy with a non-investigational SGLT2 inhibitor (canagliflozin: 1.1%; placebo: 1.5%) with the majority of subjects being off study drug (canagliflozin group: 0.9%; placebo group: 1.0%).

Treatment compliance

A log of all drug dispensed and returned was maintained. Subjects were clearly instructed with regard to compliance with study procedures at screening visit. During the course of the study, any subject who was not compliant with taking the study drug or with making required clinic visits was re-educated with additional instructions. The initial compliance was assessed during the 2-week single-blind placebo run-in period. Overall, 34 subjects (0.8%) discontinued the study medication due to poor compliance. These patients were evenly distributed over the treatment groups (canagliflozin: 0.7%; placebo: 0.8%).

Numbers analysed

The full analysis set includes all randomised patients assessed according to their randomised study drug assignment (2201 patients in the Cana group, 2199 patients in the placebo group).

The SAS includes all randomised patients who received at least 1 dose of study drug and for whom any data are available from any time after first dose of study drug until the end of the study, assessed according to the treatment they actually received.

Outcomes and estimation

Primary composite endpoint: Doubling of serum creatinine, ESKD and renal or CV death

Canagliflozin reduced the incidence of the composite endpoint of doubling of serum creatinine, ESKD and renal or CV death (ITT population: HR 0.70 [95% CI 0.59 to 0.82], p<0.0001). Except for renal death, a substantial number of events was reached for each component of the primary composite; . the number of patients with renal death was too low (n=7) for a meaningful statistical analysis.

The difference between the treatment groups with regard to CV death did not reach significance and the HR included unity (HR 0.78 [CI 0.61 to 1.00], p = 0.0502). The components of doubling of serum creatinine (p<0.0001) and of ESKD (p=0.0015) reached significance. The results from the ITT analysis set were confirmed by the on-treatment analysis set (HR: 0.64; 95% CI: 0.53 to 0.78), which, however, did not contain any renal deaths.

Table 4: Analysis of primary composite endpoint including the individual components (ITT analysis set)

	---------- Placebo ----------		---------- Cana ----------					Log-Rank[c]
Endpoint	n/N(%)	EVRT[a]	n/N(%)	EVRT[a]	HR[b] (95% CI)	P-value[b]	PH P-value	P-value
Primary Composite Endpoint	340/2199 (15.5)	61.24	245/2202 (11.1)	43.21	0.70 (0.59, 0.82)	< 0.0001	0.3116	< 0.0001
Doubling of Serum Creatinine	188/2199 (8.5)	33.78	118/2202 (5.4)	20.73	0.60 (0.48, 0.76)	< 0.0001		< 0.0001
ESKD	165/2199 (7.5)	29.44	116/2202 (5.3)	20.37	0.68 (0.54, 0.86)	0.0015		0.0014
Renal Death	5/2199 (0.2)	0.87	2/2202 (0.1)	0.35				
CV Death	140/2199 (6.4)	24.38	110/2202 (5.0)	19.01	0.78 (0.61, 1.00)	0.0502		0.0496

Note: [a] Event rate per 1000 patient-years.
Note: [b] Hazard ratio (canagliflozin compared to placebo), 95% CI and p-value are estimated using a stratified Cox proportional hazards model including treatment as the explanatory variable, and stratified by screening eGFR (≥ 30 to <45, ≥ 45 to <60, ≥ 60 to <90 mL/min/1.73m^2).
Note: [c] Log-Rank Test stratified by screening eGFR (≥ 30 to <45, ≥ 45 to <60, ≥ 60 to <90 mL/min/1.73m^2) is provided as a supportive analysis.
Note: P-value for testing proportional hazards (PH) is evaluated by including the interaction term of treatment and logarithm transformed time into the model for the primary analysis.
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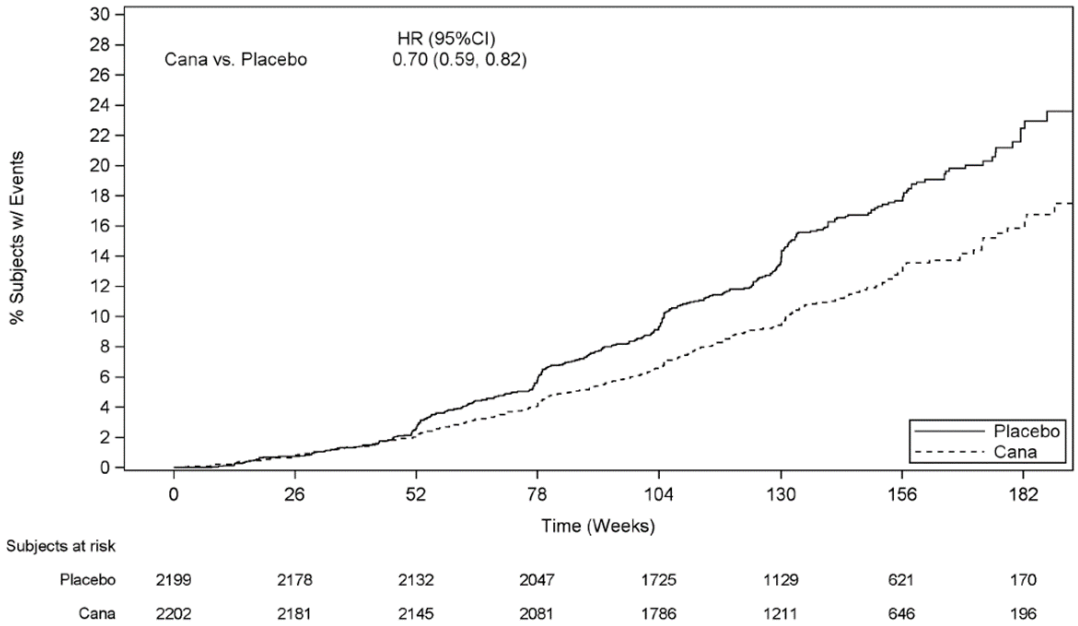
Figure 4 shows the Kaplan-Meier plot for the first occurrence of the primary composite endpoint over time:

Figure 4: Kaplan-Meier plot for first occurrence of the primary composite endpoint over time (ITT analysis set).



As demonstrated by a pre-specified multiple imputation analysis, missing follow-up data for either clinical outcomes or laboratory assessments had negligible impact on the robustness of the primary efficacy analysis. HR and CI of the multiple imputation analysis were highly consistent with the corresponding results from primary analysis.

Ancillary analyses

The consistency of the treatment effect in reducing the risk of the primary composite endpoint compared to placebo was investigated in subgroup analyses defined by demographic (age, race, sex, ethnicity, region) and baseline disease characteristics (duration of diabetes, with or without a history of CV disease, baseline HbA1c, baseline body mass index, screening eGFR strata, baseline eGFR, baseline urinary ACR, baseline SBP, history of amputation, history of heart failure).

No significant statistical heterogeneity was observed across the pre-specified subgroups, such that patients within individual subgroups experienced varying degrees of benefit, with the point estimates for all HRs less than 1.0.

However, the following differences between subgroups are noted:

(1) **Ethnicity:** Stronger canagliflozin effect in Hispanic or Latino subjects (HR: 0.62; 95% CI: 0.47, 0.81) as compared to other ethnicities (HR: 0.74; 95% CI: 0.60, 0.91)

(2) **Region:** Stronger effect of canagliflozin in patients from Central/South America (HR: 0.61; 95% CI: 0.43, 0.88) and "Rest of the World" (HR: 0.58; 95% CI: 0.43, 0.78) as compared to subjects from North America (HR: 0.84; 95% CI: 0.63, 1.13) and Europe (HR: 0.82; 95% CI: 0.54, 1.24).

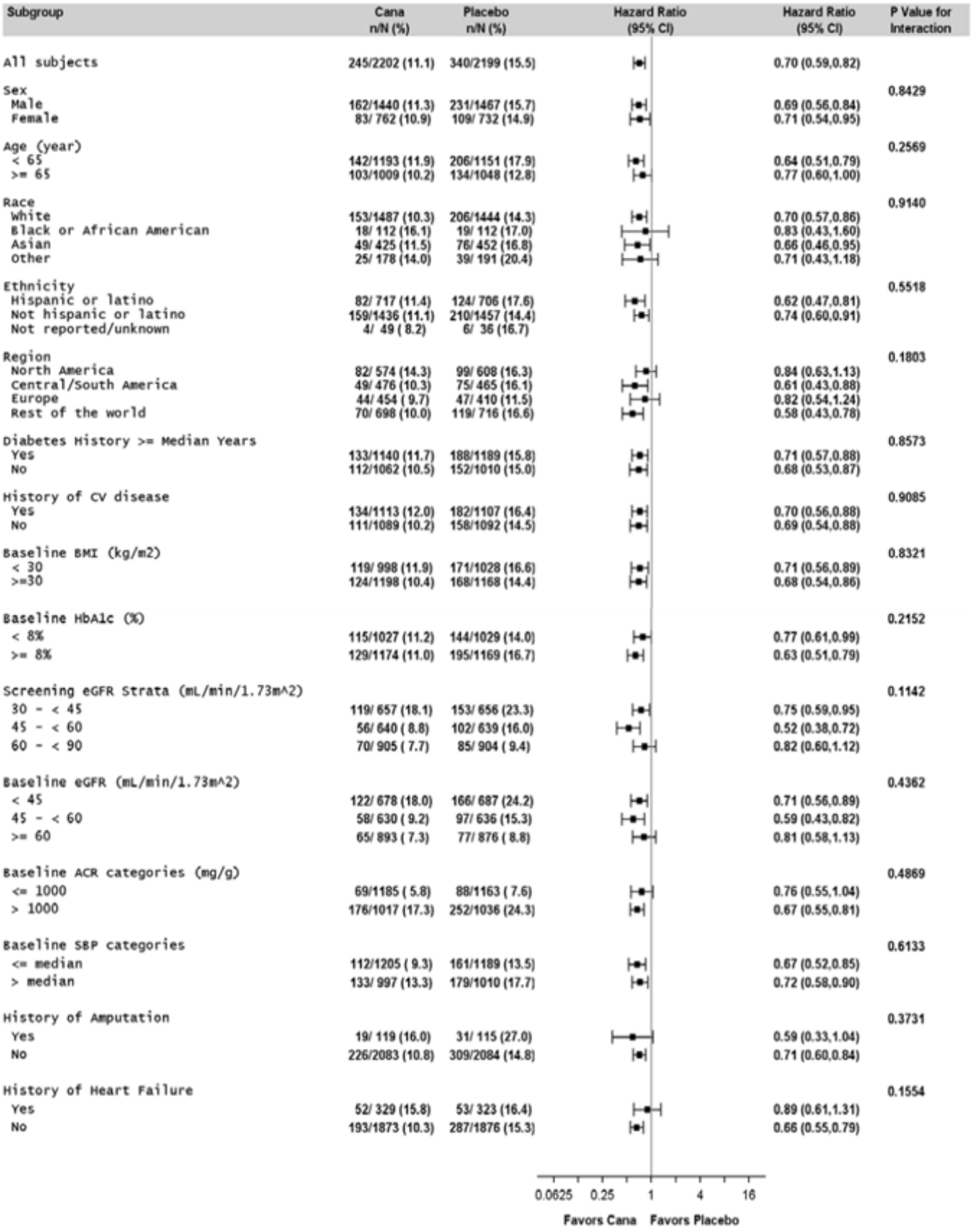
HbA1c: Stronger effect of canagliflozin in subjects with HbA1C ≥ 8% (HR: 0.63; 95% CI: 0.51, 0.79) as compared to subjects with HbA1c < 8% (HR: 0.77; 95% CI: 0.61, 0.99). This difference appears to be strongly driven by the renal components of the primary composite endpoint (cf.

Figure 10 below, showing a subgroup analysis for the secondary composite renal endpoint of "doubling of serum creatinine, ESKD and renal death").

(3) **eGFR strata:** The most pronounced canagliflozin effect was observed in the CKD stage 3a population (eGFR from 45 to <60 ml/min/1,73 m^2; HR: 0.52; 95% CI: 0.38, 0.72), while the effect was weaker for stage 3b CKD (eGFR from 30 to < 45 ml/min/1.73 m^2; HR: 0.75; 95% CI: 0.59, 0.95). The weakest effect (CI including unity) was observed for stage 2 CKD (eGFR from 60 to < 90 ml/min/1.73 m^2; HR: 0.82; 95% CI: 0.60, 1.12).

(4) **History of heart failure:** Canagliflozin was less effective with regard to the primary composite endpoint in subjects with a history of heart failure (HR: 0.89; 95% CI: 0.61, 1.31) as compared to subjects with no history of heart failure (HR: 0.66; 95% CI: 0.55, 0.79). This difference seems to be mainly caused by differences in CV death, because it was also visible in the analysis of secondary CV composite endpoints.

Figure 5: Forest Plot of Hazard Ratios and 95% CI of First Occurrence of the Primary Composite Endpoint by Subgroup (Study 28431754-DNE3001: ITT Set)



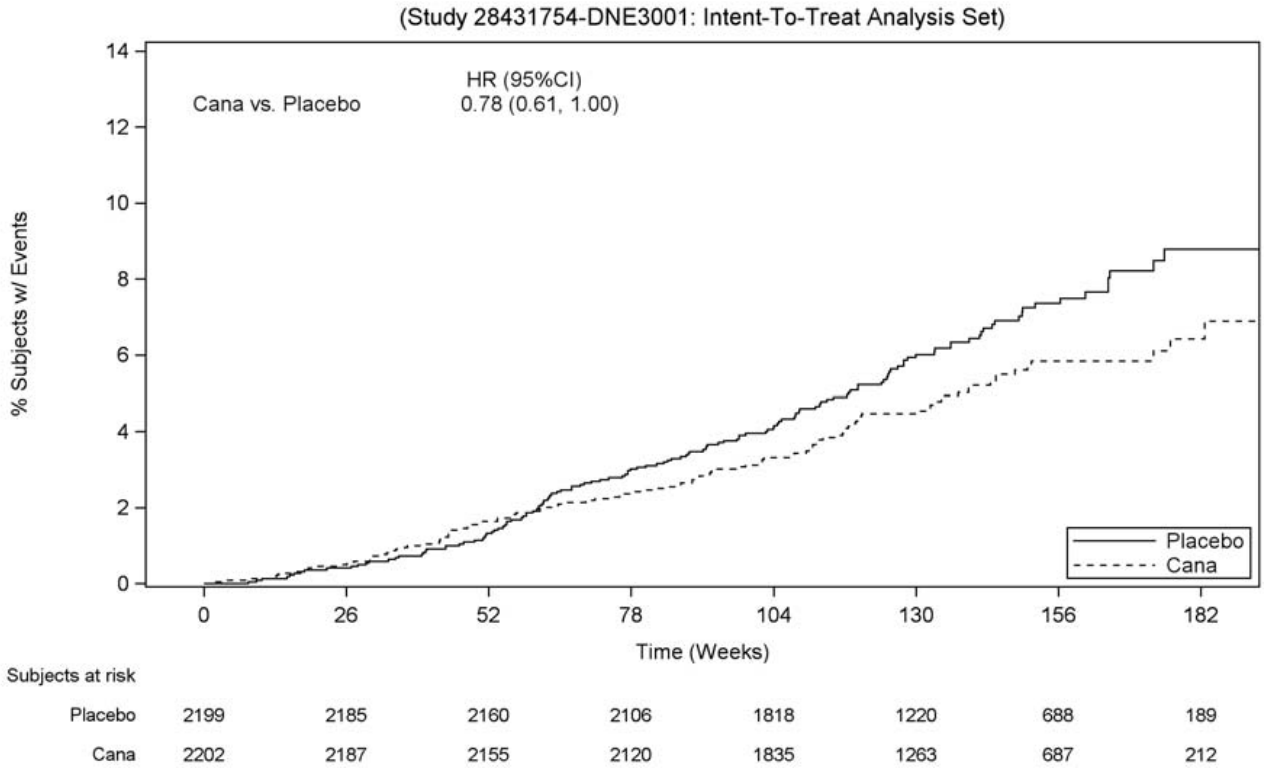
Supportive analyses including individual primary composite endpoint components

The HR was < 1 for all other primary composite endpoint components (doubling of serum creatinine, ESKD, CV death). Since the 95% CI included unity in case of CV death, no statistically significant effect of treatment was demonstrated for this primary composite endpoint component.

The most common causes of CV death in the canagliflozin as well as the placebo group were sudden cardiac death, heart failure or cardiogenic shock and undetermined death. For every cause of CV death, the incidence rate was lower in the canagliflozin group as compared to the placebo arm.

The Kaplan-Meier analysis of *"time to CV death"*, is shown in the following figure:

Figure 6: Kaplan-Meier plot of time to CV death (ITT analysis set)



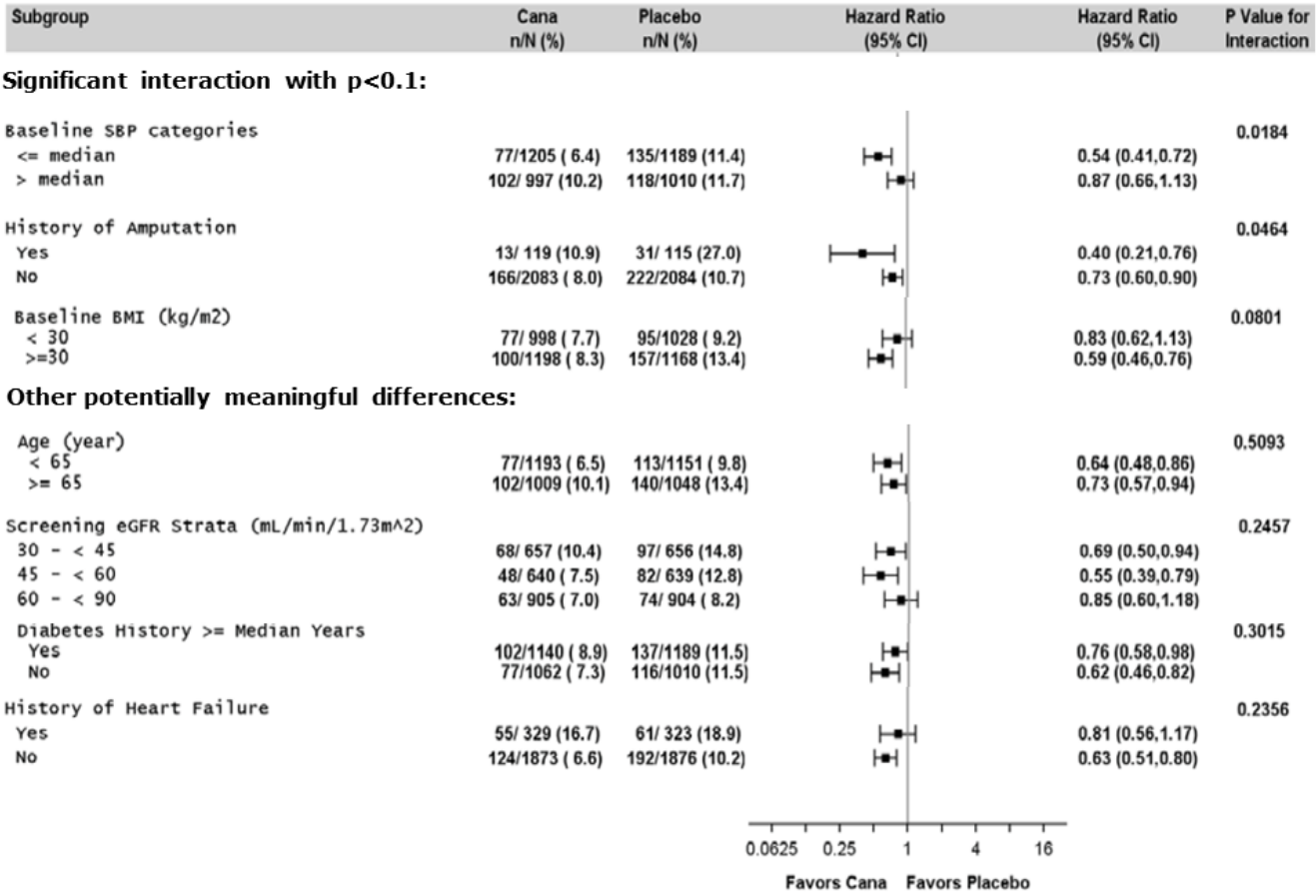
Supportive analyses including secondary efficacy outcomes:

Composite endpoint of CV death and hospitalized heart failure

The incidence of the composite endpoint of CV death and hospitalized heart failure was significantly reduced in the canagliflozin group (HR: 0.69; 95% CI: 0.57, 0.83, which was mainly due to a reduction in hospitalized heart failure; see next section below). By contrast, as discussed above, reduction of CV death was not significant (95% CI included 1). Separation of the curves in the Kaplan-Meier plot occurred after ~52 weeks. In

Figure 7, the results of a subgroup analysis of this secondary composite endpoint are shown with regard to the subgroups with the most prominent heterogeneity between strata.

Figure 7: Subgroup analysis (Forest Plot of Hazard Ratios and 95% CI) of the first occurrence of the composite endpoint of CV death and hospitalized heart failure (ITT set)



Hospitalized heart failure

The incidence of hospitalized heart failure was significantly reduced in the canagliflozin group (HR: 0.61; 95% CI: 0.47, 0.80). Separation of the curves in the Kaplan-Meier plot occurred already very early (< 10 weeks). A subgroup analysis of this secondary endpoint revealed similar differences as described for the composite endpoint of CV death and hospitalized heart failure for BMI, baseline SBP, screening eGFR strata, baseline SBP categories, history of amputation and history of heart failure. However, significance (p = 0.0228) was only reached for baseline SBP. The difference for the age subgroups was less pronounced than in the secondary composite endpoint of CV death and hospitalized heart failure .

The effect of canagliflozin on hospitalized heart failure was reduced in Hispanic or Latino subjects as compared to other ethnicities. This difference was also reflected in a reduced effect of canagliflozin in subjects from Central/South America as compared to subjects from other regions.

Composite endpoint of CV death, non-fatal myocardial infarction (MI), and non-fatal stroke (=3-point MACE)

Canagliflozin significantly reduced the risk of MACE as compared to placebo (HR=0.80; 95% CI: 0.67, 0.95; p=0.0121). As shown in Figure 14 below, separation of the curves for the 3-point MACE in the Kaplan-Meier plot occurred already very early (at < 10 weeks of treatment). Results of the individual components showed consistent effects (Table 24 below). None of the individual MACE components reached significance. Regarding the endpoint "nonfatal stroke", the most common type was ischemic stroke in both groups. Post-stroke disability was higher in the canagliflozin-treated group as compared to the placebo group (Mean change of modified Rankin scores from pre-stroke to month 3 post-stroke: 2.3 in the canagliflozin group, but

only 1.6 in the placebo group). Assessment of stroke disability had been introduced with amendment INT-1 on 12 June 2014.

Table 24: Analysis of MACE (Including Components) (Study 28431754-DNE3001: Intent-To-Treat Analysis Set)

	Placebo		Cana				Log-Rank[c]
Endpoint	n/N(%)	EVRT[a]	n/N(%)	EVRT[a]	HR[b] (95% CI)	P-value[b]	P-value
MACE	269/2199 (12.2)	48.67	217/2202 (9.9)	38.71	0.80 (0.67, 0.95)	0.0121	0.0119
CV Death	140/2199 (6.4)	24.38	110/2202 (5.0)	19.01	0.78 (0.61, 1.00)	0.0502	0.0496
Non-Fatal MI	87/2199 (4.0)	15.51	71/2202 (3.2)	12.50	0.81 (0.59, 1.10)	0.1771	0.1763
Non-Fatal Stroke	66/2199 (3.0)	11.72	53/2202 (2.4)	9.31	0.80 (0.56, 1.15)	0.2219	0.2209

Note: [a] Event rate per 1000 patient-years.
Note: [b] Hazard ratio (canagliflozin compared to placebo), 95% CI and p-value are estimated using a stratified Cox proportional hazards model including treatment as the explanatory variable, and stratified by screening eGFR strata (≥ 30 to <45, ≥ 45 to <60, ≥ 60 to <90 mL/min/1.73m2).
Note: [c] Log-Rank Test stratified by screening eGFR strata (≥ 30 to <45, ≥ 45 to <60, ≥ 60 to <90 mL/min/1.73m2) is provided as a supportive analysis.
Note: MACE=3-point Major Adverse Cardiac Event (CV death, non-fatal MI, and non-fatal stroke).
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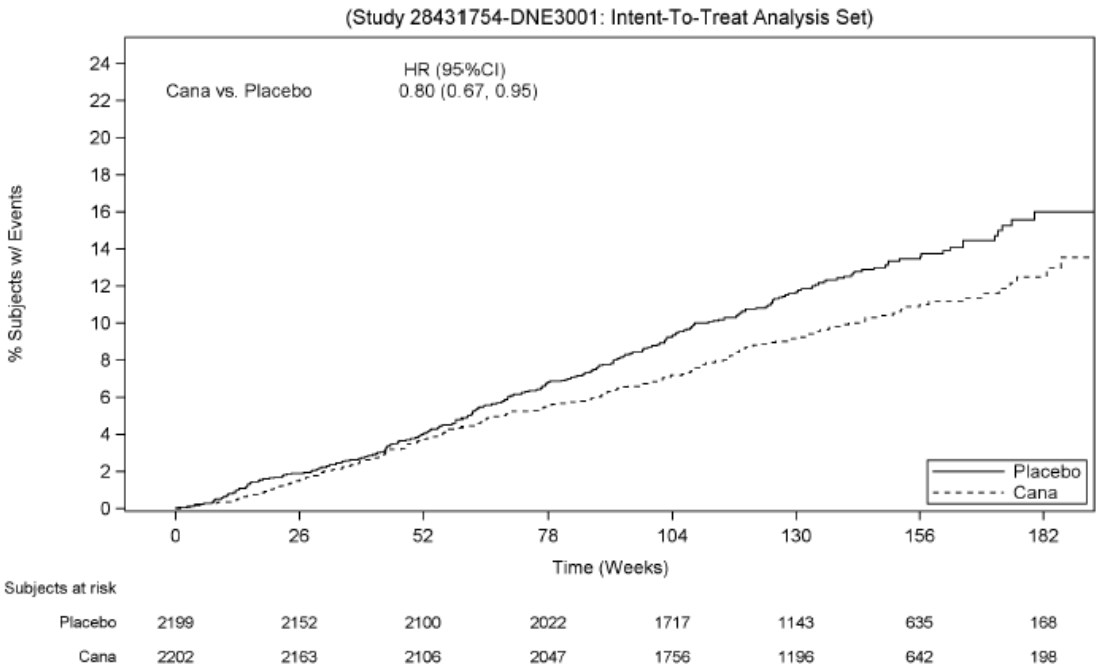
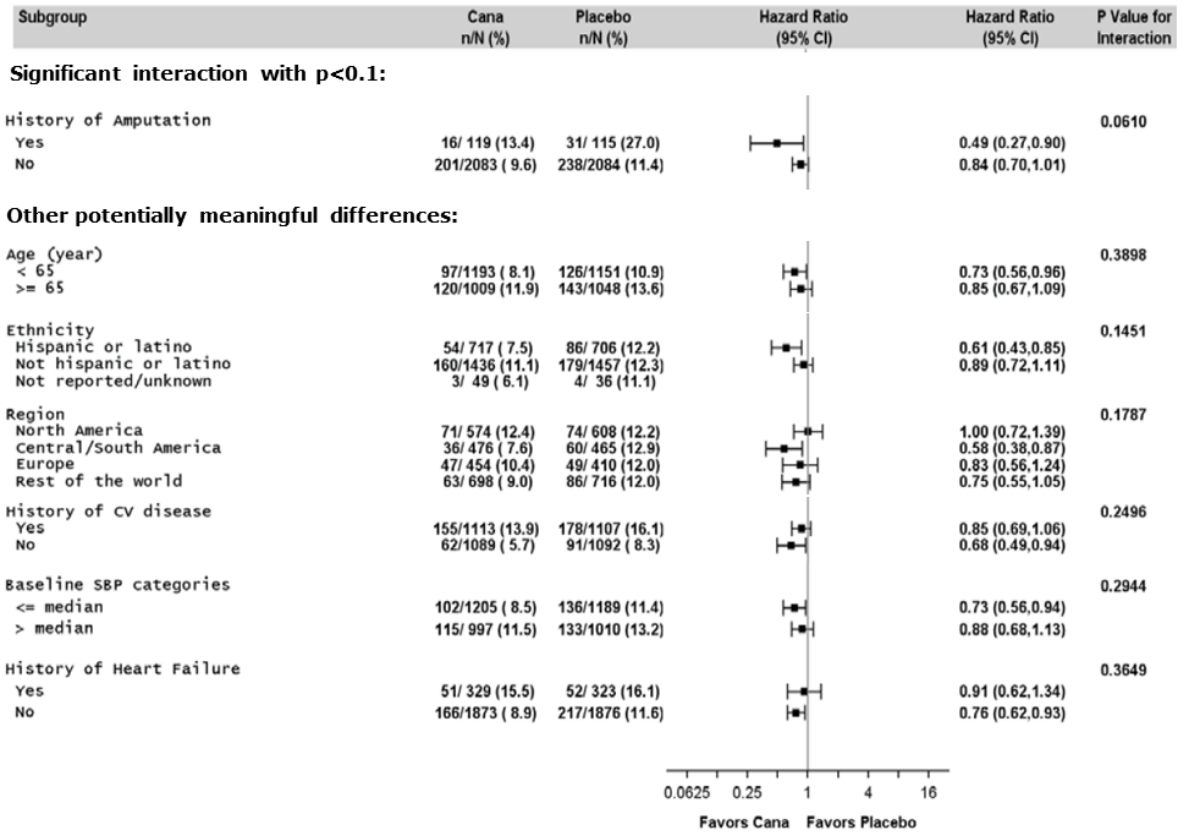
Figure 14: Kaplan-Meier Estimates of First Occurrence of MACE



In the following Figure, the results of a subgroup analysis (those with the most prominent heterogeneity) of the secondary composite endpoint MACE are shown:

Figure 8: Subgroup analysis (Forest Plot of Hazard Ratios and 95% CI) of the first occurrence of the 3-point MACE of CV death, non-fatal MI and non-fatal stroke (ITT set)



Renal composite endpoint of ESKD, doubling of serum creatinine, and renal death

The risk for the renal composite endpoint of doubling of serum creatinine, ESKD and renal death was significantly reduced by canagliflozin 100 mg as compared to placebo (HR=0.66; 95% CI: 0.53, 0.81; p<0.0001).

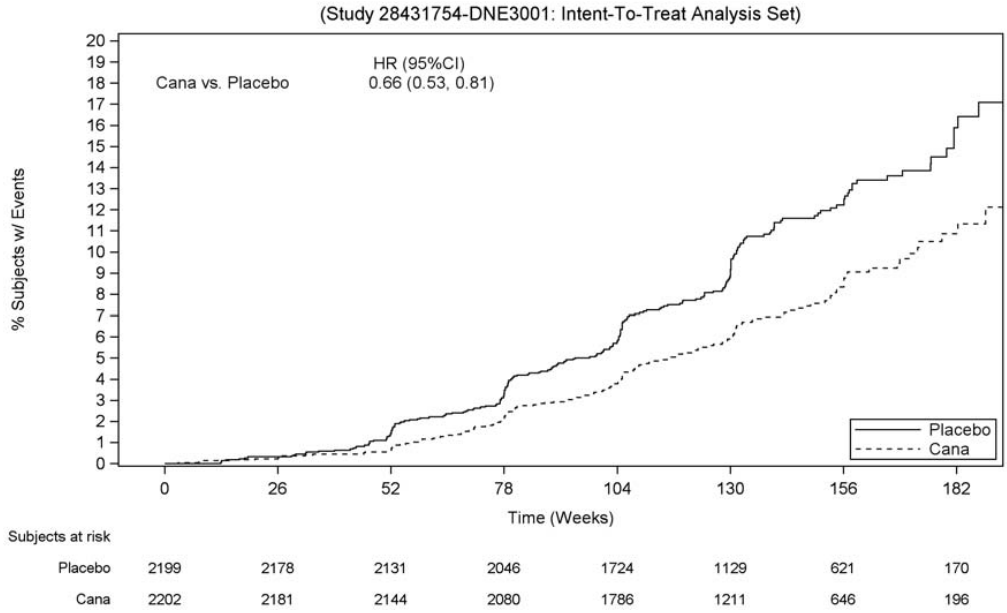
Regarding the individual endpoints of the composite, no meaningful statistical analysis could be performed for the risk of renal death, as only 7 events were counted. The two other individual endpoints, however, reached both significance (doubling of serum creatinine: HR=0.60; 95% CI: 0.48, 0.76; p<0.0001 and ESKD: HR=0.68; 95% CI: 0.54, 0.86; p=0.0015).

The individual subcomponents of the ESKD endpoint occurred with lower incidence rate in the canagliflozin as compared to the placebo group:

- eGFR < 15 ml/min/1.73 m^2: HR=0.60; 95% CI: 0.45, 0.80; p=0.0004
- dialysis initiated and kidney transplantation: HR=0.74; 95% CI: 0.55, 1.00; p=0.0486
- dialysis initiated: HR=0.75; 95% CI: 0.55; 1.01; p=0.0562

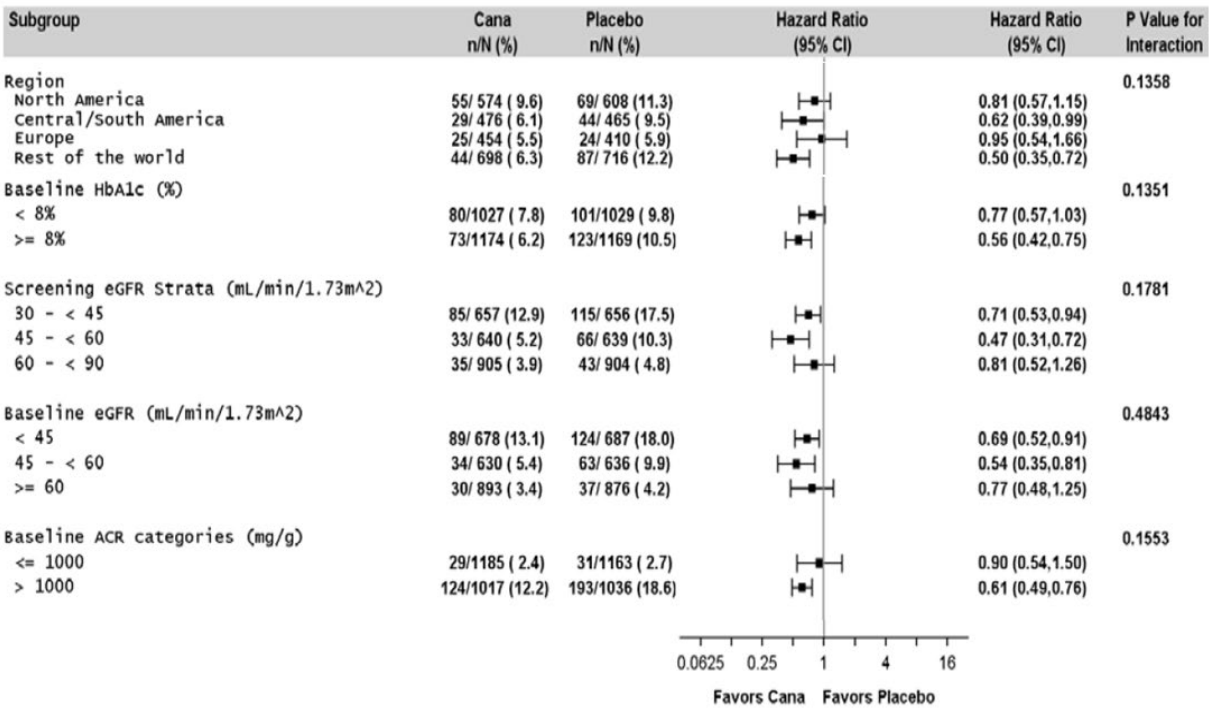
The Kaplan-Meier plot for the first occurrence of the renal composite endpoint is shown in the following table:

Figure 9: Kaplan-Meier estimates of first occurrence of renal composite endpoint (doubling of serum creatinine, ESKD, renal death; ITT set)



The analysis of the renal composite endpoint by subgroups revealed potentially meaningful interactions with regard to region, baseline HbA1c, screening and baseline eGFR as well as baseline ACR categories. None of these interactions, however, was significant. The strongest (albeit non-significant) interactions are shown in Figure 10.

Figure 10: Subgroup analysis (Forest Plot of Hazard Ratios and 95% CI) of the first occurrence of the composite renal endpoint of doubling of serum creatinine, ESKD and renal death (ITT set)



CV death

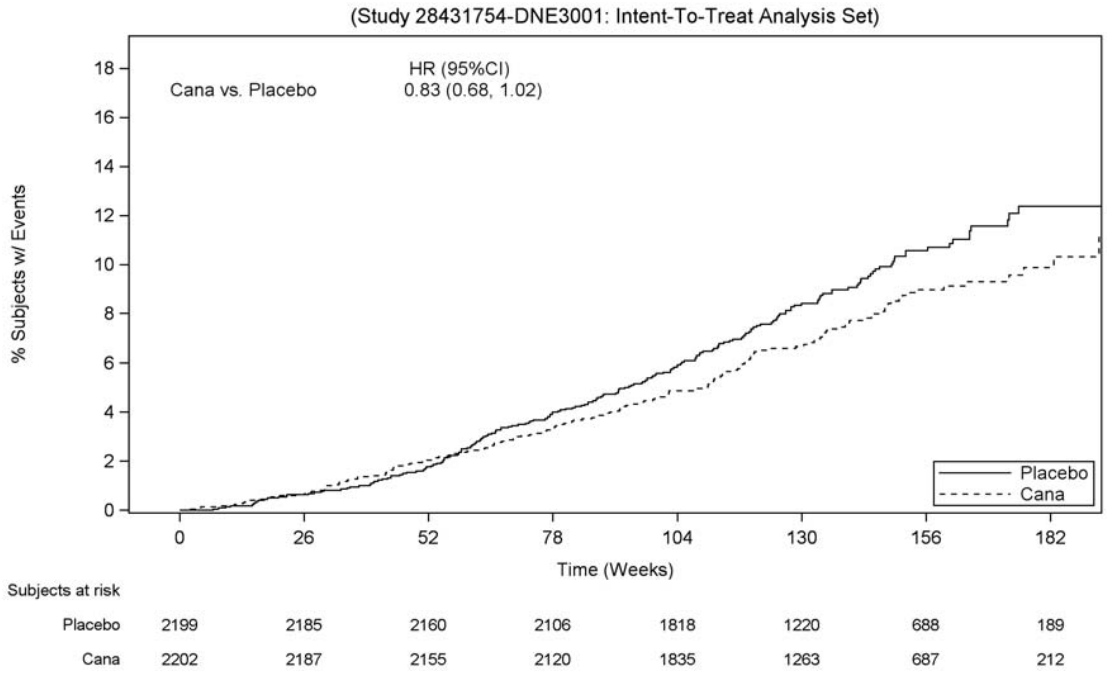
This endpoint was part of the primary efficacy endpoint. See corresponding discussion above and **Table 5** as well as **Table 6**.

As CV death did not reach significance, the hierarchical testing was stopped at this point.

All-cause mortality (not formally tested; only nominal p-values)

The risk of ACM was numerically reduced by canagliflozin (HR=0.83; 95% CI: 0.68, 1.02). The curves in the Kaplan-Meier plot **(Figure 11)** separated between week 52 and week 78. Prior to week 52, ACM was slightly increased in the canagliflozin group as compared to the placebo arm.

Figure 11: Kaplan-Meier plot of time to all-cause mortality (ITT analysis set)



CV composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalized heart failure, and hospitalized unstable angina (not formally tested; only nominal p-values)

The risk of the CV composite endpoint was nominally reduced by canagliflozin (HR=0.74; 95% CI: 0.63, 0.86; p=0.0001). Among the individual components of this composite endpoint, only hospitalized heart failure reached significance (cf. discussion in corresponding section above). The curves in the Kaplan-Meier plot separated very early (< 10 weeks).

Supportive analyses including exploratory efficacy variables

Composite endpoint of ESKD, renal and CV death

The combined secondary renal endpoint of ESKD, renal death and CV death was nominally reduced by canagliflozin (HR=0.73; 95% CI: 0.61, 0.87) with the Kaplan-Meier curves separating as early as week 52.

Individual components of the renal and cardiovascular composite

The individual components of the renal and cardiovascular composite are shown in **Table 6**.

Table 5: Analysis of the individual components of the renal and cardiovascular composite endpoints (ITT analysis set)

Table 31: Analysis of the Individual Components of the Renal and Cardiovascular Composite Endpoints (Study 28431754-DNE3001: Intent-To-Treat Analysis Set)

	---------- Placebo ----------		---------- Cana ----------				Log-Rank[c]
Endpoint	n/N(%)	EVRT[a]	n/N(%)	EVRT[a]	HR[b] (95% CI)	P-value[b]	P-value
Doubling of Serum Creatinine	188/2199 (8.5)	33.78	118/2202 (5.4)	20.73	0.60 (0.48, 0.76)	< 0.0001	< 0.0001
ESKD	165/2199 (7.5)	29.44	116/2202 (5.3)	20.37	0.68 (0.54, 0.86)	0.0015	0.0014
Renal Death	5/2199 (0.2)	0.87	2/2202 (0.1)	0.35			
CV Death	140/2199 (6.4)	24.38	110/2202 (5.0)	19.01	0.78 (0.61, 1.00)	0.0502	0.0496
Non-Fatal MI	87/2199 (4.0)	15.51	71/2202 (3.2)	12.50	0.81 (0.59, 1.10)	0.1771	0.1763
Non-Fatal Stroke	66/2199 (3.0)	11.72	53/2202 (2.4)	9.31	0.80 (0.56, 1.15)	0.2219	0.2209
MI (Fatal/Non-Fatal)	95/2199 (4.3)	16.93	83/2202 (3.8)	14.62	0.86 (0.64, 1.16)	0.3274	0.3264
Stroke (Fatal/Non-Fatal)	80/2199 (3.6)	14.20	62/2202 (2.8)	10.89	0.77 (0.55, 1.08)	0.1289	0.1278
All-Cause Mortality	201/2199 (9.1)	35.00	168/2202 (7.6)	29.04	0.83 (0.68, 1.02)	0.0727	0.0716
HHF	141/2199 (6.4)	25.33	89/2202 (4.0)	15.65	0.61 (0.47, 0.80)	0.0003	0.0003
HUSA	22/2199 (1.0)	3.86	13/2202 (0.6)	2.26	0.58 (0.29, 1.16)	0.1249	0.1204

Note: [a] Event rate per 1000 patient-years.
Note: [b] Hazard ratio (canagliflozin compared to placebo), 95% CI and p-value are estimated using a stratified Cox proportional hazards model including treatment as the explanatory variable, and stratified by screening eGFR (≥ 30 to <45, ≥ 45 to <60, ≥ 60 to <90 mL/min/1.73m2).
Note: [c] Log-Rank Test stratified by screening eGFR (≥ 30 to <45, ≥ 45 to <60, ≥ 60 to <90 mL/min/1.73m2) is provided as a supportive analysis.
Note: HHF=Hospitalized Heart Failure; HUSA=Hospitalized Unstable Angina.
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Changes in eGFR over time

The eGFR data were only analysed with the on-treatment analysis set. This was mainly due to the rebound increase of eGFR after canagliflozin discontinuation. In the ITT analysis set, this effect would have resulted in increased data variability and reduced precision of the estimates.

Baseline eGFR (± SD) was similar between treatment groups (Cana: 56.41 ± 18.18 ml/min/1.73 m^2; placebo: 56.04 ± 18.35 ml/min/1.73 m^2).

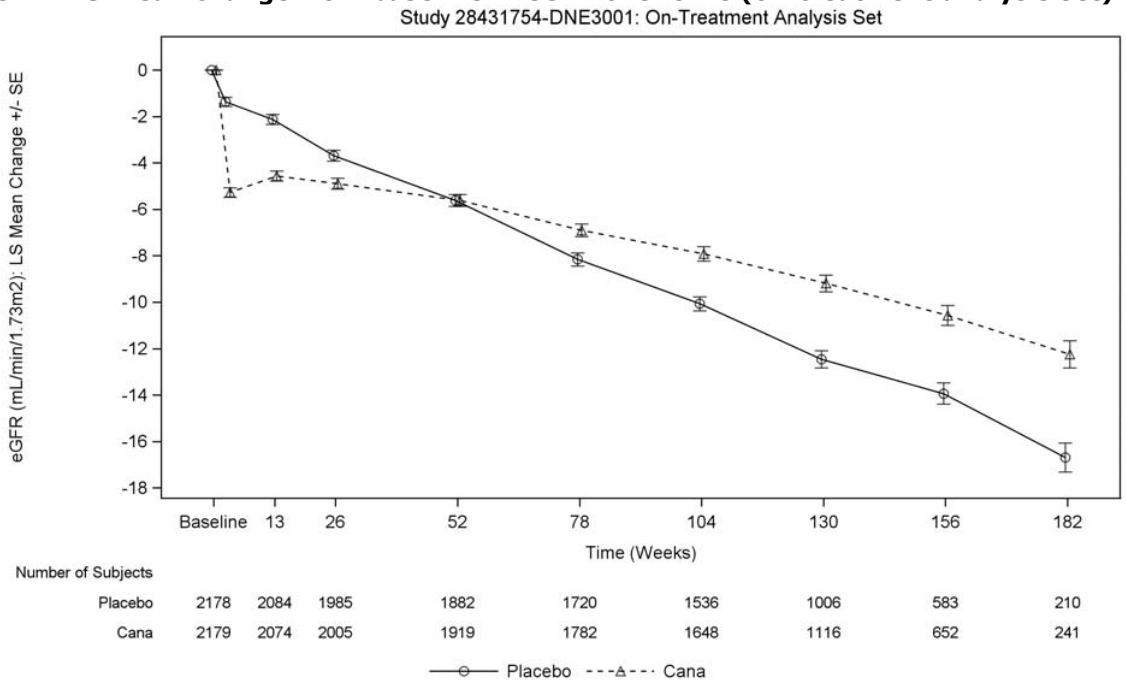
When the LS mean change from baseline of eGFR is analysed *over time*, a pronounced initial decrease of eGFR occurs immediately after onset of canagliflozin treatment, resulting in a lower kidney function as compared to the placebo group. Only after 52 weeks, the relation inverts and the canagliflozin group shows higher eGFR than the placebo group. The LS mean change from baseline in eGFR over time is shown in Figure 12.

The treatment difference in LS mean change from baseline in eGFR *over time* was numerically the highest in the lowest eGFR stratum (Table 7).

Table 6: LS mean change from baseline to eGFR over time (baseline to week 182) by eGFR stratum (on-treatment analysis set)

Stratum (ml/min/1.73 m^2)	LS mean change (ml/min/1.73 m^2)	95% CI (ml/min/1.73 m^2)
≥ 30 to < 45	6.32	4.073, 8.569
≥ 45 to < 60	4.47	1.436, 7.499
≥ 60 to < 90	3.77	0.892, 6.646

Figure 12: LS mean change from baseline in eGFR over time (on-treatment analysis set)



The least squares (LS) mean change *from baseline to end of treatment measures* (± SE) was -9.29 ± 0.29 ml/min/1.73 m^2 in the canagliflozin group and -10.90 ± 0.29 ml/min/1.73 m^2 in the placebo group.

Table 7: Change in eGFR from baseline to end of treatment measures (on treatment analysis set)

	Placebo (N=2197)	Cana (N=2200)
GFR from Creatinine Adjusted for BSA (mL/min/1.73m2)		
Value at Baseline		
N	2178	2179
Mean (SD)	56.04 (18.345)	56.41 (18.180)
Value at End Of Treatment		
N	2178	2179
Mean (SD)	45.70 (20.487)	47.57 (19.888)
Change from Baseline		
N	2178	2179
Mean (SD)	-10.34 (14.067)	-8.84 (13.631)
LS Mean (SE)	-10.90 (0.290)	-9.29 (0.289)
Diff. of LS Means (SE)(minus Placebo)		1.61 (0.403)
95% CI (a)		(0.818;2.399)

Note: (a) Pairwise comparison: CIs are based on the ANCOVA model including the effects of treatment, screening eGFR strata (≥ 30 to <45, ≥ 45 to <60, ≥ 60 to <90 mL/min/1.73m2), and baseline value.
Note: The table include subjects who had both baseline and post-baseline eGFR measurements.
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eGFR slope (total, acute, chronic)

The chronic (week 3 to end of treatment) and the total (baseline to end of treatment) eGFR slope both favoured canagliflozin. The acute eGFR slope (baseline to week 3 of treatment), however, favoured placebo, because eGFR was initially strongly reduced by canagliflozin (see also Figure 12). An overview of the eGFR slope analysis is shown in **Table 9. acute, chronic and total eGFR slope data (on-treatment analysis set)**

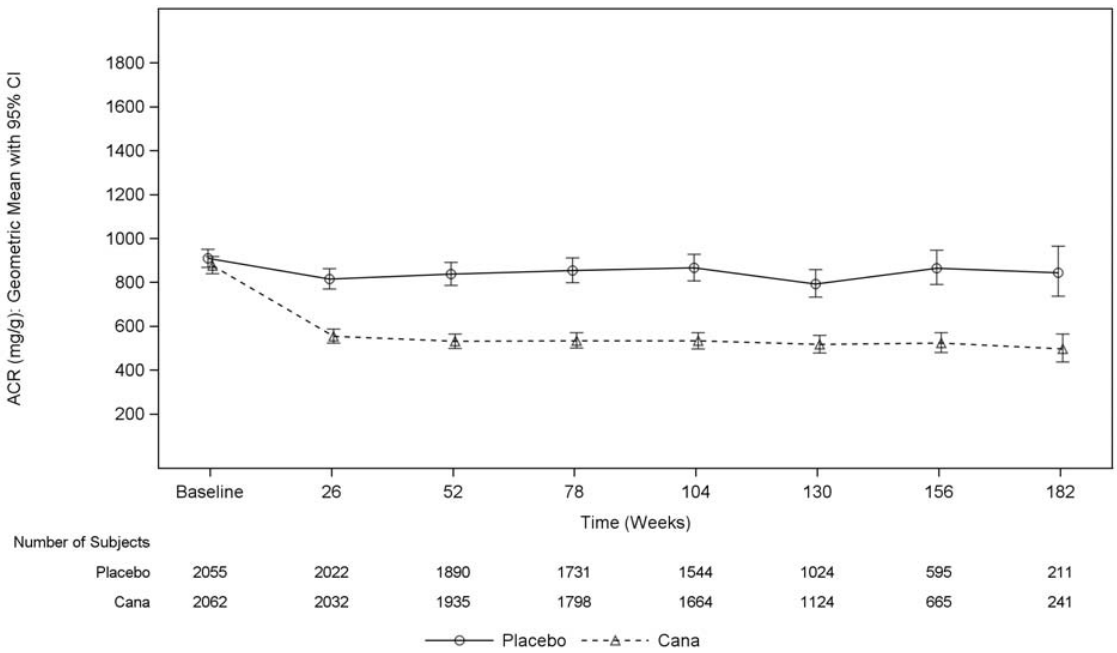
Table 9

Time Period	**Canagliflozin** slope ± SE	**Placebo** slope ± SE	Treatment difference (95% CI)
Acute (baseline to week 3)	-3.72 ± 0.253 ml/min/1.73 m^2 per 3 w	-0.55 ± 0.253 ml/min/1.73 m^2 per 3 w	-3.17 (-3.869, -2.475) ml/min/1.73 m^2 per 3 w
Chronic (week 3 to end of treatment)	-1.85 ± 0.132 ml/min/1.73 m^2 per year	-4.59 ± 0.136 ml/min/1.73 m^2 per year	2.74 (2.373, 3.109) ml/min/1.73 m^2 per year
Total (baseline to end of treatment)	-2.48 ± 0.127 ml/min/1.73 m^2 per year	-4.63 ± 0.130 ml/min/1.73 m^2 per year	2.15 ± 0.180 ml/min/1.73 m^2 per year

Changes in albuminuria over time (ACR, albumin-to-creatinine ratio)

Albuminuria (ACR) remained constant in the placebo group over the entire time of the study. By contrast, canagliflozin initially (at first scheduled assessment at week 26) strongly decreased ACR, but then the effect plateaued

Figure 13: Development of albuminuria (albumin to creatinine ratio) over time (on-treatment analysis set)



Analysis of ACR over time by eGFR strata:

The greatest effect was visible in the highest eGFR stratum. An overview of the data is shown in Table 10.

Table 8: Analysis of albumin to creatinine ratio at week 182 by eGFR strata

Stratum (ml/min/1.73 m^2)	**Canagliflozin** geom. mean ACR at week 182 (95% CI)	**Placebo** geom. mean ACR at week 182 (95% CI)	Geom. mean ratio (95% CI)
≥ 30 to < 45	659.78 mg/g (500.208, 870.246)	818.69 mg/g (606.129, 1,105.791)	0.81 (0.539, 1.205)
≥ 45 to < 60	500.05 mg/g (406.643, 614,923)	878.99 mg/g (693.746, 1,113.686)	0.57 (0.416, 0.779)
≥ 60 to < 90	380.56 mg/g (316.514, 457.572)	724.74 mg/g (602.795, 871,361)	0.53 (0.405, 0.681)

Supportive analyses including metabolic parameters:

Changes in HbA1c

In the on-treatment analysis set, the mean HbA1c values were comparable at baseline in both treatment groups (placebo: 8.27±1.327 %; canagliflozin: 8.26±1.300 %). At the end of the treatment, HbA1c was reduced by 0.25 % in the placebo group and by 0.38 % in the canagliflozin group.

The effect of canagliflozin in comparison to placebo was -0.13% (-0.212; 0.049).

Figure **14** shows that canagliflozin caused an initial strong reduction of HbA1c and remained slightly more effective than placebo throughout the study.

Table 37: Change From Baseline in HbA1c (Study 28431754-DNE3001: On-Treatment Analysis Set)

	Placebo (N=2197)	Cana (N=2200)
Hemoglobin A1c (%)		
Value at Baseline		
N	2128	2116
Mean (SD)	8.27 (1.327)	8.26 (1.300)
Value at End Of Treatment		
N	2128	2116
Mean (SD)	8.02 (1.600)	7.89 (1.444)
Change from Baseline		
N	2128	2116
Mean (SD)	-0.25 (1.557)	-0.38 (1.428)
LS Mean (SE)	-0.25 (0.030)	-0.38 (0.030)
Diff. of LS Means (SE)(minus Placebo)		-0.13 (0.042)
95% CI (a)		(-0.212;-0.049)

Note: (a) Pairwise comparison: CIs are based on the ANCOVA model including the effects of treatment, screening eGFR strata (≥ 30 to <45, ≥ 45 to <60, ≥ 60 to <90 mL/min/1.73m2), and baseline value.
Note: The table includes only the subjects who had both baseline and post-baseline HbA1c measurements.
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As shown in the following figure, HbA1c values decreased more in the canagliflozin group than the placebo group by Week 13 (the first scheduled assessment), and the canagliflozin group values remained below the placebo group values through the end of treatment.

Figure 14: Least squares mean change from baseline in HbA1c over time (on-treatment analysis set)

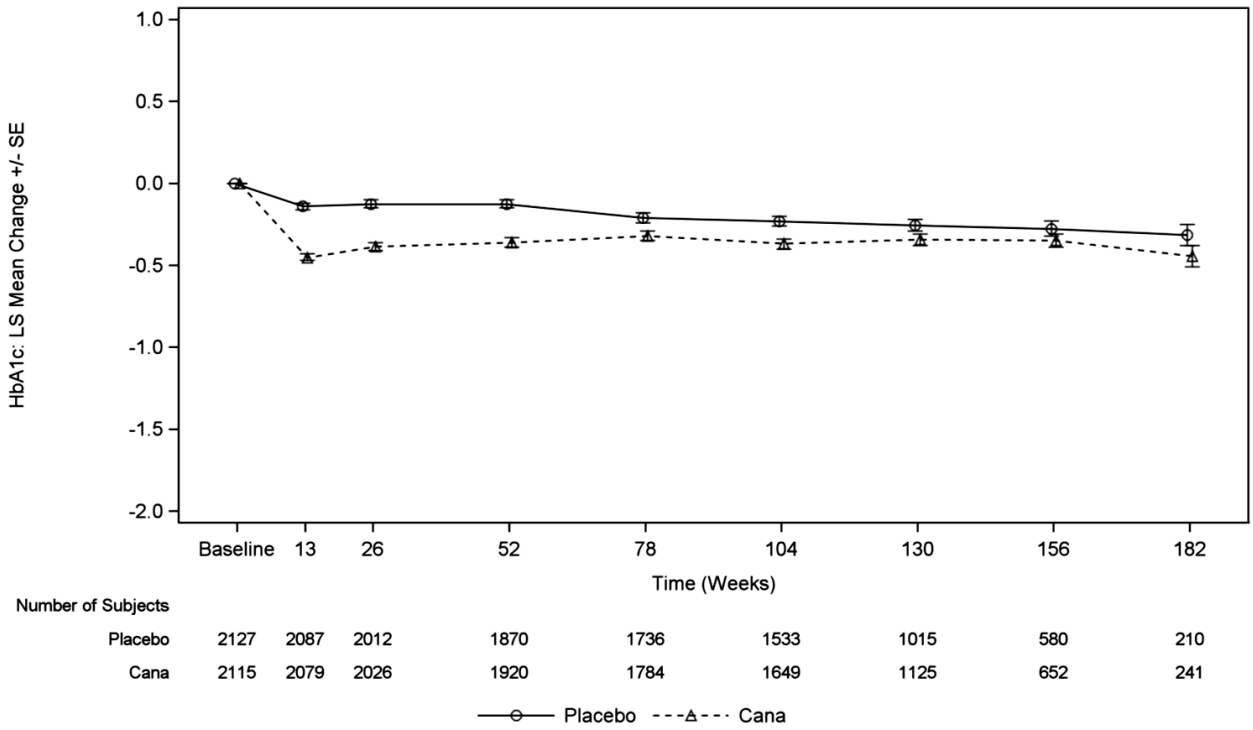

Table 12: Mean and LS Mean Change from Baseline in HbA_{1c} Over Time by eGFR Stratum (Study 28431754-DNE3001: On-Treatment Analysis Set)

	Placebo					Cana					Cana Minus Placebo	
	N	Mean	SD	Change from Baseline LS Mean	SE	N	Mean	SD	Change from Baseline LS Mean	SE	LS Mean	95%CI(a)
Screening eGFR 30 to <45 mL/min/1.73 m^2												
Hemoglobin A1c (%)												
Baseline	631	8.17	1.291			620	8.15	1.274				
Week 13	622	7.99	1.377	-0.16	0.039	605	7.75	1.270	-0.39	0.039	-0.23	(-0.338; -0.123)
Week 26	585	8.01	1.547	-0.15	0.050	584	7.85	1.387	-0.29	0.051	-0.15	(-0.286; -0.005)
Week 52	537	7.96	1.543	-0.19	0.055	551	7.87	1.412	-0.28	0.055	-0.09	(-0.246; 0.058)
Week 78	488	7.89	1.455	-0.27	0.056	490	7.89	1.335	-0.25	0.056	0.02	(-0.137; 0.174)
Week 104	419	7.86	1.454	-0.27	0.058	446	7.83	1.219	-0.29	0.057	-0.02	(-0.178; 0.142)
Week 130	263	7.77	1.387	-0.40	0.068	297	7.82	1.316	-0.32	0.065	0.08	(-0.106; 0.262)
Week 156	142	7.60	1.323	-0.48	0.081	164	7.70	1.237	-0.30	0.076	0.17	(-0.043; 0.392)
Week 182	51	7.70	1.304	-0.46	0.147	63	7.67	1.256	-0.47	0.137	-0.01	(-0.401; 0.380)
Screening eGFR 45 to <60 mL/min/1.73 m^2												
Hemoglobin A1c (%)												
Baseline	619	8.21	1.289			618	8.18	1.279				
Week 13	610	8.10	1.419	-0.09	0.038	611	7.77	1.306	-0.39	0.038	-0.30	(-0.406; -0.193)
Week 26	584	8.08	1.497	-0.10	0.046	599	7.84	1.328	-0.32	0.045	-0.22	(-0.349; -0.097)
Week 52	535	8.08	1.384	-0.09	0.049	565	7.86	1.417	-0.29	0.048	-0.20	(-0.335; -0.066)
Week 78	487	8.03	1.515	-0.16	0.056	533	7.86	1.417	-0.26	0.054	-0.10	(-0.255; 0.049)
Week 104	436	7.99	1.451	-0.20	0.056	493	7.81	1.294	-0.30	0.053	-0.11	(-0.259; 0.043)
Week 130	281	8.12	1.513	-0.15	0.069	334	7.82	1.427	-0.26	0.065	-0.12	(-0.301; 0.071)
Week 156	165	7.93	1.418	-0.20	0.081	200	7.55	1.202	-0.37	0.076	-0.17	(-0.390; 0.043)
Week 182	58	8.00	1.494	-0.21	0.115	81	7.49	1.100	-0.49	0.103	-0.27	(-0.573; 0.031)
Screening eGFR 60 to <90 mL/min/1.73 m^2												
Hemoglobin A1c (%)												
Baseline	877	8.38	1.373			877	8.41	1.320				
Week 13	855	8.21	1.432	-0.16	0.033	863	7.84	1.267	-0.54	0.033	-0.38	(-0.474; -0.293)
Week 26	843	8.24	1.492	-0.13	0.037	843	7.92	1.315	-0.49	0.037	-0.36	(-0.468; -0.261)
Week 52	798	8.24	1.524	-0.11	0.041	804	7.92	1.305	-0.47	0.041	-0.36	(-0.471; -0.241)
Week 78	761	8.13	1.480	-0.21	0.045	761	7.96	1.376	-0.41	0.045	-0.20	(-0.326; -0.078)
Week 104	678	8.09	1.472	-0.23	0.047	710	7.90	1.319	-0.47	0.046	-0.24	(-0.367; -0.110)
Week 130	471	8.04	1.503	-0.24	0.056	494	8.00	1.403	-0.41	0.055	-0.17	(-0.326; -0.017)
Week 156	273	8.04	1.565	-0.22	0.070	288	8.06	1.498	-0.37	0.068	-0.15	(-0.343; 0.039)
Week 182	101	7.79	1.478	-0.31	0.096	97	7.94	1.229	-0.37	0.093	-0.06	(-0.319; 0.202)

Note: (a) Pairwise comparison: CIs are based on a mixed model for repeated measures including the fixed effects of treatment, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction.
Note: The table includes only the subjects who had both baseline and any post-baseline HbA_{1c} measurements. eGFR: estimated glomerular filtration rate; HbA_{1c}: hemoglobin A_{1c}; LS: least squares
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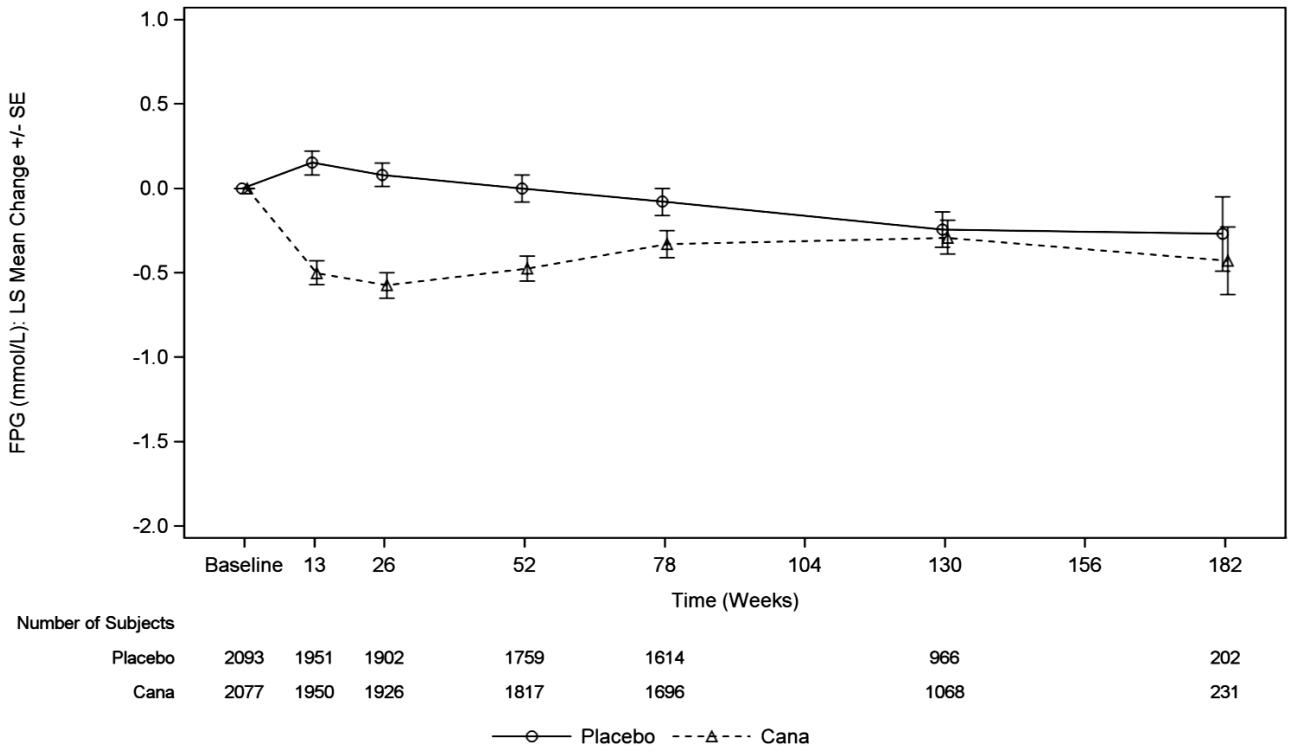
Changes in fasting plasma glucose (FPG)

In the on-treatment analysis set, the values for FPG were comparable at baseline (canagliflozin: 9.12 ± 3.547 mmol/L; placebo: 9.02 ± 3.520 mmol/L; mean ± SD).

At the end of the treatment, FPG was more effectively reduced in the canagliflozin group (LS mean change from baseline (±SE): -0.42 ± 0.077 mmol/L) as compared to placebo (LS mean change from baseline (±SE): -0.21 ± 0.077). The placebo-subtracted LS mean change from baseline was -0.21 (95% CI: -0.425, -0.002) mmol/L.

The development of FPG over time (Attachment GEFOFPG02; Figure 15) shows that there was a continuous reduction of FPG throughout the study in the placebo group. By contrast, canagliflozin only reduced FPG strongly in the first 26 weeks of the study, but then continuously lost FPR-lowering efficacy until week 139.

Figure 15: LS mean change from baseline in fasting plasma glucose over time (on treatment analysis set)



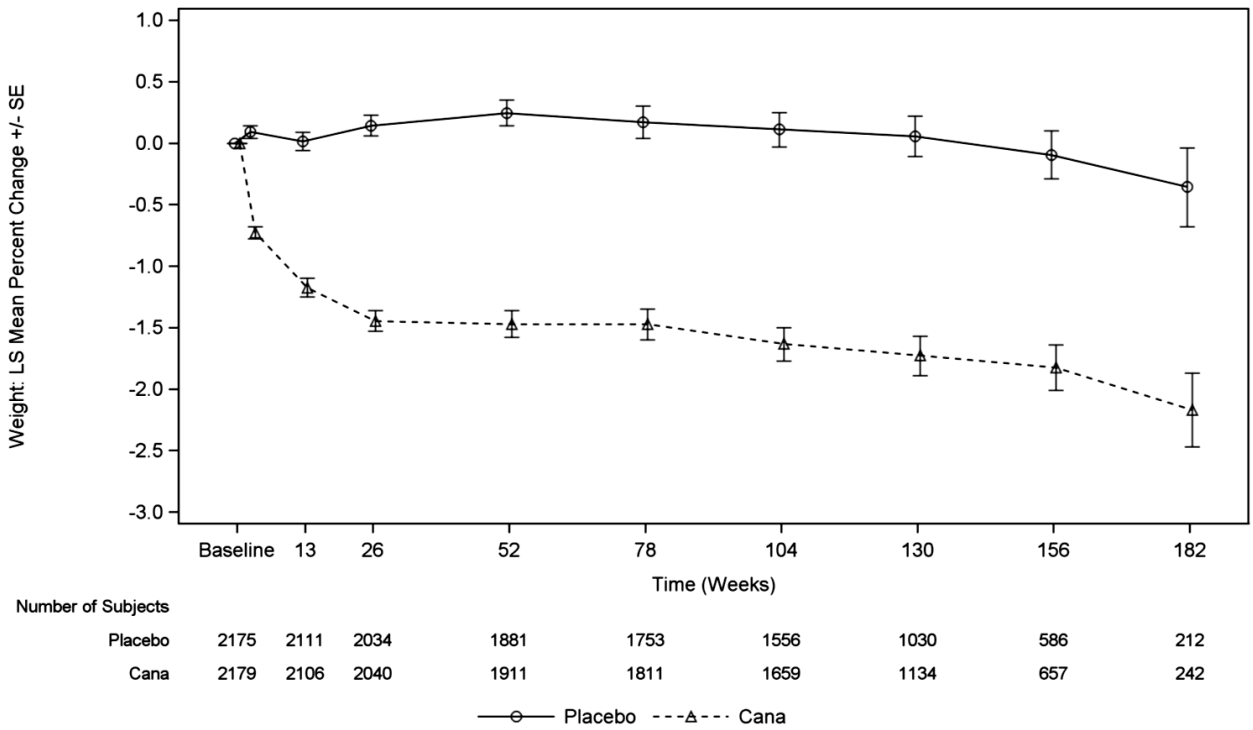
Body weight

In the on-treatment analysis set, the values for body weight were comparable in both treatment groups at baseline (canagliflozin: 87.31 ± 20.708 kg; placebo: 86.92 ± 20.653 kg; mean ± SD).

At the end of the treatment, body weight was more prominently reduced in the canagliflozin group (LS mean change from baseline (±SE): -1.75 ± 0.133 kg) as compared to placebo (LS mean of % change from baseline (±SE): -0.03 ± 0.133). The placebo-subtracted LS mean of % change from baseline was -1.72 kg (95% CI: -2.090, -1.358).

The development of the percent change from baseline in body weight over time (Figure **16**) shows that canagliflozin caused the strongest reduction in body weight during the first 26 weeks of treatment. By contrast, the body weight remained largely stable throughout the course of the study in the placebo group.

Figure 16: Least squares mean percent change from baseline in body weight over time (on treatment analysis set)



Development of body weight (mean ± SD) over time in the different eGFR strata:

eGFR ≥30 to <45 mL/min/1.73 m^2:
Canagliflozin: baseline: 88.15 ± 20.643 kg; end of treatment: 86.88 ± 20.843 kg
Placebo: baseline: 86.23 ± 19.864 kg; end of treatment: 85.82 ± 19.521 kg
LS mean % difference: -1.04% (95% CI: -1.742, -0.343)

eGFR ≥45 to <60 mL/min/1.73 m^2:
Canagliflozin: baseline: 86.23 ± 19.491 kg; end of treatment: 84.65 ± 19.490 kg
Placebo: baseline: 86.91 ± 21.951 kg; end of treatment: 86.70 ± 22.144 kg
LS mean % difference: -1.65% (95% CI: -2.348, -0.945)

eGFR ≥60 to <90 mL/min/1.73 m^2:
Canagliflozin: baseline: 87.47 ± 21.561 kg; end of treatment: 85.59 ± 21.352 kg
Placebo: baseline: 87.42 ± 20.269 kg; end of treatment: 87.48 ± 20.633 kg
LS mean % difference: -2.26% (95% CI: -2.794, -1.717)

Blood pressure

In the on-treatment analysis set, the values for SBP and DBP were comparable in both treatment groups at baseline (mean ± SD):
Canagliflozin: SBP, 139.81 ± 15.607 mmHg; DBP, 78.25 ± 9.339 mmHg
Placebo: SBP, 140.20 ± 15.596 mmHg; DBP, 78.38 ± 9.379 mmHg

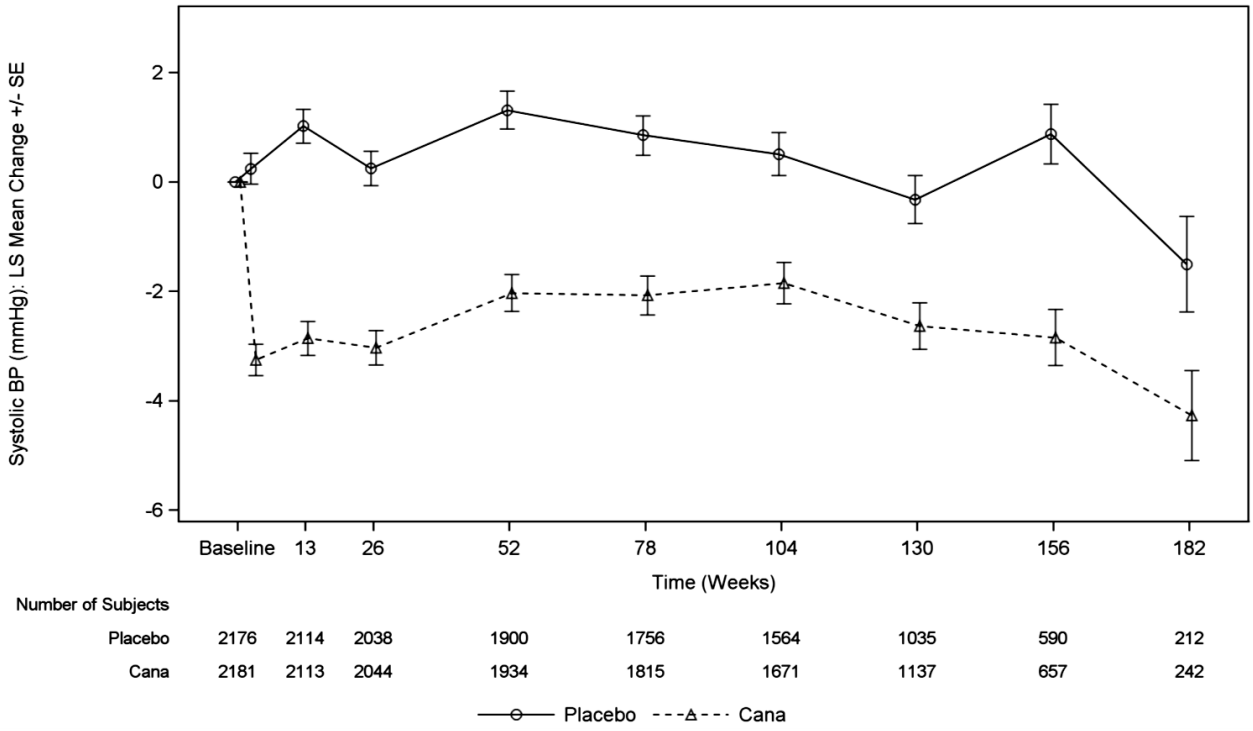
At the end of the treatment, both SBP and DBP were slightly more reduced in the canagliflozin group as compared to placebo (LS mean of % change from baseline ± SE):
Canagliflozin: SBP, -2.69 ± 0.348 mmHg; DBP, -1.59 ± 0.195 mmHg
Placebo: SBP, +0.12 ± 0.348 mmHg; DBP, -0.99 ± 0.195 mmHg

The difference of LS means compared to placebo (±SE) was for
SBP: -2.81 ± 0.489 mmHg (90% CI: -3.771; -1.853)

DNP: -0.60 ± 0.273 mmHg (90% CI: -1.132; -0.060)

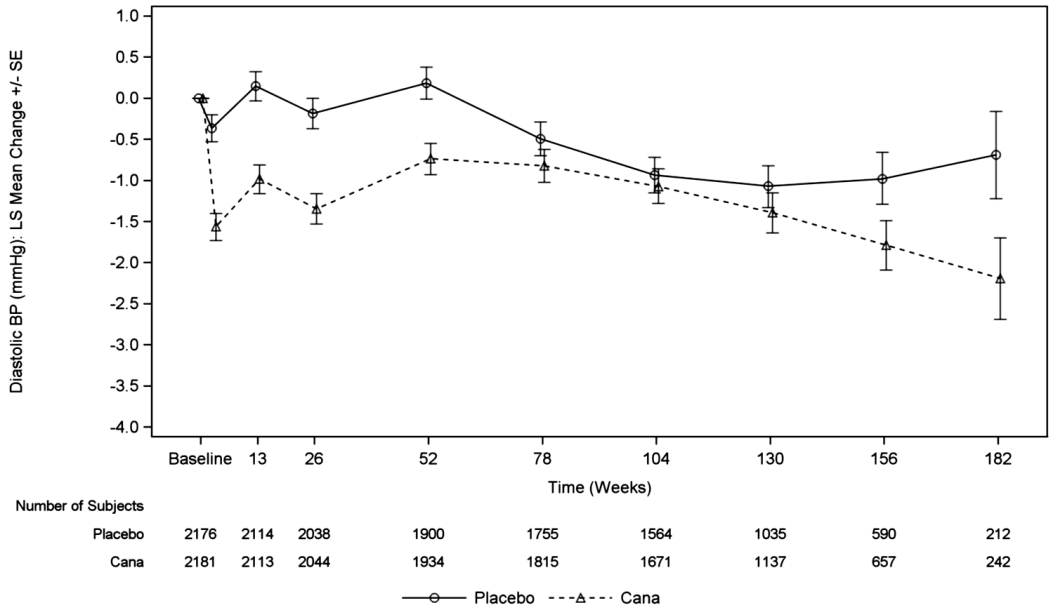
The development of SBP over time shows that most of the canagliflozin effect occurred immediately after initiation of therapy and was largely maintained throughout the course of the study. By contrast, placebo treatment was virtually ineffective (Figure 17).

Figure 17: Least Squares Mean Change From Baseline in Systolic Blood Pressure Over Time (on treatment analysis set)



The development of DBP over time also shows an effect of canagliflozin immediately after initiation of therapy. However, this effect became weaker during the following weeks, while the effect of placebo increased after week 52, resulting in both curves meeting around week 104. After week 104, the curves separated (increase of DBP in the placebo arm and decrease of DBP in the canagliflozin arm) (Figure 18).

Figure 18: Least Squares Mean Change From Baseline in Diastolic Blood Pressure Over Time (on treatment analysis set)



Development of SBP in the different eGFR strata (mean ± SD):

eGFR ≥30 to <45 mL/min/1.73 m^2:
Canagliflozin: baseline: 141.52 ± 16.348 mmHg; end of treatment: 139.06 ± 17.534 mmHg
Placebo: baseline: 140.24 ± 16.553 mmHg; end of treatment: 141.28 ± 18.585 mmHg
LS mean difference: -2.72 mmHg (95% CI:-4.561, -0.875)

eGFR ≥45 to <60 mL/min/1.73 m^2:
Canagliflozin: baseline: 138.99 ± 15.365 mmHg; end of treatment: 136.97 ± 17.633 mmHg
Placebo: baseline: 140.21 ± 15.922 mmHg; end of treatment: 140.17 ± 17.996 mmHg
LS mean difference: -2.66 mmHg (95% CI: -4.470, -0.855)

eGFR ≥60 to <90 mL/min/1.73 m^2:
Canagliflozin: baseline: 139.16 ± 15.144 mmHg; end of treatment: 135.80 ±16.301 mmHg
Placebo: baseline: 140.16 ± 14.636 mmHg; end of treatment: 139.16 ±16.761 mmHg
LS mean difference: -2.94 mmHg (95% CI: -4.372, -1.517)

Development of DBP in the different eGFR strata (mean ± SD):

eGFR ≥30 to <45 mL/min/1.73 m^2:
Canagliflozin: baseline: 77.45 ± 9.202 mmHg; end of treatment: 76.51 ± 10.082 mmHg
Placebo: baseline: 77.71 ± 9.739 mmHg; end of treatment: 76.34 ± 10.619 mmHg
LS mean difference: 0.29 mmHg (95% CI: -0.725, 1.313)

eGFR ≥45 to <60 mL/min/1.73 m^2:
Canagliflozin: baseline: 77.74 ± 9.935 mmHg; end of treatment: 76.13 ± 10.392 mmHg
Placebo: baseline: 78.07 ± 9.434 mmHg; end of treatment: 77.58 ± 10.228 mmHg
LS mean difference: -1.27 mmHg (95% CI: -2.256, -0.290)

eGFR ≥60 to <90 mL/min/1.73 m^2:
Canagliflozin: baseline: 79.18 ± 8.922) mmHg; end of treatment: 77.28 ± 9.938) mmHg
Placebo: baseline: 79.09 ± 9.030) mmHg; end of treatment: 77.99 ± 9.818) mmHg
LS mean difference: -0.76 mmHg (95% CI: -1.575, 0.065)

Fasting plasma lipids
In the on-treatment analysis set, the baseline values of the placebo and the canagliflozin group were comparable with regard to total, LDL and HDL cholesterol as well as triglycerides.

There were only minor differences in fasting plasma lipids between baseline and end of treatment. The effects of canagliflozin in comparison to placebo were negligible (placebo-subtracted LS mean changes from baseline):

Total cholesterol: 0.09 mmol/L (95% CI: 0.018, 0.167)
HDL-C: 0.02 mmol/L (95% CI: 0.006, 0.035)
LDL-C: 0.03 mmol/L (95% CI: -0.028, 0.091)
Triglycerides: 0.08 mmol/L (95% CI: -0.006, 0.175)
The 95% CIs for these comparisons excluded '0' for total cholesterol and HDL-C.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 11Summary of efficacy for the CREDENCE trial

Title: A Randomized, Double-blind, Event-driven, Placebo-controlled, Multicenter Study of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Subjects With Type 2 Diabetes Mellitus and Diabetic Nephropathy		
Study identifier	Protocol Number: 28431754DNE3001 EudraCT Number: 2013-004494-28 NCT No.: NCT02065791 Clinical Registry No.: CR103517	
Design	A randomized, double-blind, event-driven, placebo-controlled, parallel group, 2-arm Phase III study conducted at multiple sites worldwide that evaluated the effects of canagliflozin relative to placebo on progression to end-stage kidney disease (ESKD), doubling of serum creatinine (DoSC), renal or cardiovascular (CV) death in subjects with type 2 diabetes mellitus (T2DM), Stage 2 or 3 chronic kidney disease (CKD) and albuminuria, who were receiving standard of care including a maximum tolerated labelled daily dose of an by angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). The subjects were randomly assigned in a 1:1 ratio to canagliflozin 100 mg or matching placebo.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Event-driven (The study was conducted between 21 February 2014 and 30 October 2018, Global Trial End Date (GTED)). 2-week single-blind placebo run-in Not applicable

Hypothesis	Canagliflozin reduces the risk of the composite endpoint of ESKD, DoSC, and renal or CV death, relative to placebo in subjects with T2DM, stage 2 or 3 chronic kidney disease and albuminuria, who were receiving standard of care including a maximum tolerated daily dose of an ACEi or ARB. Based on the time from study Day 1 to the first occurrence of the primary efficacy endpoint, the objective of the primary efficacy analysis was to establish that canagliflozin is superior to placebo in the reduction of the rate of occurrence of the primary efficacy composite endpoint. The hypothesis of superiority on primary and major secondary efficacy endpoints of canagliflozin versus placebo was tested in a prespecified hierarchical order.	
Treatments groups	Canagliflozin 100 mg (CANA)	2202 randomized and followed for a mean duration of 136.70 weeks. 2200 received at least 1 dose of double-blind study drug and were exposed for a mean duration of 116.59 weeks.
	Placebo	2199 randomized and followed for a mean duration of 135.77 weeks. 2197 received at least 1 dose of double-blind study drug and were exposed for a mean duration of 112.64 weeks.

Endpoints and definitions	Primary	Composite of ESKD, DoSC, and renal or CV death	All events were adjudicated in a blinded fashion by an endpoint adjudication committee (EAC). Event rate was estimated based on time to first occurrence of the primary composite endpoint. Definitions of each component of the primary composite endpoint are: • ESKD: initiation of maintenance dialysis for at least 30 days, or renal transplantation, or estimated glomerular filtration rate (eGFR) of <15 mL/min/1.73m^2 (sustained and confirmed by repeat central laboratory measure after 30 days). • DoSC: from baseline average determination (sustained and confirmed by repeat central laboratory measure after 30 days). • Renal death: death in subjects who reached ESKD, die without initiating renal replacement therapy, and no other cause of death was determined via adjudication. • CV death: death due to myocardial infarction (MI), stroke, heart failure, sudden death, death during a CV procedure or as a result of procedure-related complications, or death due to other CV causes. For analytic purposes, undetermined causes of death were considered CV deaths. In determining whether a death event is CV in nature, the EAC took into consideration both the proximate and underlying causes.
	Secondary (1)	Composite of CV death and hospitalization for heart failure (HHF)	All events adjudicated in a blinded fashion by EAC. Event rate estimated based on time to first occurrence of the composite of CV death and HHF.
	Secondary (2)	MACE Composite of CV death, non-fatal MI, and non-fatal stroke	All events adjudicated in a blinded fashion by EAC. Event rate estimated based on time to first occurrence of the composite of CV death, non-fatal MI, and non-fatal stroke. This composite endpoint also referred to as 3-point major adverse cardiac event (MACE).
	Secondary (3)	HHF	All events adjudicated in a blinded fashion by EAC. Event rate estimated based on time to first occurrence of HHF.
	Secondary (4)	Composite of DoSC, ESKD, and renal death	All events adjudicated in a blinded fashion by EAC. Event rate estimated based on time to first occurrence of the composite of DoSC, ESKD, and renal death.

	Secondary (5)	CV death	All events adjudicated in a blinded fashion by EAC. Event rate estimated based on time to occurrence of CV death.
	Secondary (6)	All-cause death	All events adjudicated in a blinded fashion by EAC. Event rate estimated based on time to occurrence of all-cause death.
	Secondary (7)	Composite of CV death, non-fatal MI, non-fatal stroke, HHF, and hospitalized unstable angina	All events adjudicated in a blinded fashion by EAC. Event rate estimated based on time to first occurrence of the composite of CV death, non-fatal MI, non-fatal stroke, HHF, and hospitalized unstable angina.
Database lock	26-November-2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The Intent to treat (ITT) analysis set included all randomized subjects. The data period was defined from Day 1 to the last trial contact date up to the GTED.		
Descriptive statistics and estimate variability	Treatment group	Placebo	CANA
	Number of subjects	2199	2202
	Primary Composite endpoint of ESKD, DoSC, and renal or CV death Number of events Event rate per 1000 patient-years	 340 61.24	 245 43.21
Effect estimate per comparison	Primary Composite endpoint of ESKD DoSC, and renal or CV death	Comparison groups	CANA compared to Placebo
		Hazard Ratio	0.70
		95% confidence interval	(0.57, 0.84)
		P-value	<0.0001

	Secondary (1) Composite of CV death and HHF Number of events Event rate per 1000 patient-years	 253 45.44	 179 31.47
Effect estimate per comparison	Secondary (1) Composite endpoint of CV death and HHF	Comparison groups	CANA compared to Placebo
		Hazard Ratio	0.69
		95% confidence interval	(0.57, 0.83)
		P-value	0.0001
Descriptive statistics and estimate variability	Secondary (2) MACE Number of events Event rate per 1000 patient-years	 269 48.67	 217 38.71
Effect estimate per comparison	Secondary (2) MACE	Comparison groups	CANA compared to Placebo
		Hazard Ratio	0.80
		95% confidence interval	(0.67, 0.95)
		P-value	0.0121
Descriptive statistics and estimate variability	Secondary (3) HHF Number of events Event rate per 1000 patient-years	 141 25.33	 89 15.65
Effect estimate per comparison	Secondary (3) HHF	Comparison groups	CANA compared to Placebo
		Hazard Ratio	0.61
		95% confidence interval	(0.47, 0.80)
		P-value	0.0003

Descriptive statistics and estimate variability	Secondary (4) Composite of DoSC, ESKD and renal death Number of events Event rate per 1000 patient-years	 224 40.36	 153 26.99
Effect estimate per comparison	Secondary (4) Composite of DoSC, ESKD, and renal death	Comparison groups	CANA compared to Placebo
		Hazard Ratio	0.66
		95% confidence interval	(0.53, 0.81)
		P-value	<0.0001
Descriptive statistics and estimate variability	Secondary (5) CV death Number of events Event rate per 1000 patient-years	 140 24.38	 110 19.01
Effect estimate per comparison	Secondary (5) CV death	Comparison groups	CANA compared to Placebo
		Hazard Ratio	0.78
		95% confidence interval	(0.61, 1.00)
		P-value	NS
Descriptive statistics and estimate variability	Secondary (6) All-cause mortality Number of events Event rate per 1000 patient-years	 201 35.00	 168 29.04
Effect estimate per comparison	Secondary (6) All-cause mortality	Comparison groups	CANA compared to Placebo
		Hazard Ratio	0.83
		95% confidence interval	(0.68, 1.02)
		P-value	NS

Descriptive statistics and estimate variability	Secondary (7) Composite of CV death, non-fatal MI, non-fatal stroke, HHF, and hospitalized unstable angina Number of events Event rate per 1000 patient-years	 361 66.95	 273 49.35
Effect estimate per comparison	Secondary (7) Composite of CV death, non-fatal MI, non-fatal stroke, HHF, and hospitalized unstable angina	Comparison groups	CANA compared to Placebo
		Hazard Ratio	0.74
		95% confidence interval	(0.63, 0.86)
		P-value	NS
Notes	NS: Not significant 95% repeated confidence interval for the primary endpoint with family-wise type I error-rate controlled at a 2-sided significance level of 0.05. Testing of the primary and secondary efficacy endpoints was performed using a 2-sided alpha level of 0.022 and 0.038, respectively. A total of 4361 (99.1%) of the ITT analysis set was noted to have completed the trial, defined as having been followed until a time point between the notification of the GTED and the GTED, or until the time of death for subjects who died prior to the GTED. 15 subjects randomized to CANA and 25 subjects randomized to placebo were noted to have not completed the trial for the reasons noted below: Lost to follow-up (total 22; 13 placebo and 9 CANA), Withdrawal of consent (total 16; 11 placebo and 5 CANA), and Closed site (total 2; 1 placebo and 1 CANA). All but 6 subjects (2 placebo and 4 CANA) had a final vital status assessment made at the end of the trial.		

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The CREDENCE study was a randomized, double-blind, placebo-controlled, parallel-group, 2-arm study conducted at multiple sites worldwide that evaluated the effects of canagliflozin relative to placebo on progression to doubling of serum creatinine, ESKD and renal or CV death in subjects with T2DM, stage 2 or 3 DKD and macroalbuminuria.

The study population consisted of men and women ≥30 years-old with T2DM, HbA1c ≥6.5% to ≤12.0%, eGFR ≥30 to <90 mL/min/1.73 m^2 (as determined using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation), urinary albumin-to-creatinine ratio (ACR) >300 mg/g to ≤5,000 mg/g) on a stable maximum tolerated labelled daily dose of ACEi or ARB.

Patients with a "known medical history or clinical evidence suggesting *nondiabetic renal disease*" were excluded from participation. This is in line with the recommendation by the CHMP (SA EMA/CHMP/SAWP/607731/2013), that "the Applicant needs to ensure that only patients with diabetic nephropathy are included in the pivotal trial." In this SA it was referred to criteria given in the KDOQI 2012 Guideline, which should identify patients who are likely to suffer from parenchymal disease other than

diabetic nephropathy. These criteria comprise absence of diabetic retinopathy, rapidly decreasing GFR, rapidly increasing proteinuria, refractory hypertension, signs or symptoms of other systemic disease or >30% reduction in GFR within 2-3 months after initiation of an ACE-inhibitor or ARB. It was unclear, how meticulously these criteria were worked through at inclusion into CREDENCE. A confirmatory biopsy was not required in the study, which is in line with Guideline EMA/CHMP/500825/2016 ("*As a general rule, the renal biopsy is not required if not used in general practice to set diagnosis in case of pivotal studies, e. g diabetic nephropathy*"). Therefore, it was not clear, how many patients with non-diabetic kidney disease were included in CREDENCE.

In this context it is worth noting, that patients with CKD and diabetes mellitus can have true DKD (CKD as a consequence of diabetes) or a combination of both DKD and non-diabetic kidney disease. In biopsy studies a wide variation in prevalence of non-diabetic kidney disease has been shown. Frequencies vary in various studies between 5% and 71% (J Assoc Physician India 2001; 49: 415-20; Diabetes Care 2002; 25: 900-5: Diabetologica 1999; 14: 1846-9; Clinical Nephrology 2007; 67: 293-297).

Furthermore, the postulated MoA of cana (enhanced tubulo-glomerular feedback, decrease in glomerular hyperfiltration) seems to specifically interfere with the mechanism that leads to renal insufficiency in diabetic nephropathy, which is histologically characterized by glomerular sclerosis (e. g. Magee GM et al., Diabetologia 2009, 52: 691-697).

The initially raised MO was resolved with the Applicant`s Response to the first RSI. The target population was changed from CKD to DKD.

Cana was administered in this study in addition to current local SoC (dietary counselling, glycaemic, hypertension and lipid management). This included ACEi/ ARB -inhibitor therapy in almost all (99.9%) patients for at least four weeks prior to randomisation, with 72% of patients having received the maximum labelled ACEi/ ARB dose. The proposed indication reflected that cana was administered in CREDENCE *add-on SoC*. In section 5.1 it is explicitly stated, that SoC comprised therapy with ACEi/ ARBs. A complementary MoA of cana and ACEi/ ARBs is considered likely ($SGLT_2$ inhibitors contribute to increased sodium levels delivered to the macula densa and lead to secondary autoregulatory vasoconstriction of *afferent* glomerular arteriolae; ACEi/ARBs lead to dilatation of the *efferent* arteriolae). In order to further elucidate a potential additive effect (ACEi/ARBs + Cana) on the study outcome, the Applicant was asked to present results on the primary efficacy endpoint and on its components in the subgroup of patients who discontinued ACEi/ ARBs before week 104 of the study (about 6% of the study population). These results were consistent with the results of the entire study population.

The study amendments are considered without major impact on the study outcomes, albeit some of the changes are considered substantial: with INT-4, the global cap limiting enrolment of subjects with eGFR ≥60 to <90 mL/min/1.73 m^2 to 25 % was removed. A ratio of 60%:40% with regard to CKD stage 3 (eGFR ≥30 to <60 mL/min/1.73 m^2) vs. CKD Stage 2 (eGFR ≥60 to <90 mL/min/1.73 m^2) was allowed. As such, a higher proportion of patients with mild renal impairment were allowed to enter the study after the amendment. With amendment 5, the necessity of *two* baseline creatinine values was emphasized. Evaluation of serum creatinine from a baseline average is appreciated taking into account the high variability (due to analytical and biological reasons) associated with creatinine measurements. An OC relating to the substantiation of the validity of baseline creatinine measurements had been resolved with the Applicant`s response to the first RSI.

The canagliflozin 100 mg dose was chosen based on the B/R assessment in subjects with moderate renal impairment who participated in the canagliflozin phase 3 program, which showed similar efficacy in terms of reductions in urinary ACR for the 100 mg and 300 mg canagliflozin doses, but a safety profile favouring the 100 mg dose (dose-dependency of e. g. volume depletion and hyperkaliaemia). No dose titration was allowed in CREDENCE. Selection of the 100 mg dose for treatment of patients with DN is considered adequate.

The *primary endpoint* was the composite of the time to first occurrence of doubling of serum creatinine, ESKD, and renal or cardiovascular (CV) death. *Secondary endpoints* in the pre-specified hierarchical hypothesis testing sequence were the composite of CV death and hospitalized heart failure; the composite of CV death, nonfatal MI, and nonfatal stroke (MACE); hospitalized heart failure; renal composite of ESKD, doubling of serum creatinine, and renal death; CV death; all-cause death; and the CV composite of CV death, nonfatal MI, nonfatal stroke, hospitalized heart failure, and hospitalized unstable angina. As *exploratory endpoints* a. o. eGFR slope, treatment effects on HbA1c, and blood pressure were captured.

The primary composite endpoint comprises surrogate endpoints reflecting renal function as well as components reflecting renal and cardiovascular outcome which is considered adequate. The primary endpoint does not include all-cause mortality, in contrast to the recommendation in the scientific advice (EMA/CHMP/SAWP/607731/2013). However, the primary endpoint contains cardiovascular death (which is likely to account for the vast majority of non-renal lethal cases) and also covers "death of unknown cause". Investigation of all-cause mortality as a secondary endpoint is therefore acceptable. Likewise, the secondary endpoints are acceptable. CV secondary endpoints defined for CREDENCE are consistent with those defined in the EMA guideline on the Evaluation of Medicinal Products for Cardiovascular Disease Prevention (EMEA/CHMP/EWP/311890/2007; 25 September 2008). All renal and CV events were adjudicated by an independent EAC that was blinded to treatment assignment.

There was uncertainty with respect to the validation of eGFR measurement. To this end, the Applicant was asked to clarify, whether mGFR was determined in a pre-specified subset of patients as a confirmatory test of eGFR as recommended in Guideline EMA/CHMP/SAWP/607731/2013. Moreover, it was unclear, which assay method was used to determine creatinine concentrations and if the methodology of creatinine measurement was consistent and comparable across all participating study centres. This is specifically important, as the frequently used Jaffe method tends to overestimate creatinine in the presence of high glucose concentrations (e.g. den Elzen WPJ et al., Clin Chem Lab Med 2018, 56:e185-e187 or Weykamp C et al., Clin Chem Lab Med 2015, 53:e347-e349). It was noted that three subjects (0.1%) in both treatment arms discontinued study treatment due to site closure. The MAH was asked to clarify the reasons for closing a site during the study. All these uncertainties were sufficiently addressed in the Applicant`s Response to the first RSI and the respective OCs were resolved.

A total of 4401 subjects were randomised, with 2199 and 2202 subjects assigned to placebo and canagliflozin, respectively. Randomization was balanced by using permuted blocks with stratification by screening eGFR (≥30 to <45, ≥45 to <60, ≥60 to <90 mL/min/1.73 m^2), which is endorsed. The rate (29.9% of patients in the placebo group and 24.7% of patients in the Cana group) and nature of discontinuations (adverse events and personal reasons most common in both treatment groups) do not give rise to concern. The high proportion of patients who completed the study (99.1% of patients were followed on or off study drug until death or final visit) supports the robustness of study results.

Subjects were expected to be followed for approximately 4.5 years on average. An interim analysis was planned when the mean duration of follow-up was at least 2 years and approximately 405 subjects had experienced an adjudicated primary composite endpoint, as confirmed by the Endpoint Adjudication Committee (EAC). An Independent Data Monitoring Committee (IDMC) was to review the results of the planned interim analysis and make a recommendation whether the study should be continued as planned or terminated prematurely due to efficacy, futility, or safety reasons. The interim analysis was conducted as planned, when the efficacy objectives of the study were met, on 09 July 2018, with 413 subjects having experienced a primary composite endpoint, as confirmed by the EAC. A total of 585 primary composite endpoints were accrued through the end of the GTED on 30 October 2018. The statistical methodology of the study is considered acceptable.

Efficacy data and additional analyses

No significant imbalances in baseline demographic, anthropometric, diabetes, renal status and CV history characteristics were apparent between the cana and the placebo group.

Canagliflozin significantly reduced the risk of the *primary composite endpoint* compared to placebo by 30% (HR: 0.70, 95% CI: 0.59, 0.82, p-value <0.0001). Consistent results were obtained for the individual components of the primary composite endpoint, with the renal endpoints doubling of serum creatinine and progression to ESKD contributing most to the overall beneficial effect. Importantly, the primary efficacy result also remained robust (HR 0.72; 95% CI 0.62, 0.84; p<0.0001) in a sensitivity analysis of the primary endpoint using all-cause mortality rather than CV death and renal death. Therefore, the concern raised in the SA, that the result on the primary endpoint could be biased by non-cardiovascular/non-renal mortality could be alleviated.

Subgroup analyses for the primary endpoint showed homogenous effects of canagliflozin with no significant interaction (p<0.1) across various subgroup strata (all point estimates for all HR less than 1.0). Efficacy of canagliflozin was somewhat weaker in subjects from North America and Europe as compared to Central/South America and the "Rest of the world". An assessment was undertaken by the Applicant to evaluate whether differences in baseline characteristics by region may have contributed to this observation. Notably, Europe contributed the highest proportion of subjects over the age of 65 years (56.7% versus 46.7% overall) and the largest proportion of subjects with baseline HbA1c <8% (52.8% versus 46.7% overall), and each of these subgroups had a numerically smaller treatment effect relative to the overall population. Therefore, it is possible that these baseline imbalances may have contributed to the numerically smaller risk reduction observed for the subgroup of European subjects. Albeit this is considered a plausible explanation, given the non-randomised nature of the subgroup analyses, this may also be a chance finding.

With respect to BL eGFR, the most pronounced effect in favour of cana was observed in the CKD stage 3a population (HR: 0.59; 95% CI 0.43, 0.82). Slightly weaker, but consistent effects were observed for stage 3b CKD (HR: 0.71; 95% CI 0.56, 0.89). The weakest effect, with the CI including unity, was observed for stage 2 CKD (HR: 0.81; 95% CI 0.58, 1.13). As, according to the present labelling, canagliflozin treatment should be terminated in patients with T2DM and an eGFR of <45 mL/min/1.73m^2 due to limited antihyperglycemic efficacy (SmPC section 4.2) the renal risk reduction of approximately 29% with cana among the subgroup of subjects with a baseline eGFR of <45 mL/min/1.73 m^2 is notable. Thus, patients with CKD stage 3b represent a population distinct from the one already covered by the existing indication.

Reassuringly, results in the CANVAS program in subjects who were at high risk of cardiovascular disease or had CV disease (integrated analysis of studies DIA3008 and DIA3004) were consistent with the findings for the corresponding eGFR strata in CREDENCE: in subjects with eGFR of 45 to <60 mL/min/1.73 m^2 [n=1,485] the HR for the renal composite endpoint of doubling of serum creatinine, ESKD, renal death, and CV death was 0.91 (95% CI: 0.62, 1.33) and in subjects with eGFR 30 to <45 mL/min/1.73 m^2 [n=526] the HR was 0.92 (95% CI: 0.54, 1.56). The wide confidence intervals indicated that a population at lower risk for progression to end stage renal disease was included in the CANVAS program and therefore, the number of events turned out to be smaller.

A history of heart failure led to a considerably smaller effect of canagliflozin on the primary composite endpoint. Patients with a history of heart failure were at greater risk of experiencing a primary endpoint event (HR 0.89, 95%CI 0.51-1.31) as compared to those without (HR 0.66, CI 0.55-0.79. However no firm conclusion could be drawn due to the non-randomised nature of these subgroups.

Canagliflozin significantly reduced the risk of the following *secondary endpoints* compared to placebo: composite endpoint of CV death and hospitalized heart failure by 31% (95% CI: 0.57, 0.83; p=0.0001), MACE (comprised of nonfatal MI, nonfatal stroke and CV death) by 20% (95% CI: 0.67, 0.95; p=0.0121), hospitalized heart failure by 39% (95% CI: 0.47, 0.80; p=0.0003), renal composite endpoint (comprised of

doubling of serum creatinine, ESKD, and renal death) by 34% (HR: 0.66; 95% CI: 0.53, 0.81; p<0.0001). All-cause mortality was reduced by 17% (95% CI 0.68-1.02). With the exception of renal death (7 events) there were a substantial number of events in the renal composite endpoint, including 281 ESKD events (116 in the cana group and 165 in the placebo group).

HbA1c reductions from BL were rather small, both in the cana group (mean change from BL -0.38%) and in the placebo group (mean change from BL -0.25%), with a difference between cana and placebo of -0.13% at end of study. Initially, differences in HbA1c reductions from BL were somewhat larger in the cana group than in the placebo group (difference -0.23 to -0.38% at week 13 across subgroups) but diminished over time. These small differences in HbA1c reduction over time alone are unlikely to explain the renoprotective effect of canagliflozin. This finding was consistent across eGFR strata: the additional HbA1c reduction by canagliflozin was <0.3 % across all eGFR strata. The absence of a clinically relevant difference in antihyperglycemic efficacy between cana and placebo in this study supports the notion that mechanisms independent of blood glucose lowering also played a role in reducing the risk for the renal and CV outcomes.

At baseline, *blood pressure* targets recommended for hypertensive patients with CKD were not entirely met for SBP (BL mean SBP 140.0 mmHg, BL mean DBP 78.3 mmHg). According to the ESC Guideline, in patients with CKD, BP should be lowered to <140/90 mmHg and towards 130/80 mmHg (2018 ESC/ESH Guidelines for the management of arterial hypertension, European Heart Journal, Volume 39, Issue 33, 2018). As expected, blood pressure was reduced with Cana post-baseline. The observed difference to placebo in the reduction of SBP and DBP (-2.81mmHg and -0.60mmHg at end of study, respectively) may have contributed to the difference in results on the primary outcome parameters.

Minor differences (1-2 kg across eGFR subgroups) with respect to body weight were noted, which can be explained by nutrient loss (glucosuria) and the diuretic effect of canagliflozin.

Analysis of eGFR change over time and from baseline to end of treatment measures as well as analysis of eGFR slope confirmed efficacy of canagliflozin in slowing the progression of diabetic kidney disease. The greatest numeric benefit was seen in the lowest BL eGFR stratum (treatment difference in LS mean change of 6.32 ml/min/1.73m^2, for comparison: CKD stage 3a-4.47 ml/min/1.73m^2, CKD stage 2 -3.77 ml/ min/1.73m^2). As expected, canagliflozin caused an initial and transient reduction of eGFR below the levels of the placebo control during the first 52 weeks of treatment, while in the placebo group a progressive linear decline in eGFR was noted.

The difference in the outcome with regards to renal events between the CREDENCE study and the CANVAS program raised concerns with regards to the generalisability of the findings. In order to allow proper assessment and comparison of the data to the outcome in the CREDENCE study, the MAH was asked to provide information on baseline demographics and disease characteristics, including eGFR and albuminuria, for the subgroups with CKD3a and 3b in the CANVAS program. The assessment of the Response (analyses of data from CANVAS) led to the conclusion that findings could be generalised to the entire DKD spectrum.

Additional analysis

Additional analyses were performed to assess the impact of adjusting for *postbaseline measurements of HbA1c* and *SBP* on the primary efficacy analysis. A series of proportional hazard regression models which included postbaseline HbA1c and systolic blood pressure measurements as time-varying covariates were fit. Because changes in HbA1c have a delayed effect on cardiovascular risk, several models were constructed. In each model, HbA1c was evaluated first using the single coincident value, a single lagged value, and then as a running mean average value. Single coincident systolic blood pressure measurements were used for all analyses. These analyses showed that the primary endpoint results remained robust regardless of the approach for adjusting for time-varying HbA1c and SPB measurements.

2.4.3. Conclusions on the clinical efficacy

CREDENCE was a well-designed and well-conducted study. Efficacy of Canagliflozin in the treatment of patients with chronic kidney disease was clearly demonstrated. A robust reduction in the risk of renal and CV events has been shown when Cana was added to SoC across all eGFR strata. Notably, the treatment effect on the primary endpoint seems to be also exhibited by mechanisms unrelated to blood glucose lowering. Most likely, a combination of antihyperglycaemic, blood pressure and bodyweight lowering effects together with secondary autoregulatory vasoconstriction of afferent glomerular arteriolae (through increased local Angiotensin II) seems to contribute to the observed nephroprotective effect.

The current label (section 4.2 of the SmPC) limits the use of Cana, with the recommendation not to initiate the drug with eGFR < 60 and to stop treatment with eGFR < 45 ml/ min/ 1.73 m^2, as the anti-hyperglycaemic efficacy in patients with advanced CKD proved to be insufficient in the phase 3 studies. Therefore, at minimum the subpopulation with CKD stage 3b, would constitute a distinct population not covered by the existing posology.

Nevertheless, it considered that both the aim of treatment as well as the target population of the newly proposed indication (treatment of stage 2 or 3 diabetic kidney disease in adults with type 2 diabetes mellitus) is already covered by the approved indication (treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise). Therefore, the separate indication for T2DM patients with DKD is refused.

2.5. Clinical safety

Introduction

The safety profile of canagliflozin is known from previous studies. However, little information exists on safety of cana in patients with higher stages of renal impairment. Thus, in the CREDENCE study a focus of the safety evaluation was the AE profile in different strata of CKD severity (Stage 2, Stage 3a and Stage 3B). Given the highly differentiated patient population enrolled in the CREDENCE study, most safety data from the CREDENCE study was not pooled with the other completed studies to avoid potential dilution of differences in incidence rates in a population enriched for renal disease. Similar to what was done previously with the CANVAS Program data, this SCS presents a pooled analysis of all 15 Phase 3 and Phase 4 studies, including CREDENCE, for the low-frequency adverse events of pancreatitis and photosensitivity (DS8). This pooling provides the broadest possible dataset for assessment of these low-frequency adverse events, and renal function was not known to change the risk for pancreatitis or photosensitivity. Although, previously the evaluations of DKA and lactic acidosis had been included as pooled analyses in prior Risk Management Plans (RMPs) and the Integrated Summary of Safety (ISS) for the CANVAS Program, due to the differences in risk for acidosis with renal function, neither DKA nor lactic acidosis was included in a pooled assessment that included CREDENCE data; DKA is presented with prior analyses based on the CANVAS/CANVAS-R and Non-CANVAS/Non- CREDENCE datasets and lactic acidosis with the prior analysis from DS6M (Pooled Phase 3 and Phase 4 Studies except CREDENCE – Metformin Dataset).

Patient exposure

CREDENCE Study:

The total exposure of subjects to study drug was 9,658.4 subject-years, with 4,915.8 and 4,742.6 subject-years in the canagliflozin and placebo groups, respectively. The mean duration of exposure to study

drug was 114.62 weeks (116.59 and 112.64 weeks for canagliflozin and placebo, respectively), with 40.6% of all subjects having more than 130 weeks of exposure; for further details, see table below.

Table 12Duration of Exposure to Study Medication (Study 28431754-DNE3001: On-Treatment Analysis Set)

	Placebo	Cana	Total
N	**2197**	**2200**	**4397**
Total duration of exposure (weeks)			
Category, n (%)			
<13 weeks	56 (2.5)	72 (3.3)	128 (2.9)
13-<26 weeks	91 (4.1)	62 (2.8)	153 (3.5)
26-<52 weeks	132 (6.0)	118 (5.4)	250 (5.7)
52-<78 weeks	164 (7.5)	127 (5.8)	291 (6.6)
78-<104 weeks	410 (18.7)	401 (18.2)	811 (18.4)
104-<130 weeks	500 (22.8)	478 (21.7)	978 (22.2)
130-<156 weeks	429 (19.5)	483 (22.0)	912 (20.7)
⩾ 156 weeks	415 (18.9)	459 (20.9)	874 (19.9)
Mean (SD)	**112.64 (46.681)**	**116.59 (46.663)**	**114.62 (46.708)**
Median	116.71	120.86	118.71
Range	(0.4;225.9)	(0.9;227.4)	(0.4;227.4)
Total Exposure (subject years)	**4742.6**	**4915.8**	**9658.4**

Dataset 8 (DS8; all phase 3 and phase 4 studies)**:**

In order to obtain more reliable information on rare adverse events of interest (particularly pancreatitis and photosensitivity), safety data were pooled across all phase 3 and phase 4 studies. A total of 13278 patients received cana in this pool; around 40% of them were exposed for two years or more. Total exposure in the cana group was 27874 patient-years. In the comparator group (all comparators pooled), 9367 patients were included with a total exposure of 18332 patient-years. Further details are provided in the following table.

Table 13Duration of Exposure to Study Medication (DS8: Safety Analysis Set)

	All Non-cana	All Cana	Total
N	**9367**	**13278**	**22645**
Total Duration of Exposure (Weeks)			
Category, n (%)			
<13 Weeks	496 (5.3)	776 (5.8)	1272 (5.6)
13-<26 Weeks	740 (7.9)	1153 (8.7)	1893 (8.4)
26-<52 Weeks	1215 (13.0)	1911 (14.4)	3126 (13.8)
52-<78 Weeks	1170 (12.5)	1729 (13.0)	2899 (12.8)
78-<104 Weeks	1840 (19.6)	2039 (15.4)	3879 (17.1)
104-<130 Weeks	1917 (20.5)	2401 (18.1)	4318 (19.1)
130-<156 Weeks	652 (7.0)	788 (5.9)	1440 (6.4)
156-<182 Weeks	367 (3.9)	422 (3.2)	789 (3.5)
182-<208 Weeks	133 (1.4)	183 (1.4)	316 (1.4)
208-<234 Weeks	46 (0.5)	67 (0.5)	113 (0.5)
234-<260 Weeks	40 (0.4)	70 (0.5)	110 (0.5)
260-<286 Weeks	44 (0.5)	75 (0.6)	119 (0.5)
286-<312 Weeks	252 (2.7)	612 (4.6)	864 (3.8)
⩾ 312 Weeks	455 (4.9)	1052 (7.9)	1507 (6.7)
Mean (SD)	**102.12 (78.423)**	**109.54 (93.149)**	**106.47 (87.434)**
Median	94.29	94.00	94.14
Range	(0.1;365.1)	(0.1;365.0)	(0.1;365.1)
Total Exposure (subject years)	**18332.5**	**27874.1**	**46206.6**

Adverse events

Safety evaluation of CREDENCE is based on 4,397 subjects who received at least 1 dose of double-blind study drug and were included in the On-treatment analysis set and the On-study analysis set. The distinction between these 2 analysis sets relates to the observation period, see Table below.

Table 14 Summary of Analysis Sets

Analysis Set	Analysis Population	Data Period
On-study	Treated subjects	Day 1 to the last study contact date up to the GTED[a]
On-treatment	Treated subjects	Day 1 to the last dose date plus X[b] days or the last study contact date, whichever was earlier

a For each subject, data collected up to the final visit was used for analysis. If the final visit could not be arranged, the reported data such as public search of mortality was bounded by the GTED.
b X is 2 days for laboratory and vital sign measurements, and 30 days for adverse events, CV, renal, and mortality endpoints.

Overview of AEs

The incidence rate of any adverse events was lower in subjects receiving cana than placebo. Accordingly, the percentage of patients suffering at least one AE or SAE was lower with cana than with plc. The same is true for AEs and SAEs leading to discontinuation. Merely in the category "AE related to study drug" a higher frequency was observed with cana compared to plc. This could be related to the fact that many typical AEs for SGLT2 inhibitors are known so that relatedness is easily to derive. For further details, see table below.

Table 15 Summary of Adverse Events - Exposure adjusted (Study 28431754-DNE3001: On-Treatment Analysis Set)

	Placebo (N=2197)		**Cana (N=2200)**	
	n(%)	Rate/1000 pt-yrs**	n(%)	Rate/1000 pt-yrs**
Any Adverse Events	**1860 (84.7)**	**379.28**	**1784 (81.1)**	**351.40**
Adverse Events Leading to Discontinuation	286 (13.0)	58.32	267 (12.1)	52.59
Adverse Events Related to Study Drug*	361 (16.4)	73.61	469 (21.3)	92.38
Adverse Events Related to Study Drug* and Leading to Discontinuation	55 (2.5)	11.22	75 (3.4)	14.77
Serious Adverse Events	**806 (36.7)**	**164.36**	**737 (33.5)**	**145.17**
Serious Adverse Events Leading to Discontinuation	159 (7.2)	32.42	134 (6.1)	26.39
Serious Adverse Events Related to Study Drug*	42 (1.9)	8.56	62 (2.8)	12.21
Serious Adverse Events Related to Study Drug* and Leading to Discontinuation	15 (0.7)	3.06	16 (0.7)	3.15
Death	**122 (5.6)**	**24.88**	**109 (5.0)**	**21.47**

Percentages calculated with the number of subjects in each group as the denominator.
*Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related.
**The Denominator is the total of each subject's exposure of the study medication plus 30 days.
Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Death is based on the number of subjects who have AE with fatal outcome.

AE frequency by renal function

The MAH also provided an AE analysis according to renal function (at the time of screening) to exclude decreasing tolerability of cana with decreasing renal function. It turned out that the incidence (per 1000 subject-years) was higher in patients with lower renal function. However, in none of the different CKD stages (2, 3A and 3B) AE or SAE incidence was higher with cana than with plc. Incidence of SAEs was similar between cana and plc in patients with better renal function (CKD Stage 2). Notably, in CKD Stages 3A and 3B, SAE incidence was considerably lower with cana compared to plc. For further details, see the following table.

Incidence (per 1,000 Subject-years) for Adverse Events as a Function of Screening eGFR Strata (Study 28431754-DNE3001)

	Overall		**eGFR 30 to <45**		**eGFR 45 to <60**		**eGFR 60 to <90**	
	Placebo	**Cana**	**Placebo**	**Cana**	**Placebo**	**Cana**	**Placebo**	**Cana**
	(N=2197)	(N=2200)	(N=656)	(N=655)	(N=638)	(N=640)	(N=903)	(N=905)
All AEs	379.3	351.4	413.5	394.8	387.7	345.7	351.4	326.6
Serious AEs	164.4	145.2	204.6	174.6	177.4	141.3	129.4	128.3
AEs leading to D/C	58.3	52.6	85.3	78.5	61.3	45.1	38.7	40.6
Fatal AEs	24.9	21.5	29.6	23.8	27.8	19.2	19.8	21.5
AEs of Interest								
Osmotic diuresis[b]	8.2	10.1	10.8	13.3	11.4	6.0	4.3	10.7
Volume depletion[b]	23.5	28.4	26.0	49.1	25.7	23.2	20.3	18.2
UTI[b]	45.1	48.3	53.5	55.4	49.9	49.1	36.4	42.9
Female GMI[b]	6.1	12.6	9.9	6.3	1.9	9.5	7.1	18.8
Renal-related AEs[b]	79.1	57.1	128.0	94.7	83.4	51.1	44.4	36.4
Male GMI[b]	0.9	8.4	0	5.3	2.3	11.2	0.7	8.6
Lower limb amputation[a]	11.2	12.3	10.2	13.7	14.1	8.9	9.9	13.8
Fracture (adjudicated)[a]	12.1	11.8	13.2	13.7	14.1	11.4	9.9	10.7

AE: adverse event; Cana: canagliflozin; D/C: discontinuation; DKA: diabetic ketoacidosis; eGFR: estimated glomerular filtration
rate expressed in mL/min/1.73 m2; GMI: genital mycotic infection; UTI: urinary tract infection
a On-study analysis set.
b On-treatment analysis set
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Denominators are restricted to the respective gender for testicular cell cancer and breast cancer, and male and female mycotic genital infections.
Note: For adverse events of interest, analysis by screening eGFR strata was limited to the events shown in this table as per the CREDENCE SAP.
Note: For amputation and fracture, incidence rates per 1,000 subject-years are calculated from Day1 to the first event date. For other adverse events of interest, incidence rates per 1,000 subject-years are either calculated using the total of each subject's exposure of study medication plus 30 days (on-treatment analysis set) or the total follow-up time (for on-study analysis set).

AEs by organ system

In line with the overall reduced AE incidence with cana compared to plc, AEs in the individual organ systems were also similar or fewer with cana than with plc. The most salient difference, "Investigations", 20.5% vs 15.6% (plc vs. cana), was driven by a higher incidence of "Blood creatinine increased" in the plc group; this is in line with the efficacy findings. For details see table below.

Table 16 : Adverse Events by Body System (Study 28431754-DNE3001: On-Treatment Analysis Set)

Body System or Organ Class	Placebo (N=2197) n (%)	Cana (N=2200) n (%)
Total no. subjects with the AEs	**1860 (84.7)**	**1784 (81.1)**
Blood and lymphatic system disorders	200 (9.1)	120 (5.5)
Cardiac disorders	393 (17.9)	300 (13.6)

Congenital, familial and genetic disorders	6 (0.3)	9 (0.4)
Ear and labyrinth disorders	77 (3.5)	77 (3.5)
Endocrine disorders	55 (2.5)	57 (2.6)
Eye disorders	257 (11.7)	234 (10.6)
Gastrointestinal disorders	475 (21.6)	463 (21.0)
General disorders and administration site conditions	382 (17.4)	288 (13.1)
Hepatobiliary disorders	74 (3.4)	70 (3.2)
Immune system disorders	20 (0.9)	22 (1.0)
Infections and infestations	1016 (46.2)	932 (42.4)
Injury, poisoning and procedural complications	304 (13.8)	307 (14.0)
Investigations	451 (20.5)	343 (15.6)
Metabolism and nutrition disorders	690 (31.4)	604 (27.5)
Musculoskeletal and connective tissue disorders	468 (21.3)	443 (20.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	122 (5.6)	132 (6.0)
Nervous system disorders	419 (19.1)	396 (18.0)
Pregnancy, puerperium and perinatal conditions	0	2 (0.1)
Product issues	4 (0.2)	2 (0.1)
Psychiatric disorders	112 (5.1)	93 (4.2)
Renal and urinary disorders	423 (19.3)	339 (15.4)
Reproductive system and breast disorders	92 (4.2)	101 (4.6)
Respiratory, thoracic and mediastinal disorders	310 (14.1)	263 (12.0)
Skin and subcutaneous tissue disorders	324 (14.7)	313 (14.2)
Social circumstances	1 (<0.1)	1 (<0.1)
Surgical and medical procedures	1 (<0.1)	0
Vascular disorders	387 (17.6)	365 (16.6)

AEs of special interest

An overview of the AEs of special interest (AEIs) is provided in the table below. AEIs were selected based on prior observation of side effects related to cana (or SGT2 inhibitor in general). Particularly in case of the malignancies it is not yet clear whether they are related to cana because an association between treatment and neoplasm is difficult to derive from clinical trials. Therefore, data on malignancies are further collected. Salient differences, disfavouring cana, are highlighted in the table (done by the rapporteur).

Reassuringly, VTE, an important sequel of dehydration, was rather infrequent and only increased to a small amount by cana (4.14 vs. 3.26 events per 100 patient-years, cana vs. plc). Also lower-limb amputations were increased by cana by a small degree only. Notably, during course of the study, preventive measures came into force, no longer allowing inclusion of patients with a history of amputation or other signs of diabetic foot. It is understood that patients at risk included before this amendment remained in the study.

Table 17: Incidence Rate and Incidence Rate Difference for Selected Adverse Events of Interest (Study 28431754-DNE3001)

	Placebo (N=2197)		**Canagliflozin (N=2200)**		**Canagliflozin vs. Placebo**	
	n (%)	Rate (/1000 subj-years)	n (%)	Rate (/1000 subj-years)	IRD (/1000 subj-years)	95% CI
On-study Analysis Set						
Lower limb amputation	63 (2.9)	11.19	70 (3.2)	12.34	1.16	(-2.87, 5.18)
Fracture (adjudicated)	68 (3.1)	12.09	67 (3.0)	11.80	-0.29	(-4.35, 3.77)
DKA (adjudicated)	***2 (0.1)***	***0.35***	***12 (0.5)***	***2.08***	***1.73***	***(0.32, 3.14)***
Malignancy (Renal cell) (adjudicated)	3 (0.1)	0.52	1 (<0.1)	0.17	-0.35	(-1.22, 0.52)

Malignancy (Bladder)	9 (0.4)	1.57	10 (0.5)	1.73	0.16	(-1.41, 1.73)
Malignancy (Breast)	***3 (0.4)***	***1.59***	***8 (1.1)***	***4.08***	***2.49***	***(-1.25, 6.23)***
Pheochromocytoma	0	0.00	0	0.00	0.00	
Leydig cell tumors	0	0.00	0	0.00	0.00	
On-treatment Analysis Set						
Renal related AEs (including AKI)	388 (17.7)	79.12	290 (13.2)	57.12	-22.00	(-32.27, -11.73)
Hypoglycemia	240 (10.9)	48.94	225 (10.2)	44.32	-4.62	(-13.12, 3.88)
UTI	221 (10.1)	45.07	245 (11.1)	48.26	3.19	(-5.30, 11.69)
Volume depletion	115 (5.2)	23.45	144 (6.5)	28.36	4.91	(-1.42, 11.25)
Osmotic diuresis	40 (1.8)	8.16	51 (2.3)	10.05	1.89	(-1.89, 5.67)
Hepatic injury	32 (1.5)	6.53	28 (1.3)	5.52	-1.01	(-4.11, 2.09)
Hypersensitivity/cutaneous reactions	30 (1.4)	6.12	23 (1.0)	4.53	-1.59	(-4.51, 1.34)
Male GMI	***3 (0.2)***	***0.92***	***28 (1.9)***	***8.41***	***7.49***	***(4.08, 10.91)***
Female GMI	***10 (1.4)***	***6.14***	***22 (2.9)***	***12.60***	***6.46***	***(-0.26, 13.17)***
VTE	16 (0.7)	3.26	21 (1.0)	4.14	0.87	(-1.58, 3.33)
Pancreatitis (adjudicated)	***2 (0.1)***	***0.41***	***5 (0.2)***	***0.98***	***0.58***	***(-0.68, 1.83)***
Photosensitivity	1 (<0.1)	0.20	1 (<0.1)	0.20	-0.01	(-0.79, 0.78)

AE: adverse event; AKI: acute kidney injury; Cana: canagliflozin; CI: confidence interval; DKA: diabetic ketoacidosis; GMI: genital mycotic infection; IRD: incidence rate difference; VTE: venous thromboembolic events; UTI: urinary tract infection

The most important AEIs are discussed in more detail in the following.

Hypoglycaemia

No relevant differences in the incidence of any hypoglycaemia, severe or documented hypoglycaemia were observed between cana- and plc-treated patients (see table below). The event rate of documented hypoglycaemia was numerically lower for cana than for plc.

Table 18: Documented Hypoglycemia Episodes - Biochemically Documented and/or Severe (Study 28431754-DNE3001: On-Treatment Analysis Set)

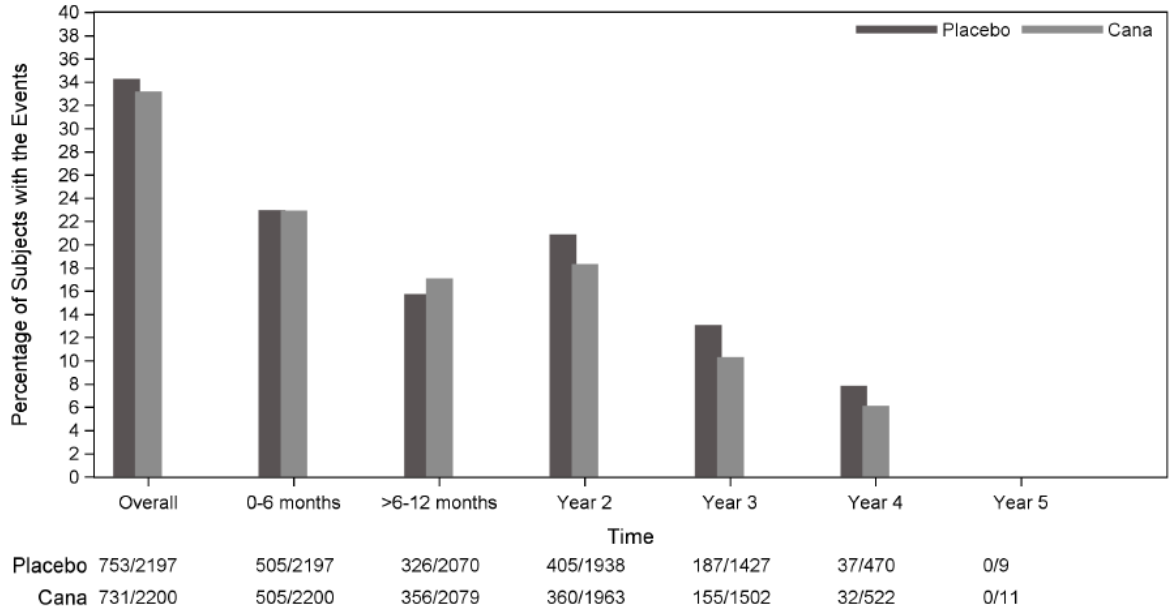
	Placebo (N=2197) n(%)	Cana (N=2200) n(%)
Subjects with any documented hypoglycaemia	**756 (34.4)**	**732 (33.3)**
Biochemically documented hypoglycemia	747 (34.0)	729 (33.1)
Severe hypoglycemia	**70 (3.2)**	**57 (2.6)**
Subjects with episodes of biochemically documented hypoglycemia*	747 (34.0)	729 (33.1)
⩽ 70 mg/dL (3.9 mmol/L)	747 (34.0)	729 (33.1)
< 56 mg/dL (3.1 mmol/L)	405 (18.4)	348 (15.8)
< 36 mg/dL (2.0 mmol/L)	45 (2.0)	40 (1.8)
Total number of episodes of documented hypoglycaemia	9696	8742
Subjects with numbers of documented hypoglycaemia	756 (34.4)	732 (33.3)
1 episode	176 (8.0)	175 (8.0)
2 episodes	100 (4.6)	100 (4.5)
⩾ 3 episodes	480 (21.8)	457 (20.8)
Event rate of documented hypoglycemia per subject-year exposure**	**1.98**	**1.72**

Note: Count and (%) are based on number of subjects, not number of episodes.

* Subjects with any biochemically documented hypoglycemia episodes; Results of LOW are included in all the three glucose categories (i.e., ≤ 70, <56, and/or <36 mg/dL). Note: A subject may be counted in each of the three glucose categories.

** The Denominator is the total of each subject's exposure of the study medication plus 30 days.

The MAH also pointed out that hypoglycaemia events became less frequent during the course of the CREDENCE Study, particularly after Year 2. This is depicted in the figure below. This lower hypoglycaemia rate was not accompanied by an unfavourable increase in HbA1c or fasting blood glucose (see efficacy section).



Placebo	753/2197	505/2197	326/2070	405/1938	187/1427	37/470	0/9
Cana	731/2200	505/2200	356/2079	360/1963	155/1502	32/522	0/11

Figure 19 : Over Time Summary of Subjects with Documented Hypoglycemia Episodes (Study 28431754-DNE3001: On-Treatment Analysis Set)

DKA

Diabetic ketoacidosis and possible ketone-related adverse events were identified by the sponsor using a prespecified list of MedDRA terms and adjudicated by an independent adjudication committee. Although the term "hyperglycemia" was not included in the list of prespecified terms, 1 event of "hyperglycemia" was submitted for adjudication. Prior to the decision to form an external DKA adjudication committee, this case had been reviewed by an internal DKA committee and determined to be a DKA event. This case was also reviewed by the DKA adjudication committee and adjudicated as a DKA event.

For adverse events that were not serious, only those presenting with signs and symptoms suggestive of DKA and/or those that required medical intervention (as captured on the DKA eCRF) were to be adjudicated. This approach was aimed at eliminating the need to adjudicate incidental findings of limited clinical relevance (e.g., presence of urine ketones or low bicarbonate levels in the absence of symptoms and/or treatment). For cases adjudicated as events of DKA, the adjudication committee was also required to adjudicate for the presence of precipitating factors, severity (based on clinical and biochemical parameters), evidence of autoimmune diabetes (based on availability of auto-antibodies results), blood glucose level at the time of diagnosis, and whether the event was a primary event or secondary event (i.e., leading to hospitalization or occurring in the context of other condition for which subject was already hospitalized).

Of the 52 cases submitted for adjudication, 13 (25.0%) were adjudicated as DKA events (either confirmed, probable, or possible). Of the 13 cases adjudicated as DKA events, 12 were reported as adverse events of DKA in 11 subjects in the cana group, and 1 was reported as hyperglycaemia in the placebo group. The event rate was markedly higher in the cana than in the plc group: 2.17 per 1000 subject-years in the cana group vs. 0.2/1000 subj-y in the plc group. For further details, see table below.

Table 19: Summary of Adjudicated Diabetic Ketoacidosis - Exposure-adjusted (Study 28431754-DNE3001: On-Treatment Analysis Set)

	Placebo (N=2197)		**Canagliflozin (N=2200)**	
	n (%)	Rate (/1000 subj-years)	n (%)	Rate (/1000 subj-years)
Any DKA Adverse Event	**1 (<0.1)**	**0.20**	**11 (0.5)**	**2.17**
Adverse Events Leading to Discontinuation	1 (<0.1)	0.20	6 (0.3)	1.18
Adverse Events Related to Study Drug*	0	0.00	2 (0.1)	0.39
Adverse Events Related to Study Drug* and Leading to Discontinuation	0	0.00	2 (0.1)	0.39
Serious DKA Adverse Event	**1 (<0.1)**	**0.20**	**9 (0.4)**	**1.77**
Serious Adverse Events Leading to Discontinuation	1 (<0.1)	0.20	4 (0.2)	0.79
Serious Adverse Events Related to Study Drug*	0	0.00	2 (0.1)	0.39
Serious Adverse Events Related to Study Drug* and Leading to Discontinuation	0	0.00	2 (0.1)	0.39
Death	0	0.00	0	0.00

*Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related

Severity: In the 11 cana patients suffering DKA, 12 events occurred. Of these, 3 were considered mild, 4 moderate and 5 severe. The case in the placebo group was considered moderate.

According to the MAH, in ten of the twelve events in the cana group, precipitating factors for DKA were present. Among others, as precipitating factors were counted: Recent reduction in insulin dose, drugs affecting carbohydrate metabolism, reduction in caloric/carbohydrate intake, recent alcohol consumption, dehydration.

DKA and renal function: Of the eleven subjects in the cana group suffering DKA, six had Stage 3B CKD (eGFR 30 to <45), three had Stage 3A (eGFR 45 to <60) and two had Stage 2 (eGFR 60 to <90). In total, 655 subjects in the cana group had Stage 3B CKD, 640 patients had Stage 3A and 905 patients Stage 2. Thus, DKA risk increased with decreasing renal function, from 2/905 (0.2%) in Stage 2 via 3/640 (0.5%) in Stage 3A to 6/655 (0.9%) in Stage 3B. The case in the placebo group had CKD Stage 3B.

Lower-limb amputation

Following CREDENCE protocol Amendment INT-5 (06 May 2016), lower-extremity amputation was designated as an adverse event of interest and a Lower-extremity Amputation eCRF form was employed to systematically capture details relating to the amputation procedure. Prior to the introduction of the dedicated eCRF page, events of amputation were recorded by the investigators within the Diagnostic and Therapeutic Procedures eCRFs.

CREDENCE protocol Amendment INT-5 also added a criterion to exclude subjects with a history of atraumatic amputation within 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening. No subjects were recorded to have been excluded due to this criterion. Protocol Amendment INT-5 instructed sites to interrupt study drug for subjects who developed conditions that may be associated with amputation (e.g., lower-extremity infection, skin ulcer, osteomyelitis, gangrene, or critical limb ischemia), until the condition had resolved based upon the investigator assessment. Following the release of the amendment, a total of 130 (3.0%) subjects were noted to have prematurely discontinued study drug resulting from an adverse event of the lower-extremity or personal choice relating to the risk of lower-extremity amputation. These discontinuations were balanced between treatment groups (65 patients in the cana and 65 patients in the plc group). In the event of an

amputation, restarting study drug was only to be done after careful consideration of the individual risk-benefit and following discussion with the sponsor.

Approximately 70% of subjects had been randomized at the time when protocol Amendment INT-5 was issued (May 2016). While the majority of subjects had been randomized at this time, less than 20% of total follow-up time was before the amendment. It is unclear what impact, if any, the amendment had on the risk of amputation as the number of subjects experiencing their first event was generally comparable between treatment groups before and after May 2016. Specifically, there were 16 and 12 subjects in the placebo group and cana group, respectively, who experienced an amputation prior to when the amendment was issued as compared to 47 and 58 subjects who experienced an amputation after the amendment was issued, in the same respective groups.

The following table lists the amputation events in CREDENCE and their localisation. The total amputation rate was slightly higher in the cana compared to the plc group (12.14 vs. 11.02 events per 100 subject-years). Reassuringly, the rate of major amputations (ankle or above) was lower with can than with plc (3.82 vs. 4.90, cana vs. plc).

Table 20: Post-Randomization Atraumatic Lower Limb Amputation by the Highest Location (Study 28431754-DNE3001: On-Study Analysis Set)

	Placebo (N=2197)		Cana (N=2200)		Cana vs. Placebo			
	n (%)	Rate (/1000 subj-y)	n (%)	Rate (/1000 subj-y)	IRD(/1000 subj-y)	95% CI	**HR**	95% CI
Total amputations	63 (2.9)	11.02	70 (3.2)	12.14	1.12	(-2.84, 5.09)	**1.11**	(0.79, 1.56)
Minor amputation	35 (55.6)	6.12	48 (68.6)	8.33	2.20	(-0.94, 5.35)	**1.37**	(0.88, 2.11)
Toe	31 (49.2)	5.42	39 (55.7)	6.77	1.34	(-1.55, 4.24)		
Trans-metatarsal	4 (6.3)	0.70	9 (12.9)	1.56	0.86	(-0.48, 2.20)		
Major amputation	28 (44.4)	4.90	22 (31.4)	3.82	-1.08	(-3.55, 1.38)	**0.78**	(0.44, 1.36)
Ankle	1 (1.6)	0.17	0	0.00	-0.17			
Below-knee	16 (25.4)	2.80	10 (14.3)	1.73	-1.06	(-2.88, 0.75)		
Above-knee	11 (17.5)	1.92	12 (17.1)	2.08	0.16	(-1.56, 1.87)		

AEs related to lower extremity other than amputation

As shown in the following table, the incidence of lower extremity events (beside amputation) was slightly higher in the cana than in the plc group (55.5 vs. 51.6 events per 100 pat-years, cana vs. plc). This difference was mainly driven by the term "diabetic foot".

Table 21: Post-Randomization Lower-extremity Event by Preferred Term in at Least 0.5% of Subjects in Any Treatment Group (Study 28431754-DNE3001: On-Study Analysis Set)

	Placebo	**Cana**
	(N=2197)	(N=2200)
Dictionary-Derived Term	n (%)	n (%)
Total no. subjects with the AEs	**295 (13.4)**	**320 (14.5)**
Incidence rate per 1000 person-years	**51.61**	**55.52**
Cellulitis	64 (2.9)	58 (2.6)
Diabetic foot	***33 (1.5)***	***49 (2.2)***
Erysipelas	10 (0.5)	9 (0.4)
Extremity necrosis	10 (0.5)	13 (0.6)
Gangrene	18 (0.8)	18 (0.8)
Infected skin ulcer	15 (0.7)	10 (0.5)
Intermittent claudication	6 (0.3)	11 (0.5)
Localised infection	19 (0.9)	19 (0.9)
Osteomyelitis	24 (1.1)	24 (1.1)
Peripheral arterial occlusive disease	38 (1.7)	45 (2.0)

Peripheral ischaemia	11 (0.5)	3 (0.1)
Peripheral vascular disorder	20 (0.9)	16 (0.7)
Skin ulcer	87 (4.0)	110 (5.0)
Wound	14 (0.6)	9 (0.4)

The imbalance in diabetic foot AE obviously was not caused by an imbalance of this condition at baseline as shown in the following table. "Peripheral Diabetic Neuropathy" was well balanced between the treatment groups at baseline, 40.7 vs. 40.4% (plc vs. cana).

Table 22 (shortened): Baseline Diabetes Characteristics (Study 28431754-DNE3001: Intent-to-Treat Analysis Set)

Subjects with microvascular complications of diabetes, n (%)	Placebo	Cana	Total
N	2199	2202	4401
Any	2199 (100)	2202 (100)	4401 (100)
Autonomic Neuropathy	121 (5.5)	112 (5.1)	233 (5.3)
Other Diabetic Neuropathy	327 (14.9)	327 (14.9)	654 (14.9)
Peripheral Diabetic Neuropathy	***894 (40.7)***	***890 (40.4)***	***1784 (40.5)***
Diabetic Retinopathy	947 (43.1)	935 (42.5)	1882 (42.8)
Diabetic Nephropathy	2199 (100)	2202 (100)	4401 (100)

Fracture

In the initial MAA of cana a higher rate of fractures was observed with cana vs. comparators. It was not clear whether this observation was due to increased number of falls due to cana-related dehydration / syncope or whether cana can affect bone mineral density via effects on calcium metabolism (which would become more pronounced after longer treatment). In the CREDENCE Study (see table below), no major difference in fracture rate between the cana and the plc group was observed.

Table 23: Rate Difference and 95% CI of Post-Randomization Adjudicated Fracture by Fracture Type (Study 28431754-DNE3001: On-Study Analysis Set)

	Placebo (N=2197)		Cana (N=2200)		Cana vs. Placebo	
	n (%)	Rate (/1000 subj-y)	n (%)	Rate (/1000 subj-y)	IRD(/1000 subj-y)	95% CI
Total no. subjects with adjudicated fracture	**68 (3.1)**	**12.09**	**67 (3.0)**	**11.80**	-0.29	(-4.35, 3.77)
Total no. subjects with adjudicated fracture	68 (100)	12.09	67 (100)	11.80	-0.29	(-4.35, 3.77)
High trauma	10 (14.7)	1.78	7 (10.4)	1.23	-0.55	(-2.07, 0.98)
Low trauma	48 (70.6)	8.53	51 (76.1)	8.98	0.45	(-3.04, 3.93)
Pathological	2 (2.9)	0.36	1 (1.5)	0.18	-0.18	(-1.03, 0.67)
Stress	0	0.00	2 (3.0)	0.35	0.35	
Other	10 (14.7)	1.78	6 (9.0)	1.06	-0.72	(-2.21, 0.76)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Also, the Kaplan-Meier plot shown below does not indicate an increasing fracture risk with cana over time.

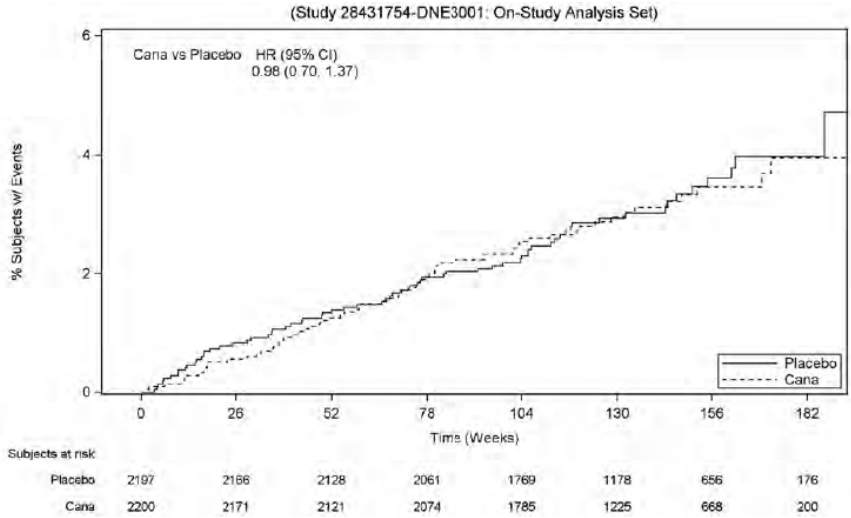


Figure 20: Kaplan-Meier Plot of Post-Randomization Adjudicated Fracture

Breast cancer

Imbalances in the incidence of certain malignancies were observed in some clinical trials or were suspected based on the mode of action. In the CREDENCE trial, cases of breast cancer were rather frequent, and there was a numerical imbalance between the cana and the plc group:

Eight women in the canagliflozin group and 3 women in the placebo group experienced adverse events of breast cancer. The incidence rate of any adverse event of breast cancer was **4.08** and **1.59** per 1,000 subject-years in the canagliflozin and placebo groups, respectively.

Three of the adverse events (all in subjects in the canagliflozin group) occurred within the first 6 months after study drug initiation.

The incidence rate excluding subjects with events in the first 6 months after study drug initiation was **3.16** and **1.96** per 1,000 subject-years in the canagliflozin and placebo groups, respectively.

Male GMI

Mycotic genital infection, also in males, is a known side effect of SGLT2 inhibitors. For the CREDENCE study, in the On-treatment analysis set among male subjects, a higher incidence of mycotic genital infection adverse events was reported in the canagliflozin group than in the placebo group. The incidence rates were 8.41 and 0.92 per 1,000 subject-years in the canagliflozin and placebo groups, respectively. No event was considered serious; most were considered related to study drug by the investigator (even in the plc group), and around one sixth led to discontinuation. For further details, see table below.

For comparison, in the CANVAS/CANVAS-R pooled dataset, the adjusted-incidence rates of any male mycotic genital infection were 31.74 and 9.62 per 1,000 subject-years in the combined canagliflozin and placebo groups, respectively.

Table 24 (shortened): Summary of Male Mycotic Genital Infection - Exposure-adjusted (Study 28431754-DNE3001: On-Treatment Analysis Set)

	Placebo (N=1466)		**Cana (N=1439)**	
	n(%)	Rate/1000pt-yrs	n(%)	Rate/1000pt-yrs
Any AE of Male Mycotic Genital Infection	**3 (0.2)**	**0.92**	**28 (1.9)**	**8.41**
Adverse Events Leading to Discontinuation	0	0.00	5 (0.3)	1.50
Adverse Events Related to Study Drug	2 (0.1)	0.61	23 (1.6)	6.91
Serious Adverse Events	0	0.00	0	0.00

Female GMI

The incidence of female mycotic genital infection was around twice in the cana group compared to the plc group (12.60 vs. 6.14 events per 1000 subject-years, see table below). No events were considered serious and only a small fraction led to discontinuation. However, many events were considered related to the study drug, also in the plc group. This may be due to the fact that mycotic genital infection is a known side effect of SGLT2 inhibitors so that a relationship was suspected by the investigators.

For comparison, in the CANVAS INT-6 dataset, the adjusted-incidence rate of any female mycotic genital infection adverse event was 68.85 per 1,000 subject-years in the cana group and 17.52 per 1,000 subject-years in the plc group.

Table 25: Summary of Female Mycotic Genital Infection - Exposure-adjusted (Study 28431754-DNE3001: On-Treatment Analysis Set)

	Placebo (N=731)		**Cana (N=761)**	
	n(%)	Rate/1000pt-yrs	n(%)	Rate/1000pt-yrs
Any AE of Female Mycotic Genital Infection	**10 (1.4)**	**6.14**	**22 (2.9)**	**12.60**
Adverse Events Leading to Discontinuation	0	0.00	2 (0.3)	1.15
Adverse Events Related to Study Drug	4 (0.5)	2.46	13 (1.7)	7.44
Serious Adverse Events	0	0.00	0	0.00

VTE

Dehydration is a known side effect of SGLT2 inhibitors. Venous Thromboembolic Events (VTEs) are rare but serious consequences of dehydration. Therefore, VTE was specifically addressed in large studies such as CREDENCE.

VTEs were numerically more frequent with cana than with plc (4.14 vs. 3.26 events per 1000 subj-years, cana vs. plc) in CREDENCE. No imbalance was observed in VTE regarded serious. VTE most often did not lead to discontinuation of study drug and was not considered related to study drug by the investigator. There was an imbalance disfavouring cana in respect to fatal VTEs (3 events vs. 1 event, cana vs. plc). For further details, see the following table.

Table 26: Summary of Venous Thromboembolic Events - Exposure-adjusted (Study 28431754-DNE3001: On-Treatment Analysis Set)

	Placebo (N=2197)		Cana (N=2200)	
	n(%)	Rate/1000pt-yrs	n(%)	Rate/1000pt-yrs
Any Adverse Event of VTE	**16 (0.7)**	**3.26**	**21 (1.0)**	**4.14**
Adverse Events Leading to Discontinuation	2 (0.1)	0.41	1 (<0.1)	0.20
Adverse Events Related to Study Drug	1 (<0.1)	0.20	1 (<0.1)	0.20
Serious Adverse Events	**11 (0.5)**	**2.24**	**11 (0.5)**	**2.17**
Serious Adverse Events Leading to Discontinuation	2 (0.1)	0.41	1 (<0.1)	0.20
Serious Adverse Events Related to Study Drug*	0	0.00	1 (<0.1)	0.20
Death	**1 (<0.1)**	**0.20**	**3 (0.1)**	**0.59**

Pancreatitis

In the CREDENCE trial it turned out that there was a numerical imbalance in the incidence of pancreatitis between the cana and the plc group. Due to the low number of cases per study, the MAH also provided a pooled analysis of pancreatitis across all phase 3 and phase 4 studies (Data Set [DS] 8). The results are tabulated below. The incidence of pancreatitis was small; around 0.1% of the patients had a pancreatitis event. There was a numerical imbalance in incidence also in the pooled analysis (0.59 vs. 0.32 events per 1000 subj-years).

Summary of Treatment-Emergent Adverse Events - Adjudicated Pancreatitis (DS8)

	All Cana (N=13278)	All Non-cana (N=9367)
n(%) With at least one pancreatitis AE (b)	**17 (0.13)**	**6 (0.06)**
Incidence Rate per 1000 person-years exposure (d)	**0.59**	**0.32**
Odds Ratio & 95% confidence interval (a)	2.00 (0.75,6.20)	
Seriousness (n,(%))		
Was Serious	16 (0.12)	6 (0.06)
Severity (n,(%))		
Severe	9 (0.07)	6 (0.06)
Mild/Moderate	8(0.06)	0
Total No. Pancreatitis Events	19	8
Outcome (c)		
Recovered/Resolved	19 (100)	8 (100)
Recovering/Resolving	0	0
Not Recovered/Not Resolved	0	0
Recovered/Resolved with Sequelae	0	0
Fatal	0	0
Unknown	0	0
Not Reported	0	0

(a) Based on Fisher's exact test.
(b) Denominators are the total number of subjects in each group; the subject is counted only once regardless of the number of events or the number of occurrences.

(c) Denominators are the total number of events in each group.
(d) Exposure adjusted incidence rate is calculated as 1000*(the total number of subjects with at least one specified event divided by the total person-year exposure in each treatment group).

Photosensitivity

During MAA there were remaining uncertainties whether cana is phototoxic. Therefore, this issue was now addressed with the pool of phase 3 and phase 4 studies (Data Set 8 [DS8]), including the CREDENCE study and the complete CANVAS programme. As shown in the table below, photosensitivity events were rare but were numerically more frequent with cana (incidence rate 0.93 vs. 0.47 events per 1000 subject-years).

Summary of Treatment-Emergent Adverse Events - Photosensitivity (DS8)

	All Cana (N=13278)	All Non-cana (N=9367)
n(%) With at least one photosensitivity AE (b)	**27 (0.20)**	**9 (0.10)**
Incidence Rate per 1000 person-years exposure (d)	**0.93**	**0.47**
Odds Ratio & 95% confidence interval (a)	2.12 (0.97,5.12)	
Seriousness (n,(%))		
Was Serious	0 (0.0)	0 (0.0)
Severity (n,(%))		
Severe	2(<0.1)	0
Mild/Moderate	25 (0.2)	9 (0.1)
Total No. Photosensitivity Events	29	11
Outcome (c)		
Recovered/Resolved	23 (79.3)	9 (81.8)
Recovering/Resolving	1 (3.4)	2 (18.2)
Not Recovered/Not Resolved	4 (13.8)	0
Recovered/Resolved with Sequelae	1 (3.4)	0
Fatal	0	0
Unknown	0	0
Not Reported	0	0

(a) Based on Fisher's exact test.
(b) Denominators are the total number of subjects in each group; the subject is counted only once regardless of the number of events or the number of occurrences.
(c) Denominators are the total number of events in each group.
(d) Exposure adjusted incidence rate is calculated as 1000*(the total number of subjects with at least one specified event divided by the total person-year exposure in each treatment group).

Lactic acidosis

There is a theoretical concern that cana administered to renally insufficient patients could increase the risk of metformin-related lactic acidosis. Therefore, in the CREDENCE study, a post hoc review of lactic acidosis cases was performed. On-treatment events of lactic acidosis occurred in 7 subjects (4 canagliflozin subjects and 3 placebo subjects). Cases of lactic acidosis generally occurred in the presence of a serious adverse event of hypovolemia, or respiratory or circulatory compromise.

In the **DS6M dataset** (pooled patients receiving metformin from all phase 3 and phase 4 studies except CREDENCE), there were 6 events of lactic acidosis (canagliflozin: 3 subjects; placebo: 3 subjects). The incidence rates were 0.16 per 1,000 subject-years for cana and 0.27 per 1,000 subject-years for plc. The odds ratio was 0.69 (95% CI: 0.09, 5.17). Half of the subjects reported serious events and most events were severe. There were 2 fatal events (canagliflozin: 1 subject; placebo: 1 subject) and all other events resolved or were resolving.

In conclusion, there is no hint that cana increases the risk for metformin-related lactic acidosis.

Serious adverse event/deaths/other significant events

Deaths

Fatal events were less frequent in the cana than in the plc group of the CREDENCE trial. This is in line with the efficacy findings that CV mortality and all-cause mortality were (at least numerically) reduced by cana compared to plc. On the other hand, HR for CV death (0.78) was somewhat more favourable than for all-cause death (0.83) so that the question remains what were the reasons of death in patients dying from non-CV events, i.e. is there a condition which more frequently leads to death in the cana than in the plc group.

Fatal AEs:

Imbalance disfavouring cana was observed for respiratory disorders (see table below). No specific condition underlying this observation could be clearly identified; acute pulmonary oedema and respiratory failure appear to play a role. Otherwise the number of events is too small for firm conclusions.

TSFAE00_FATAL_OS_A: Any Post-Randomization Fatal Adverse Events by Body System and Preferred Term with Rate Difference and 95% CI (Study 28431754-DNE3001: On-Study Analysis Set)

	Placebo (N=2197)		**Canagliflozin (N=2200)**		**Canagliflozin vs. Placebo**	
	n (%)	Rate (/1000 subj-years)	n (%)	Rate (/1000 subj-years)	IRD (/1000 subj-years)	95% CI
Respiratory, thoracic and mediastinal disorders	**15 (0.7)**	**2.62**	**22 (1.0)**	**3.82**	**1.19**	**(-0.94, 3.33)**
Acute pulmonary oedema	1 (<0.1)	0.17	3 (0.1)	0.52	0.35	(-0.52,1.21)
Acute respiratory distress syndrome	0	0.00	1 (<0.1)	0.17	0.17	
Acute respiratory failure	5 (0.2)	0.87	6 (0.3)	1.04	0.17	(-1.09,1.42)
Chronic respiratory failure	0	0.00	1 (<0.1)	0.17	0.17	
Laryngeal haematoma	0	0.00	1 (<0.1)	0.17	0.17	
Pneumonia aspiration	2 (0.1)	0.35	0	0.00	-0.35	
Pulmonary embolism	1 (<0.1)	0.17	2 (0.1)	0.35	0.17	(-0.66,1.01)
Pulmonary infarction	0	0.00	1 (<0.1)	0.17	0.17	
Pulmonary oedema	3 (0.1)	0.52	1 (<0.1)	0.17	-0.35	(-1.22,0.52)
Respiratory arrest	0	0.00	1 (<0.1)	0.17	0.17	
Respiratory failure	4 (0.2)	0.70	6 (0.3)	1.04	0.34	(-0.87,1.55)

SAEs

The total number of SAEs was lower in the cana than in the plc group of the CREDENCE study (see section "overview of AEs" above). The following table lists SAEs per organ system. In all organ classes SAE incidence was similar between cana and plc or was lower in the cana group with the exception of skin / subcutaneous tissue. This difference was due to a higher incidence of diabetic foot and skin ulcer in the cana group. Lower limb amputation (due to diabetic foot disease) was defined as AE of special interest and is discussed in the respective section above.

Most pronounced differences between cana and plc (cana better) were observed for "Metabolism and nutrition disorders" and "Investigations: Blood creatinine increased". This is in line with the desired effect of cana.

TSFAE01C_SAE: Serious Adverse Events in at Least 0.5% of Subjects in Any Treatment Group by Body System and PreferredTerm (Study 28431754-DNE3001: On-Treatment Analysis Set)

Body System Or Organ Class	**Placebo N=2197 n (%)**	**Cana N=2200 n (%)**
Total no. subjects with SAE	806 (36.7)	737 (33.5)
Blood and lymphatic system disorders	**18 (0.8)**	**16 (0.7)**
Anaemia	10 (0.5)	7 (0.3)
Cardiac disorders	**261 (11.9)**	**198 (9.0)**
Acute coronary syndrome	8 (0.4)	12 (0.5)
Acute myocardial infarction	38 (1.7)	38 (1.7)
Angina pectoris	14 (0.6)	21 (1.0)
Angina unstable	29 (1.3)	17 (0.8)
Atrial fibrillation	19 (0.9)	16 (0.7)
Cardiac failure	50 (2.3)	34 (1.5)
Cardiac failure congestive	48 (2.2)	24 (1.1)
Coronary artery disease	23 (1.0)	9 (0.4)
Myocardial infarction	27 (1.2)	22 (1.0)
Infections and infestations	**265 (12.1)**	**211 (9.6)**
Cellulitis	26 (1.2)	18 (0.8)
Gangrene	15 (0.7)	10 (0.5)
Gastroenteritis	19 (0.9)	6 (0.3)
Osteomyelitis	11 (0.5)	11 (0.5)
Pneumonia	86 (3.9)	63 (2.9)
Sepsis	12 (0.5)	11 (0.5)
Septic shock	12 (0.5)	5 (0.2)
Urinary tract infection	21 (1.0)	25 (1.1)
Investigations	**29 (1.3)**	**13 (0.6)**
Blood creatinine increased	20 (0.9)	7 (0.3)
Metabolism and nutrition disorders	**88 (4.0)**	**71 (3.2)**
Diabetes mellitus	10 (0.5)	5 (0.2)
Diabetes mellitus inadequate control	12 (0.5)	7 (0.3)
Hyperglycaemia	11 (0.5)	1 (<0.1)
Hyperkalaemia	10 (0.5)	10 (0.5)
Hypoglycaemia	11 (0.5)	17 (0.8)
Musculoskeletal and connective tissue disorders	**44 (2.0)**	**32 (1.5)**
Osteoarthritis	11 (0.5)	10 (0.5)
Nervous system disorders	**111 (5.1)**	**106 (4.8)**
Cerebrovascular accident	36 (1.6)	30 (1.4)
Ischaemic stroke	17 (0.8)	14 (0.6)
Transient ischaemic attack	4 (0.2)	10 (0.5)
Renal and urinary disorders	**115 (5.2)**	**101 (4.6)**
Acute kidney injury	50 (2.3)	41 (1.9)
Chronic kidney disease	12 (0.5)	12 (0.5)
Diabetic nephropathy	10 (0.5)	12 (0.5)
End stage renal disease	23 (1.0)	16 (0.7)
Renal impairment	7 (0.3)	10 (0.5)
Respiratory, thoracic and mediastinal disorders	**66 (3.0)**	**59 (2.7)**
Chronic obstructive pulmonary disease	16 (0.7)	9 (0.4)
Respiratory failure	10 (0.5)	10 (0.5)
Skin and subcutaneous tissue disorders	**21 (1.0)**	**42 (1.9)**
Diabetic foot	10 (0.5)	15 (0.7)
Skin ulcer	8 (0.4)	18 (0.8)
Vascular disorders	**71 (3.2)**	**69 (3.1)**
Peripheral arterial occlusive disease	11 (0.5)	10 (0.5)

Laboratory findings

Serum chemistry

In general, changes in serum chemistry values from baseline to end of treatment were small to moderate in magnitude and consistent with the known effects of canagliflozin. Generally, the trends for the overall population was similar in each of the 3 eGFR strata (30 to <45, 45 to <60 and 60 to <90 mL/min/1.73 m^2, respectively).

Blood urea nitrogen increased in both treatment groups from baseline to end of treatment. The difference between cana and plc was small.

Creatinine was balanced across treatment groups at baseline. Subjects in both treatment groups demonstrated an increase in creatinine from baseline to end of treatment (30.54 and 38.81 µmol/L for the cana and placebo groups, respectively). The difference in LS means was -8.27 µmol/L; see also efficacy section

Urate was balanced across treatment groups at baseline. Subjects in the cana group demonstrated a mean decrease (-5.21 µmol/L) from baseline to end of treatment in serum urate while subjects in the placebo group demonstrated a mean increase (6.84 µmol/L) from baseline to end of treatment. The difference in LS means was -12.05 µmol/L. Change from baseline to end of treatment in urate varied by eGFR strata, with larger between-group differences observed with increasing baseline eGFR (-4.14, -10.92 and -18.65 µmol/L in the eGFR 30 to <45, 45 to <60 and 60 to <90 mL/min/1.73 m^2 stratum, respectively).

Magnesium: A higher proportion of subjects in the cana group (2.1%) than in the placebo group (0.6%) experienced any postbaseline increased values of magnesium (>ULN and >25% increase from baseline). There was a steep increase in serum magnesium in the cana group from baseline to Week 13. Thereafter, the difference between cana and plc remained essentially constant.

Otherwise the number of subjects with serum chemistry values (including liver function parameters) outside the predefined limits for any postbaseline value was similar for the cana and the plc group.

Regarding serum cholesterol, no difference in LDL/HDL ratio between cana and plc was observed; see also efficacy section.

Haematology

There was a sharp increase in haemoglobin and haematocrit immediately after starting of treatment in the cana group compared to plc. This is a known effect of SGLT2 inhibitors and most likely reflects dehydration.

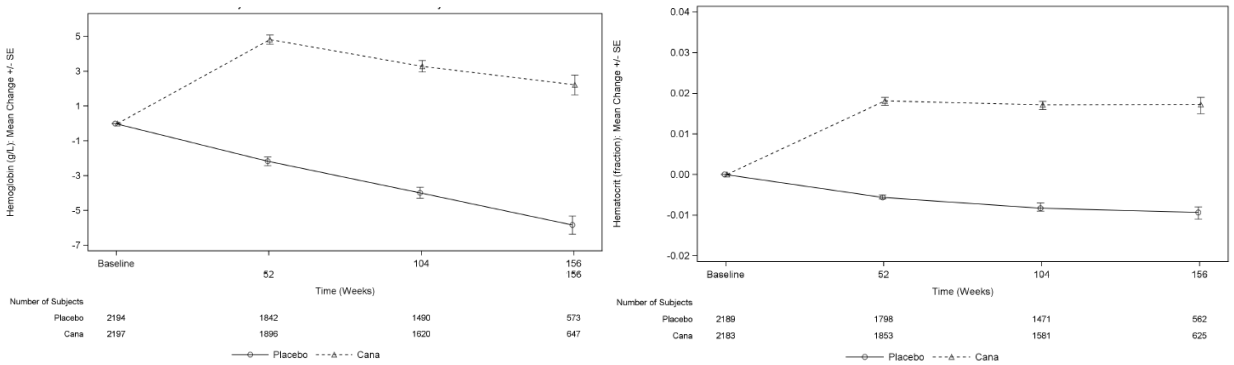


Figure GSFLAB09A: Mean change from baseline in haemoglobin (left) and haematocrit (right) over time; Study DNE-3001, on-treatment analysis set

No relevant differences between cana and plc were observed in respect to white blood cells and platelets.

Vital signs

Blood pressure (BP)

The was a marked decrease in systolic and (less pronounced) diastolic blood pressure immediately after commencing treatment in the cana group. Thereafter, the difference between the cana and plc group remained relatively constant. This effect was not dependent on renal function. The following figure shows an example (systolic BP in patient with eGFR between 30 and <45 mL/min/1.73m^2. At Week 13, the difference between cana and plc was around -4 mmHg in this eGFR stratum. At the end of treatment, the difference in systolic BP was -2.7 mmHg (all patients) and in diastolic BP -1.5 mmHg; see also efficacy section.

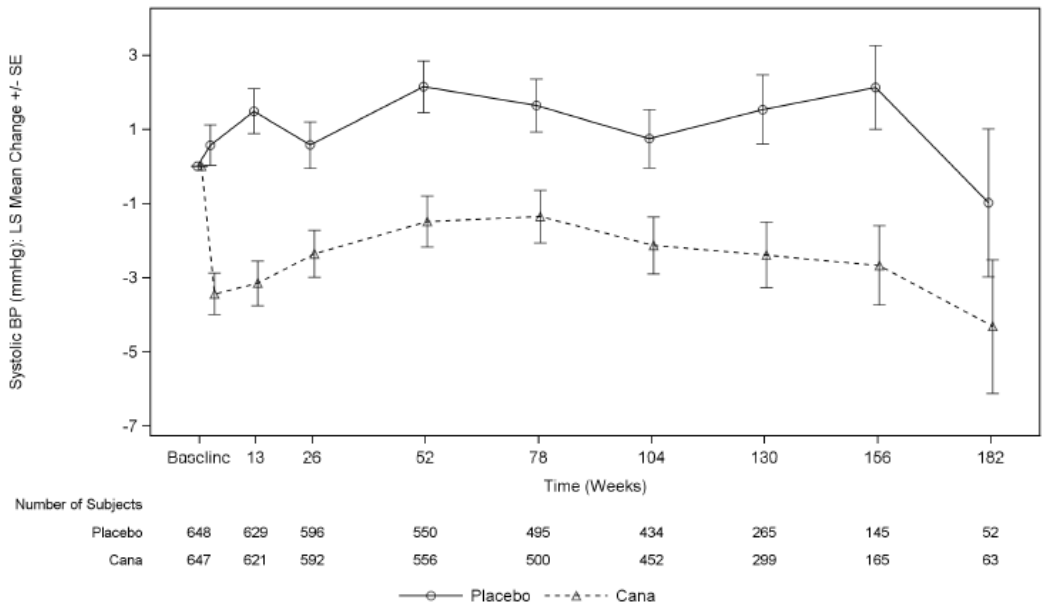


Figure GEFOBP02A_GFR1: LS Mean Change from Baseline in Systolic Blood Pressure Over Time for Screening eGFR Stratum >=30 to <45 mL/min/1.73m^2

Heart rate

Heart rate did not differ between the cana and the plc group.

Discontinuation due to adverse events

AEs leading to discontinuation were fairly balanced between the cana and the plc group, 286 pts. (13.0%) receiving plc vs.267 pts. (12.1%) receiving cana discontinued due to an AE.

The most prominent cause for discontinuation due to AE were renal and urinary disorders (43 [2.0%] vs. 42 [1.9%] patients, plc vs. cana).

SAEs leading to discontinuation were numerically more frequent in the placebo group: 159 pts. (7.2%) receiving plc vs. 134 pts. (6.1%) receiving cana discontinued due to a serious AE.

The most prominent causes for discontinuation due to SAE were cardiac disorders (35 vs. 15 patients, plc vs. cana) and infections/infestations (36 vs. 22 patients [1.6% vs. 1.0%] plc vs. cana).

2.5.1. Discussion on clinical safety

The safety profile of canagliflozin is already known in general from previous clinical trials conducted for achieving initial MA, including a cardiovascular outcome trial (CANVAS). The evaluation of the CREDENCE trial particularly provided information on the safety profile of cana in patients with higher degrees of renal insufficiency. Furthermore, CREDENCE enlarged the data pool of large trials which can provide information on rare adverse events.

The most frequently reported AEs (n>5) for canagliflozin versus placebo were hypoglycaemia (10% vs. 11%), urinary tract infections (10.0% vs. 9.1%), hypertension (6.8% vs. 9.1%), blood creatinine increased (6.5% vs. 9.2%), hyperkalaemia (6.1% vs. 7.2%) and nasopharyngitis (5.9% vs. 6.1%). The total number and percentage of patients experiencing at least one adverse event were lower in the canagliflozin than in the placebo group (1784 [81.1%] vs. 1860 [84.7%]). Serious AEs were also less frequent with cana.

The overall high incidence of documented hypoglycaemia (33.1% vs. 34.0% [CANA vs placebo]) is expected, given the high rate (94-98% across the eGFR strata) of insulin and sulphonylurea use at baseline. The incidence of documented hypoglycaemia increased with decreasing eGFR. The incidence rates of severe hypoglycaemia were lower with canagliflozin compared to placebo across all three eGFR strata, and the highest incidence of severe hypoglycaemia was seen in subjects with the eGFR 30 to <45 mL/min/1.73 m2 (3.8% for CANA vs 4.1% for placebo).

Events of volume depletion were reported more frequently with canagliflozin (6.5%) than with placebo (5.2%). The incidence rate for volume depletion adverse events increased with decreasing eGFR. In subjects with eGFR ≥30 to <45 mL/min/1.73 m2, the rate of volume depletion was two times higher in the canagliflozin group (11%) compared to the placebo group (5.5%); however, in the subgroups eGFR ≥45 to <60 and eGFR ≥60 to <90 mL/min/1.73 m2, the incidence of volume depletion was similar in the canagliflozin and placebo group. Subjects ≥75 years of age had a higher incidence rate of volume depletion (9.8% vs 10.5% for canagliflozin vs placebo) compared with subjects <75 years (6.2% and 4.6% for canagliflozin vs placebo). Moreover, use of a loop diuretic at baseline increased the incidence rate of volume depletion (8.6% vs 6.5% for canagliflozin vs placebo) compared with no use of a loop diuretic at baseline (6.0% vs 4.9% for canagliflozin vs placebo). Overall, the increased incidence of volume depletion in the CKD Stage 3B subgroup could be explained by the markedly decreased renal function, advanced age and high proportion of known risk factors. Moreover, a greater proportion of subjects with eGFR 30-<45 (33%) used loop diuretics at baseline compared to subjects with eGFR 45-<60 (20%) and 60<90 (14%).

Renal-related events occurred frequently in both groups but less frequent in the canagliflozin group (13%) compared with the placebo group (18%). Serious and severe renal-related events were also lower in the canagliflozin group versus placebo. The incidence rates of renal-related events were lower with canagliflozin relative placebo across all three eGFR strata; the highest incidence of renal-related events was seen in subjects with the eGFR ≥30 to <45 mL/min/1.73 m2 stratum group (21% vs 27% for canagliflozin vs placebo). In the CREDENCE study, eGFR after study discontinuation was not assessed. In the CANVAS-R study, where assessments of eGFR after study drug discontinuation were performed, the eGFR for canagliflozin returned towards baseline after discontinuation. This demonstrates that canagliflozin-dependent decreases in eGFR were functional in nature and do not indicate renal damage.

Reassuringly, the total number of AEs and SAEs was lower in the cana than in the plc group. This was most pronounced for patients with higher degree of renal insufficiency (CKD Stage 3A and 3B). A possible explanation for this observation could be the fact that many AEs were related to kidney function (e.g. "Investigations: blood creatinine increased") or cardiovascular disease. In this respect the AE profile reflected the desired beneficial effects of cana.

However, the risk of diabetic ketoacidosis (DKA) appears to increase with decreasing renal function. There was a markedly increased rate of adjudicated DKA in the cana group compared to the plc group in the whole

study population (overall DKA: 2.17 vs. 0.2 cases per 1000 patient years, serious DKA: 0.2 vs. 1.77 cases per 1000 patient years, respectively). Still, the incidence was low, and most of the DKA events in the cana group occurred in patents with Stage 3B kidney disease. Since the absolute number of events was low, firm conclusions are not possible on the relation between CKD stage and DKA.

Efficacy evaluation revealed that the beneficial effect of cana on all-cause mortality was numerically smaller than on cardiovascular mortality. Analysis of fatal AEs suggested that the non-CV causes of death could be related to respiratory problems because fatal AEs related to respiration were slightly more frequent with cana than with plc. However, due the low number of cases, a chance finding cannot be excluded. Also, there is no clear mechanistic rationale for this observation.

A search for side effects of cana which were not detected previously revealed an imbalance in the incidence of pancreatitis, disfavouring cana. The incidence of pancreatitis was low (around 0.1% of patients affected) so that this type of AE was investigated in a pooled safety dataset, encompassing all phase 3 and phase 4 studies. In the large dataset, the incidence rate of pancreatitis was still larger in the pooled cana than in the pooled non-cana group (around two-fold), but since the absolute incidence was low, this is not considered to relevantly affect the benefit-risk profile of cana.

Another potential side effect of cana is photosensitisation. Studies performed for the initial MAA did not yield unambiguous results. Analysis using the large phase 3 / phase 4 dataset revealed a numerically higher incidence of events of photosensitivity with cana vs, non-cana treatments, but the incidence was still low, also in the cana group, so that this is not considered a safety concern. No specific measures to avoid sunlight exposure were recommended in the clinical studies so that a warning for users does not appear necessary.

Other potential safety issues of cana not yet fully elucidated include lower limb amputation and bone fracture. For the latter, the CREDENCE study revealed no relevant differences between the cana and the plc group, and Kaplan-Meier analysis gave no hint that fracture rate increased over time (which would be the case when one assumes that cana affects bone mineral density, e.g. via disturbance of calcium homeostasis). This is in line with previous evaluations of bone mineral density (BMD).

In the plc group of the CREDENCE study, 11.2 events of lower limb amputation per 1000 subject-years were observed vs. 12.3 events per 1000 subj-y in the cana group. This difference is small compared to the results of the CANVAS programme. The rate of major amputations (ankle or above) was not increased. For reduction of amputation risk, precautionary measures were introduced during the course of the CREDENCE study as Amendment INT-5. Further recruitment of patients at increased risk for amputation was stopped after this amendment, but patients at risk who were recruited prior to the amendment remained in the study. These patients could have contributed to the observed small increase in amputation rate with cana as compared to plc. The MAH intended updating the labelling in the SmPC stating that there was no difference in amputation rate between can and plc in this study. However, for better understanding why in CREDENCE virtually no increased amputation risk was observed, the SmPC was further amended by mentioning that the low or absent cana-related amputation risk in CREDENCE was due to precautionary measures. The study findings suggest that the precautionary measures, which are also included in the SmPC, are effective to minimize amputation risk.

Furthermore, AEs related to the lower limb other than amputation such as "diabetic foot" or "skin ulcer" were also slightly increased with cana. A more detailed analysis, also considering time-course, later revealed that the risk for diabetic foot increased in the first year of treatment only. This could be related to the fact that the effects of cana on circulation (dehydration, drop in blood pressure, decrease in eGFR) are most pronounced after initiation of therapy and become weaker thereafter, probably because of counter-regulatory mechanisms. This transient effect also explains why amputation risk during cana treatment was virtually not increased in patients without pre-existing diabetic foot.

The overall incidence of malignancies was balanced between the groups (6.7% vs 6.3% for canagliflozin vs placebo). The following malignancies 'of special interest' was discussed separately: Breast, bladder, renal and colorectal cancer. The incidence of colon cancer was low but imbalanced; 0.5% vs 0.2% for canagliflozin vs placebo when excluding events with an onset <180 days.

2.5.2. Conclusions on clinical safety

In patients with higher stages of CKD, the safety profile was in general comparable to the established safety profile in patients with better renal function. Incidence of AEs and SAEs was numerically lower in the cana compared to the plc group, particularly in patients with higher-stage CKD. This was due to the desired effects of cana, i.e. reduced number of AEs related to kidney function and cardiovascular disease.

Events of volume depletion were reported more frequently with canagliflozin than with placebo. The incidence rate increased with decreasing eGFR; the rate of volume depletion was approximately two times higher in the canagliflozin group vs placebo in subjects eGFR ≥30 to <45 mL/min/1.73 m2; however, in the subgroups eGFR ≥45 to <60 and eGFR ≥60 to <90 mL/min/1.73 m2, the incidence of volume depletion was similar in the canagliflozin and placebo group.

The rate of UTI was higher than the rate of genital infections; balanced between treatment groups for UTI and imbalanced for genital infections (higher incidence for canagliflozin compared with placebo for both female and male genital infections).

CREDENCE confirmed that cana increases the risk for DKA in patients with Type 2 diabetes several-fold. However, the number of events/event rate was still low. The results suggest that the DKA risk increases with decreasing renal function; most of the DKA events were regarded serious, also in the placebo group.

The CREDENCE study also expanded the safety data pool of phase 3 and phase 4 trials so that a new evaluation of less frequent but serious AEs such as lower limb amputation can be performed. This will be done in a separate procedure. In CREDENCE, the amputation risk was not relevantly increased with cana suggesting that the precautionary measures, which are also included in the SmPC, are effective in minimising the risk.

Taken together, except for an increased DKA risk, no specific safety concerns of canagliflozin use in a patient population with significantly impaired renal function became obvious.

2.5.3. 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.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.5 is acceptable. The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 8.5 with the following content:

Safety concerns

Summary of Safety Concerns

Important identified risks	Diabetic ketoacidosis with atypical presentation
Important potential risks	Pancreatitis
Missing information	Use in pregnancy Use in nursing mothers

Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Nonclinical Study 1 Effect of SGLT2 inhibition on ketone clearance Ongoing	To evaluate the effects of canagliflozin on ketone clearance and production	Diabetic ketoacidosis with atypical presentation	Initial protocol submission:	3Q 2016
			Final report:	To be determined
Nonclinical Study 2 Effect of SGLT2 inhibition on ketone clearance Ongoing	To evaluate the effects of canagliflozin on ketone clearance and production during prolonged fast	Diabetic ketoacidosis with atypical presentation		
Retrospective Drug Utilization Study [a] Planned	To evaluate drug utilization patterns of canagliflozin including off-label usage in T1DM	Diabetic ketoacidosis with atypical presentation	Feasibility assessment submission:	2Q 2020

[a] A feasibility assessment was conducted and provided to EMA in 2016, which concluded that the study was not feasible due to the small market size in EU, and that the US was not a suitable substitute in this case due to differing prescribing patterns. A second feasibility assessment was conducted and provided to EMA in 2Q 2018 that concluded that an EU study was still not possible. A third feasibility assessment is required for submission 2Q 2020.

Risk minimisation measures

Summary Table of Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures
Diabetic ketoacidosis with atypical presentation	Routine risk minimization measures: • SmPC Section 4.8 and PL Section 4. • Recommendations regarding appropriate dosing and patient management (including advice on discontinuation and restart) provided in SmPC Section 4.4; • Advice to patients who have DKA, including a warning that canagliflozin should not be used to treat this condition, is provided in PL Sections 2 and 4; • Advice on when to suspect DKA is provided in SmPC Section 4.4 and PL Sections 2 and 4; • Description of factors that may predispose patients to DKA, and advice on use in patients at higher risk for DKA are provided in SmPC Section 4.4 and PL Section 2; • Warning not to use canagliflozin in patients with T1DM is provided in Section 4.4 and PL Section 2.

Safety Concern	Risk Minimization Measures
	Additional risk minimization measures: • DHPC.
Pancreatitis	No risk minimization measures (routine or additional) are proposed.
Use in pregnancy	Routine risk minimization measures: • SmPC Section 4.6 and PL Section 2. • Recommendation regarding use of canagliflozin during pregnancy is provided in SmPC Section 4.6 and PL Section 2. Additional risk minimization measures: • None.
Use in nursing mothers	Routine risk minimization measures: • Section 4.6 and PL Section 2. • Recommendation regarding use of canagliflozin during breast-feeding is provided in SmPC Section 4.6 and PL Section 2. Additional risk minimization measures: • None.

2.7. Update of the Product information

As a result of this variation, sections 4.1 , 4.2, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics were updated based on the data obtained with the CREDENCE study. Disposal advice was included in section 6.6. Furthermore, minor editorial changes were made in other sections of the SmPC. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives.

Please refer to Attachment 1 which includes all changes to the Product Information and the respective assessment.

2.7.1. 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 as only minor changes were introduced to the PIL.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The initially *proposed indication* in this type II variation is as follows (in the following the existing and the new indication are depicted):

"Invokana 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.*

Invokana is indicated for the treatment of Stage 2 or 3 ***chronic kidney disease*** *and albuminuria, as an adjunct to standard of care, in adults with type 2 diabetes mellitus.*

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

With the Response to the first RSI, the Applicant **changed the target indication** to patients with diabetic kidney disease, as this was the target population included in CREDENCE (resolution of the respective MO). Hence, the updated new indication reads as follows:

"Invokana is indicated for the treatment of Stage 2 or 3 ***diabetic kidney disease*** *and albuminuria, as an adjunct to standard of care, in adults with type 2 diabetes mellitus. "*

With the Response to the third RSI the Applicant revised the indication as follows:

"Invokana 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

-in addition to standard of care for the treatment of diabetic kidney disease.

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

All three proposals for modifications of section 4.1 were rejected by CHMP (see section 3.7.3 below)

Chronic kidney disease is one of the most frequent complications of both T1DM and T2DM. Currently, more than 3 million people are estimated to be receiving treatment for kidney failure globally, and this figure is predicted to increase to over 5 million by 2035 (Liyanage T et al., Lancet 2015; 385:1975-1982). It was estimated that approximately half of all patients with T2DM and one third of those with T1DM will develop CKD over the course of their lifetime (Koye DN et al., Chronic Kidney Dis 2018; 25(2): 121-132). People with diabetes are more likely to have CKD than those without diabetes, with an overall odds ratio of 2.43 in a global kidney disease database (Ene-Iordache et al, Lancet Global health 2016: 4(5): 307-319) 2016). CKD

is identified and monitored upon presence and progression of kidney dysfunction (usually by estimated glomerular filtration rate [eGFR]<60 mL/min/1.73 m^2) and/or kidney damage (usually by albuminuria, assessed as urinary albumin-to-creatinine ratio (ACR) >30 mg/g). Increased albuminuria and decreased eGFR are each independently and additively associated with an increase in all-cause mortality and CV mortality. Diabetes is the leading cause of end-stage renal disease (ESRD) (Tuttle KE et al. Am J Kidney Dis 2014: 64(4): 510-533).

3.1.2. Available therapies and unmet medical need

Renin-angiotensin-aldosterone system (RAAS) blockade, through use of angiotensin receptor blocker (ARB) drugs, is the only treatment currently approved for preventing the decline of kidney function and development of kidney failure in T2DM, based primarily on the results of 2 trials completed over 17 years ago (RENAAL study with losartan [Brenner 2001]; IDNT study with irbesartan [Lewis 2001]). Angiotensin-converting enzyme inhibitor (ACEi) agents, such as ramipril and captopril, have also shown benefit in preventing progression of nephropathy (ie, worsening albuminuria) in T2DM and T1DM (HOPE 2000; Laffel 1995). Despite the recommended widespread use of RAAS inhibition in patients with diminished renal function, patients with T2DM and CKD remain at high risk of developing ESKD and CV events. Thus, development of novel interventions to protect kidney function and to reduce (CV) mortality in patients with DN can be considered an unmet medical need.

3.1.3. Main clinical studies

CREDENCE was a multinational, randomized, placebo-controlled trial that evaluated the effects of canagliflozin relative to placebo on the primary composite endpoint of doubling of serum creatinine, ESKD, renal or CV death in subjects with T2DM, stage 2 or 3 CKD, and albuminuria. This study involved patients with T2DM receiving standard of care therapy, including ARBs/ ACEis.

3.2. Favourable effects

Canagliflozin significantly reduced the risk of the *primary composite endpoint* compared to placebo by 30% (HR: 0.70, 95% CI: 0.59, 0.82, p-value <0.0001). Consistent results were obtained for the individual components of the primary composite endpoint, with the renal endpoints doubling of serum creatinine and progression to ESKD contributing most to the overall beneficial effect. This favourable treatment effect was consistent across numerous subgroups, including those with a screening eGFR ≥30 to <45 mL/min/1.73 m^2. The primary efficacy result remained robust (HR 0.72; 95% CI 0.62, 0.84; p<0.0001) in a sensitivity analysis of the primary endpoint using all-cause mortality rather than CV death and renal death.

Similarly, treatment with canagliflozin favourably influenced the following secondary endpoints; it

- reduced the risk of the composite endpoint of CV death or hospitalization for heart failure (HR: 0.69; 95% CI: 0.57, 0.83, p=0.0001);
- reduced the risk of the composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalized heart failure, hospitalized unstable angina (HR: 0.74 95% CI: 0.63, 0.86, p = 0.0001)
- reduced the risk of MACE (comprised of nonfatal MI, nonfatal stroke and CV death, ie, 3 point MACE) (HR: 0.80; 95% CI: 0.67, 0.95; p=0.0121);
- reduced the risk of hospitalized heart failure (HR: 0.61; 95% CI: 0.47, 0.80; p=0.0003); and
- reduced the risk of the renal composite of ESKD, doubling of serum creatinine and renal death (HR: 0.66; 95% CI: 0.53, 0.81; p<0.0001).

Notably, all components of these endpoints favoured treatment with canagliflozin, including all subcomponents of ESKD.

Analysis of eGFR change over time and from baseline to end of treatment as well as analysis of eGFR slope confirmed a favourable effect of canagliflozin (less pronounced decline of eGFR with canagliflozin compared to placebo). In addition, canagliflozin reduced albuminuria.

Modest effects in favour of canagliflozin were shown for SBP and DBP (placebo-subtracted LS mean change from baseline to study end was -2.81 mmHg for SBP and -0.60 mmHg for DBP, respectively).

3.3. Uncertainties and limitations about favourable effects

The experience in patients with eGFR <30 mL/min is very limited. Canagliflozin should not be initiated in these patients but can be continued until dialysis and renal transplantation in patients already on treatment.

3.4. Unfavourable effects

In the CREDENCE study, a total of 2,200 subjects were treated with canagliflozin with 1,948 subjects (89%) being treated for at least 52 weeks, 942 subjects (43%) for at least 2.5 years and 459 subjects (21%) for at least 3 years. Total exposure to canagliflozin amounts to 4,916 PY.

The general safety profile of canagliflozin is established. The known side effects (e.g. dehydration, mycotic genital infection, diabetic ketoacidosis [DKA]) were also observed in the CREDENCE study. Reassuringly, the total number of AEs and SAEs was numerically lower in the cana than in the plc group (81.1% vs. 84.7% of patients with at least one AE, cana vs. plc).

The safety evaluation of the CREDENCE study is relevant for the question whether decreased renal function alters the B/R profile of canagliflozin. In patients with higher degrees of CKD (Stage 3A and 3B) the incidence of AEs and SAEs was lower with canagliflozin than with placebo (Stage 3A, AEs, 346 vs. 388 events per 1000 subject-years, cana vs. plc; Stage 3A, SAEs, 141 vs. 177; Stage 3B, AEs, 395 vs. 414; Stage 3B, SAEs, 175 vs. 205). This was due to a decreasing number of events related to kidney (e.g. "blood creatinine increased") and cardiovascular disease.

Contrary to this trend, the incidence of diabetic ketoacidosis (DKA) appeared to increase with decreasing renal function (six patients with DKA had Stage 3B CKD, three had Stage 3A and two had Stage 2). The absolute number of events was low and no firm conclusions can be drawn.

In CREDENCE study, initiation of canagliflozin treatment was prohibited by protocol for subjects with eGFR <30 mL/min/1.73 m^2. However, subjects who developed eGFR <30 mL/min/1.73 m^2 after initiation of treatment were permitted to remain on canagliflozin (or placebo) until dialysis or renal transplantation. The cohort of subjects with an eGFR of <30 mL/min/1.73 m^2 at the last on-treatment measurement (n=929; of which 417 subjects treated with canagliflozin) had a higher incidence of AEs and SAEs, including fatal cases, compared to the population in the overall on-treatment analysis but the incidence rates of AEs/SAES were comparable for canagliflozin and placebo within the eGFR <30 mL/min/1.73 m^2 population.

3.5. Uncertainties and limitations about unfavourable effects

In a pooled safety analysis of all phase 3 and phase 4 studies including CREDENCE, pancreatitis and photosensitivity were numerically increased in incidence in the pooled canagliflozin group vs. the pooled non- canagliflozin group (pancreatitis: 17 (0.13%) in the pooled cana group versus 6 (0.06%) in the pooled non-cana group; photosensitivity: 27 (0.20%) in the pooled cana group versus 9 (0.10%) in the pooled non-cana group). For both adverse drug reactions the absolute number of cases was low.

Non-traumatic lower limb amputations (due to microvascular disease) were recognised to be more frequent in diabetic patients with pre-existing microvascular disease (e.g. identified by previous amputation). In CREDENCE, these patients at risk were excluded during the course of the study by an amendment and no relevant differences in the number of amputations between canagliflozin and placebo were observed at study end (70 (3.2%) in the cana group versus 63 (2.9%) in the placebo group). The AE "diabetic foot" was reported more often in the canagliflozin than in the placebo group.

The risk of lower limb amputations and precautionary measures are appropriately addressed in the SmPC.

Events of documented hypoglycaemia and events of severe hypoglycaemia for canagliflozin vs placebo and across the three eGFR strata had been presented as requested by CHMP and no differences were shown. Other concerns which dealt with an increased incidence of events related to volume depletion with decreasing GFR and with respect to eGFR changes over time per eGFR stratum could likewise be resolved.

3.6. Effects Table

Table 27Effects Table

Effect	Short description	Unit	Treat-ment (Cana)	CTRL (Plc)	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary composite endpoint						
Primary composite endpoint	(1) first occurrence of ESKD (2) doubling of serum creatinine (3) renal death (4) **or** CV death	n (%)	245 (11.1)	340 (15.5)	HR (95% CI) 0.70 (0.59, 0.82) p < 0.0001	CREDENCE ITT analysis set
Secondary composite endpoints						
Secondary CV composite endpoint	(1) CV death (2) hospitalized heart failure	n (%)	179 (8.1)	253 (11.5)	HR (95% CI) 0.69 (0.57, 0.83)	CREDENCE ITT analysis set
Secondary CV composite endpoint	(1) CV death (2) non-fatal MI (3) non-fatal stroke (4) hospitalized heart failure (5) hospitalized unstable angina	n (%)	273 (12.4)	361 (16.4)	HR (95% CI) 0.74 (0.63, 0.86) p = 0.0001	
Secondary 3-point MACE	(1) CV death (2) non-fatal myocardial infarction (MI) (3) non-fatal stroke	n (%)	217 (9.9)	269 (12.2)	HR (95% CI) 0.80 (0.67, 0.95) p = 0.0121	
Secondary renal composite endpoint	(1) ESKD (2) doubling of serum creatinine (3) renal death	n (%)	153 (6.9)	224 (10.2)	HR (95% CI) 0.66 (0.53, 0.81) p < 0.0001	
Individual primary and secondary endpoint components						
Doubling of serum creatinine		n (%)	118 (5.4)	188 (8.5)	HR (95% CI) 0.60 (0.48, 0.76) p < 0.0001	CREDENCE ITT analysis set
ESKD	• eGFR < 15 ml/min/1.73 m^2 • Dialysis initiated + kidney	n (%)	116 (5.3)	165 (7.5)	HR (95% CI) 0.68 (0.54, 0.86) p = 0.0015	

Effect	Short description	Unit	Treat-ment (Cana)	CTRL (Plc)	Uncertainties / Strength of evidence	References
	transplantation • Dialysis initiated					
Renal Death		n (%)	2 (0.1)	5 (0.2)	case number too low for statistics	
CV death	Cardiovascular death	n (%)	110 (5.0)	140 (6.4)	HR (95% CI) 0.78 (0.61, 1.00) p = 0.0502	
Non-fatal MI	Non-fatal myocardial infarction	n (%)	71 (3.2)	87 (4.0)	HR (95% CI) 0.81 (0.59, 1.10) p = 0.1771	
Non-fatal Stroke		n (%)	53 (2.4)	66 (3.0)	HR (95% CI) 0.80 (0.56, 1.15) p = 0.2219	
HHF	Hospitalized heart failure	n (%)	89 (4.0)	141 (6.4)	HR (95% CI) 0.61 (0.47, 0.80) p=0.0003	
HUSA	Hospitalized unstable angina	n (%)	13 (0.6)	22 (1.0)	HR (95% CI) 0.58 (0.29, 1.16) p = 0.1249	
All-cause death	All-cause death	n (%)	168 (7.6)	201 (9.1)	HR (95% CI) 0.83 (0.68, 1.02) p = 0.0727	
Other effect parameters: change from baseline until end of treatment						
eGFR	Estimated GFR	LS mean (SE) ml/min/ 1.73 m^2	-9.29 (0.289)	-10.90 (0.290)	Δ LS means (SE) 1.61 (0.403) 95% CI: 0.818, 2.399	CREDENCE on-treat-ment analysis set
Urinary ACR	Urinary albumin to creatinine ratio GM at end of treatment	mg/g (95% CI)	523,7 (494.04; 555.24)	818.5 (772.09; 867.69)	GM ratio (95% CI) 0.64 (0.590, 0.695)	
HbA1c	% glycosylated hemoglobin	LS mean (SE) %	-0.38 (0.030)	-0.25 (0.030)	Δ LS means (SE) -0.13 (0.042) 95% CI: -0.212, -0.049	
Body weight		LS mean (SE), % change	-1.75 (0.133)	-0.03 (0.133)	Δ LS means (SE) -1.72 (0.187) 95% CI: -2.090, -1.358	
SBP	Systolic blood pressure	LS mean (SE) mmHg	-2.69 (0.348)	0.12 (0.348)	Δ LS means (SE) -2.81 (0.489) 95% CI: -3.771, -1.853	
DBP	Diastolic blood pressure	LS mean (SE) mmHg	-1.59 (0.195)	-0.99 (0.195)	Δ LS means (SE) -0.60 (0.273) 95% CI: -1.132, -0.060	
Unfavourable Effects						
All AEs	affected patients, on-treatment	n (%)	1784 (81.1)	1860 (84.7)		CREDENCE study

Effect	Short description	Unit	Treat-ment (Cana)	CTRL (Plc)	Uncertainties / Strength of evidence	References
	data set					
All SAEs	affected patients, on-treatment data set	n (%)	737 (33.5)	806 (36.7)		
SAEs per renal function	Incidence	per 1000 subj-y				
eGFR 30-<45			174.6	204.6		
eGFR 45-<60			141.3	177.4		
eGFR 60-<90			128.3	129.4		
DKA, adjudicated	Incidence on treatment	per 1000 subj-y	2.17	0.20	probably rate increasing with decreasing renal function	
Lower limb amputation (non-traumatic	Incidence on study	per 1000 subj-y	12.14	11.02		
Diabetic foot	affected patients, on study data set	n (%)	43 (2.2)	33 (1.5)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Diabetic kidney disease is a major cause of progressive renal insufficiency. Despite widespread use of ARBs or ACEi, patients with diabetic kidney disease remain at high risk of becoming dialysis-dependent and experiencing CV events.

Canagliflozin, on top of an ARB or ACEi, resulted in a statistically significant and clinically relevant 30% reduction in the risk of the primary composite endpoint of doubling of serum creatinine, ESKD, and renal or CV death compared to placebo in a T2DM population with established CKD (60% of whom had a screening eGFR <60 mL/min/1.73 m^2), which is an important favourable effect. Consistency across numerous subgroups, including that with a screening eGFR ≥30 to <45 mL/min/1.73 m^2 was shown.

The efficacy of canagliflozin on renal outcomes in a CKD population with T2DM was further shown by the 34% reduction achieved in the risk of the secondary renal composite endpoint (ESKD, doubling of serum creatinine, and renal death). Moreover, canagliflozin significantly reduced the risk of the first occurrence of progression to ESKD by 32% compared with placebo, with clinically meaningful reductions seen for each subcomponent of the ESKD endpoint (~25% for dialysis or renal transplantation; 40% for a sustained eGFR <15 mL/min/1.73 m^2).

With respect to secondary cardiovascular outcomes, the point estimates were below one, but statistically significant only for hospitalization for heart failure. The results are in line with those seen in CANVAS, which was a dedicated CV outcome study.

With respect to the mechanism leading to renal benefits, it is hypothesized that a combination of antihyperglycaemic, blood pressure and bodyweight lowering effects, and, secondary autoregulatory

vasoconstriction of afferent glomerular arteriolae (through increased local Angiotensin II) leading to reduced intraglomerular pressure may contribute to the observed relevant nephroprotective effect of canagliflozin.

The adverse effect profile of SGLT2 inhibitors is well-established including increased risk of DKA, dehydration and mycotic genital infections. The most important unfavourable effect observed with canagliflozin in the Credence study was an increased risk of DKA, which appeared to increase with decreasing renal function. This is indeed a serious adverse event, even if it is acknowledged that the absolute number of events was low.

3.7.2. Balance of benefits and risks

Canagliflozin has demonstrated clinically relevant beneficial effects on renal function in patients with diabetic kidney disease. Although an increased risk of water/electrolyte imbalance, DKA and amputations are noted, these risks are considered manageable and are, together with precautionary measures, appropriately addressed in the SmPC. Therefore, the beneficial effects of canagliflozin are considered to outweigh the adverse effects in patients with DKD.

3.7.3. Additional considerations on the benefit-risk balance

Results from the CREDENCE study are considered robust and clinically relevant.

Since the already approved indication "treatment of patients with insufficiently controlled type 2 diabetes" is considered to cover both the aim of the treatment, which is not limited to glycaemic control but covers as well other treatment goals including the proposed treatment goal of "prevention of worsening of diabetic complications" and the target population (patients with DKD are not excluded from the current indication), the CHMP considers that a separate indication for the treatment of diabetic kidney disease in section 4.1 of the SmPC as was proposed by the MAH is not warranted. Also the later revised proposal from the MAH, to list in section 4.1 of the SmPC treatment in addition to SoC for DKD within a third bullet point under the existing broad T2DM indication (see section 7.1.1.), was not agreed by CHMP.

Instead section 4.2 of the SmPC has been updated to include treatment recommendations for patients with stage 3b diabetic kidney disease which were excluded by the current posology recommendations. The updated text includes the recommendation that canagliflozin should be used in addition to, and not instead of an ARB or ACEi, which is the current standard of care in patients with DKD. It was also considered important to reflect in section 4.2 that the glucose lowering effect of canagliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe renal impairment. However, the revised text explains that canagliflozin can be initiated for prevention of worsening of DKD also in the lower eGFR-range.

In addition section 5.1 of the SmPC has been updated to present the results of the CREDENCE study. The latter is in line with previous regulatory decisions taken for reflection of results from cardiovascular outcome trials (CVOTs) where the results from new studies performed in the approved target population are presented in SmPC section 5.1 and in the EPAR to communicate the new information to the prescriber and to other stakeholders.

In conclusion, the CHMP was of the view that the use of Invokana for the treatment of diabetic kidney disease *in addition to standard of care* is already covered by the existing T2DM indication wording and that the results from CREDENCE and important information for prescribers are best reflected in sections 4.2. 4.4, 4,8 and 5.1 of the SmPC; the clarification that canagliflozin should be used on top of SoC for DKD has been adequately provided in the Invokana SmPC sections 4.2 and 5.1.

The CHMP also accepted a *new cross-reference in the last sentence of the Invokana SmPC section 4,1, emphasizing that new data is available from the CREDENCE study.*

3.8. Conclusions

The overall B/R of Invokana for treatment of patients with diabetic kidney disease is positive.

A separate indication or separate indent for treatment of DKD in SmPC 4.1 is not approvable. The use of Invokana in addition to standard of care for the treatment of diabetic kidney disease is covered by the current indication "*Treatment of adults with insufficiently controlled type 2 diabetes mellitus".* Minor update to SmPC 4.1 and addition of relevant information to other SmPC sections (mainly 4.2, 4.4, 4.8 and 5.1) were agreed.

The overall B/R of Invokana is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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

Update of sections 4.1 , 4.2, , 4.4, 4.8, 5.1 and 6.6 of the Summary of Product Characteristics to modify the therapeutic indication for INVOKANA (canagliflozin) based upon new clinical efficacy and safety data from the Phase 3 study: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial (CREDENCE) (DNE3001). This study provides data on the use of Invokana in addition to standard of care in diabetic kidney disease patients. The Package Leaflet is updated accordingly. The RMP version 8.5 has also been agreed. In addition, the list of local representatives in the Package Leaflet has been revised.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).