Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Canagliflozin (as hemihydrate)

Proprietary Product Name: Invokana, Prominad

Sponsor: Janssen-Cilag Pty Ltd

Date of CER: 12 April 2013

TGA Health Safety Regulation

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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List of abbreviations

Abbreviation	Meaning
AE	Adverse event
AGI	Alpha-glucosidase inhibitor
AHA	Anti-hyperglycaemic agent
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
ASCVD	Atherosclerotic cardiovascular disease
AUC_{0-2}	Area under the curve from time 0 to 2 hours
AUC_{0-24}	Area under the curve from time 0 to 24 hours
BMI	Body mass index
CI	Confidence interval
CRU	Clinical research unit
CSR	Clinical study report
CV	Coefficient of variance
DAE	Adverse event leading to discontinuation
DNA	Deoxyribonucleic acid
EC_{50}	Concentration at which 50% maximal effect is achieved
EC_{90}	Concentration at which 90% maximal effect is achieved
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EGP	Endogenous glucose production
E_{max}	Maximum effect
EOT	End of treatment

Abbreviation	Meaning
FBC	Full blood count
FBG	Fluid-Bed Granulation
FFA	Free fatty acids
FS-MMTT	Frequently-sampled mixed-meal tolerance test
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide-1
GMR	Geometric mean ratio
HbA1c	Glycosylated haemoglobin
HDL-C	High density lipoprotein cholesterol
HOMA	Homeostasis model assessment
HOMA2-%	Homeostasis model assessment (beta-cell function)
HOMA2-IR	Homeostasis model assessment (insulin resistance) ISR insulin secretion rate
HR	Hazard ratio
HSG	High-Shear Granulation
INR	International Normalised Ratio
INR AUC	Area under the curve for INR
INR_{max}	Maximum INR
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
k_e	Elimination rate constant
LDL-C	Low density lipoprotein cholesterol
LLT	Lower-level term
MACE	CV death, nonfatal myocardial infarction (MI), and nonfatal stroke

Abbreviation	Meaning
MACE-plus	MACE and hospitalized unstable angina (UA).
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MET	Metformin
MPG_{0-24h}	Mean 24 hour plasma glucose concentration defined as the area under the plasma glucose concentration-time curve from 0 to 24 hours, divided by the actual time (h) during the 0 to 24 hour interval.
MPG_{0-4h}	Mean 4 hour plasma glucose concentration defined as the area under the plasma glucose concentration-time curve from 0 to 4 hours, divided by the actual time (h) during the 0 to 4 hour interval, and measured after the meal (breakfast, lunch and dinner)
MMTT	Mixed meal tolerance test
PD	Pharmacodynamic
PK	Pharmacokinetic
PPARγ	Peroxisome proliferator-activated receptor gamma
PPG	Postprandial plasma glucose
PYY	Peptide YY
RaO	Rate of systemic appearance of orally administered glucose
RBC	Red blood cell
$RT_{glucose}$	Renal threshold for glucose excretion
RT_{Gmin}	For $RT_{glucose}$ the estimates for the minimum achievable
Rd	Rate of glucose disposal
t1/2	elimination half-life
t_{max}	Time to reach the maximum observed plasma concentration

Abbreviation	Meaning
$t_{max,ss}$	Time to reach the maximum plasma concentration during a dosing interval at steady-state
TZD	Thiazolidinedione
SAE	Serious adverse event
SD	Standard deviation
SGLT1	Sodium-glucose transporter-1
SGLT2	Sodium-glucose transporter-2
SMBG	Self monitored blood glucose
SOC	System organ class
SU	Sulfonylurea
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
UGE	Urinary glucose excretion
UGE_{0-24h}	Cumulative urinary glucose excretion, equal to amount of urine glucose excreted into the urine over the entire urine collection interval, 0 to 24 hours, calculated as the sum of all the UGEt1-t2 values
WBC	White blood cell

1. Introduction

1.1. Drug class and therapeutic indication

Canagliflozin is a member of a new drug class of sodium glucose co-transporter 2 (SGLT2) inhibitors. The low-affinity/high capacity SGLT2 transporter in the proximal renal tubule reabsorbs most of the filtered glucose, and a relatively small amount of glucose is reabsorbed by the high affinity/low capacity sodium glucose co-transporter 1 (SGLT1) isoform. Pharmacological inhibition of SGLT2 has been shown to decrease renal glucose re-absorption, and thereby increase urinary glucose excretion and lower plasma glucose.

The proposed indication is:

> *INVOCANA is indicated in adults with type 2 diabetes mellitus to improve glycaemic control as:*
>
> *Monotherapy:*
>
> *When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.*
>
> *Add-on therapy:*
>
> *Add-on therapy with other anti-hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see PRECAUTIONS; INTERACTIONS WITH OTHER MEDICINES and PHARMACOLOGY for available data on different add-on therapies).*

1.2. Dosage forms and strengths

The submission proposes registration of the following dosage forms and strengths:

- INVOCANA/ PROMINAD (canagliflozin) 100 mg film-coated tablets
- INVOCANA/ PROMINAD (canagliflozin) 300 mg film-coated tablets

1.3. Dosage and administration

INVOCANA/ PROMINAD should be taken orally once a day, preferably taken before the first meal of the day.

In patients on loop diuretics, patients with moderate renal impairment (eGFR 30 to < 60 ml/min/1.73 m^2), or patients ≥ 75 years of age, a starting dose of 100 mg once daily should be considered. In patients with evidence of volume depletion, consideration should be given to correcting this condition prior to initiation of canagliflozin. In patients started on canagliflozin 100 mg who need additional glycaemic control and are adequately tolerating canagliflozin, a dosage of canagliflozin 300 mg is appropriate.

For patients with mild renal impairment (eGFR 60 to < 90 ml/min/1.73 m^2), no dose adjustment is required.

Canagliflozin is not recommended for use in patients with severe renal impairment (eGFR < 30 ml/min/1.73 m^2), end stage renal disease (ESRD), or in patients on dialysis as canagliflozin is not expected to be effective in these patient populations.

2. Clinical rationale

The Sponsor's rationale for the development of canagliflozin is as follows:

> "In Australia, diabetes is a national health priority area. It is the fastest growing chronic disease and is the sixth leading cause of death. The Australian Bureau of Statistics' 2007-08 National Health Survey estimated that 898,800 Australians have been diagnosed with diabetes and of these patients, the majority (approximately 787,500 Australians) were diagnosed with T2DM. By 2023, T2DM diabetes is projected to be the leading specific cause of disease burden for males and second for females.
>
> There are currently agents from a number of different classes that are available for the treatment of T2DM. Most patients with T2DM are initially managed with single agent therapy, usually metformin. Despite initial monotherapy, many patients have progressive loss of glycaemic control, requiring combinations of agents, and often eventually insulin therapy. Underlying this progressive deterioration in glycaemic control is a gradual loss of beta-cell function. Thus, there remains a substantial unmet medical need for new medications to treat patients with T2DM that are well tolerated and efficacious, provide good durability, beneficially impact beta-cell function and insulin secretion."

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5

- 40 clinical pharmacology studies, including 25 that provided pharmacokinetic data and 15 that provided pharmacodynamic data.
- One population pharmacokinetic analyses and one population PKPD analysis.
- Eight pivotal efficacy/safety studies.
- Two dose-finding studies.
- Two other efficacy/safety studies.
- Integrated Summary of Efficacy, and Integrated Summary of Safety.

Module 1

- Application letter, application form, draft Australian PI and CMI
- Module 2
- *Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.*

3.2. Paediatric data

The submission did not include paediatric data. The applicant has submitted a Paediatric Investigation Plan to the European Union which covers the age range 10 to 18 years inclusive. The Sponsor has been granted a waiver for the age ranges <10 years. The studies in the 10 to 18 years age group were deferred.

3.3. Good clinical practice

All the submitted studies were stated to have been performed according to Good Clinical Practice. Good Clinical Practice appears to have been adhered to.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The clinical evaluation included the following pharmacokinetic/pharmacodynamic studies.

Table 1. Phase 1 Clinical Studies of Canagliflozin

Type of Study	Population/Number of Studies
Absolute bioavailability, relative bioavailability, and food effect	Healthy subjects, 4 studies
Mass-balance	Healthy subjects, 1 study
Single-dose PK and PK/PD	Healthy subjects, 3 studies
Multiple-dose, PK/PD	Healthy subjects, 3 studies Subjects with T2DM, 3 studies
Pharmacodynamic	Healthy subjects, 1 study Subjects with T2DM, 2 studies
Hepatic impairment	1 study
Renal impairment	1 study
Non-Caucasian subjects	Japanese/Indian subjects, 3 studies
Drug-drug interaction	Healthy subjects,12 studies
QT/QTc	Healthy subjects, 1 study
Photosensitivity	Healthy subjects, 4 studies

Key: PD=pharmacodynamic, PK=pharmacokinetic, T2DM=type 2 diabetes mellitus
Note: Studies were conducted in Caucasian subjects unless otherwise indicated.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Absorption

4.2.1.1.1. Sites and mechanisms of absorption

Canagliflozin is absorbed primarily from the small bowel. Median T_{max} following canagliflozin 300 mg, administered orally in the fasted state was 1.5 hours in Study DIA1021. Median T_{max} was 2 hours in Study DIA1017. In healthy volunteers, in the dose range 50 mg to 300 mg T_{max} was 1.5 hours (Study DIA1015).

4.2.1.2. Bioavailability

4.2.1.2.1. Absolute bioavailability

The mean absolute oral bioavailability in the fasted state of canagliflozin is 64.9% (Study DIA1021).

4.2.1.2.2. Bioavailability relative to an oral solution or micronised suspension

Not provided.

4.2.1.2.3. Bioequivalence of clinical trial and market formulations

The Phase 1 formulation was manufactured by HSG and the subsequent Phase 2 and Phase 3 formulation by FBG. The 300 mg formulations were demonstrated to be bioequivalent in Study

DIA1017. The geometric mean ratio (90% CI) FBG/HSG for $AUC_{0-\infty}$ was 103.32 (99.63 to 107.15) and for C_{max} was 102.29 (93.97 to 111.35)

4.2.1.2.4. Bioequivalence of different dosage forms and strengths

In healthy volunteers, in the dose range 50 mg to 300 mg AUC and C_{max} were dose proportional (Study DIA1015).

4.2.1.2.5. Influence of food

Bioavailability of canagliflozin is not significantly influenced by food. The geometric mean ratio (90% CI) fed/fasted for a 300 mg oral dose for $AUC_{0-\infty}$ was 108.09 (103.45 to 112.95) and for C_{max} was 100.51 (89.47 to 112.93) (Study DIA1043).

In healthy Japanese male volunteers for a 200 mg dose, food decreased C_{max} by 33% but did not significantly affect AUC (Study TA7284-01).

4.2.1.2.6. Dose proportionality

In healthy Japanese males AUC and C_{max} were dose proportional in the dose range 25 mg to 200 mg (Study TA-7284-03).

In healthy volunteers, in the dose range 50 mg to 300 mg C_{max} was dose proportional (Study DIA1015). At oral dose levels in the range of 800 mg to 1600 mg, C_{max} was not dose proportional and there was a plateau at the 1200 mg dose level (Study DIA1001).

In healthy volunteers, in the dose range 50 mg to 300 mg AUC was dose proportional (Study DIA1015). At oral dose levels in the range of 800 mg to 1600 mg, AUC was dose proportional (Study DIA1001).

In healthy Japanese male volunteers, AUC and C_{max} were dose dependent for single doses in the range 30 mg to 800 mg (Study TA7284-01).

In Study DIA1030 the C_{max} and AUC were similar for single and multiple doses for the dose range 50 mg to 300 mg daily. C_{max} and AUC were dose proportional in the range 50 mg to 300 mg for both single and multiple doses.

Overall exposure to canagliflozin was similar for the same daily dose delivered as once daily or twice daily dosing. The mean ratio (90% CI) for AUC0-24 was 97.08 (94.59 to 99.62) % for 100 mg per day and 99.32 (94.71 to 104.16) % for 300 mg per day (Study DIA1032).

4.2.1.3. Distribution

4.2.1.3.1. Volume of distribution

In healthy volunteers, in the dose range 50 mg to 300 mg Vd/F was in the range 218 to 239 L (Study DIA1015).

4.2.1.3.2. Plasma protein binding

Protein binding was 99% and was independent of renal function (Study DIA1003).

4.2.1.4. Metabolism

4.2.1.4.1. Interconversion between enantiomers

Canagliflozin does have an optical isomer: JNJ-41538757. In Study DIA1023 there were 30 samples from five subjects in the 100 mg daily and five in the 300 mg daily dose groups collected over 7 days of treatment and analysed for presence of the α-anomer (JNJ-41538757). Three samples from two subjects, both in the 300 mg group and at Day 7, had concentrations >LLOQ for the α-anomer: 6.83 ng/mL, 5.15 ng/mL and 5.05 ng/mL. The Sponsor states that: "Anomerization between β-anomer (canagliflozin, JNJ-28431754) to α-anomer (JNJ-41538757) requires a multistep reaction, a ring opening and a closure and as a result, this conversion is considered unlikely to occur *in vivo*."

4.2.1.4.2. Sites of metabolism and mechanisms / enzyme systems involved

Unchanged [^{14}C]-canagliflozin is the major circulating component in plasma (Study DIA1021). Preclinical studies indicated that canagliflozin is glucuronidated by *UGT1A9* and *UGT2B4* enzymes. Hence metabolism is primarily hepatic.

4.2.1.4.3. Non-renal clearance

Biliary excretion is one of the major elimination pathways for total [^{14}C] radioactivity as 34.1% of the administered radioactive intravenous dose was recovered in faeces (Study DIA1021).

Enterohepatic circulation of canagliflozin appears to be negligible (Study DIA1021).

4.2.1.4.4. Metabolites identified in humans

- **Active metabolites**

No active metabolites were identified.

- **Other metabolites**

In a study using orally administered ^{14}C-canagliflozin 196 mg as a single, oral dose the mean (range) total faecal and urinary excretion at 1 week was 92.9% (89.7% to 96.0%) of the dose (Study NAP1006). Mean (SD) faecal excretion was 60.4 (5.73) % of the dose and urinary excretion was 32.5 (5.11) % of the dose. The unchanged drug was the major drug-related component in plasma and accounted for 45.4% to 98.7% of the total drug-derived components in the radio-chromatograms of 0 to 24 hr plasma samples. The remaining drug-derived materials in 1.5 to 12 hour plasma samples were accounted for by two O-glucuronides of unchanged drug (M7 [16.0% to 28.8%] and M5 [1.9% to 29.6%]) and a hydroxylated metabolite M9 (2.42% to 3.70%). All the radioactivity in the urine was accounted for by the two O-glucuronide metabolites M5 (13.3%) and M7 (17.2%). The radioactivity in faeces was accounted for by unchanged drug (41.5%), the hydroxylated metabolite M9 (7.0%) and the O-glucuronide metabolite M7 3.2%.

4.2.1.4.5. Pharmacokinetics of metabolites

The C_{max} and AUC of the M7 and M5 metabolites were dose proportional (linear) in the dose range 100 mg to 400 mg and there was no significant accumulation over 14 days of dosing (Study NAP1002).

4.2.1.4.6. Consequences of genetic polymorphism

In Study DIA1023, only one subject with the UGT1A9*3 variation was identified in the 100-mg dose group. On Day 1 and Day 7, plasma M7 AUC and C_{max} were two-fold lower while canagliflozin AUC was slightly elevated in this subject (14% to 23%) compared to the mean canagliflozin AUC for the other study subjects.

4.2.1.5. Excretion

4.2.1.5.1. Routes and mechanisms of excretion

In healthy Japanese males t1/2 was approximately 13 hours with a 25 mg oral dose and 17 hours with a 200 mg oral dose (Study TA-7284-03). In healthy adult males, at oral dose levels in the range of 800 mg to 1600 mg, t½ was in the range 16.4 to 23.2 hours (Study DIA1001). In healthy volunteers, in the dose range 50 mg to 300 mg t½ was in the range 9.42 to 11.1 hours (Study DIA1015).

In healthy adult males, at oral dose levels in the range of 800 mg to 1200 mg, the fraction of the dose excreted unchanged in the urine was 0.624 and 0.646 respectively, and at the 1600 mg dose level it was 0.388 (Study DIA1001).

In healthy volunteers, in the dose range 50 mg to 300 mg CL/F was in the range 15.0 to 16.3 L/h (Study DIA1015).

4.2.1.5.2. Renal clearance

Renal clearance of parent canagliflozin was negligible. Less than 1% of the administered dose was recovered as unchanged drug in urine.

4.2.1.6. Intra- and inter-individual variability of pharmacokinetics

In the population PK study, the %CV for V/F was 15% and for k_e was 123%. Intra-individual variability was not estimated.

4.2.2. Pharmacokinetics in the target population

In subjects with T2DM, at steady state mean (SD) t½ was 14.7 (4.1) hours for a 100 mg dose and 11.8 (2.9) hours for 300 mg twice daily (Study DIA1007).

Median (range) T_{max} was 4.00 (1.5 to 6.0) for the 100 mg daily dose and 2.75 (1.5 to 3.0) for 300 mg twice daily.

In Study DIA1023, conducted in subjects with T2DM, the PK of canagliflozin and its major metabolites were linear in the dose range 50 mg to 300 mg. The t½ of canagliflozin was approximately 15 hours, of the M7 metabolite was 15 hours and the M5 metabolite was 14 hours. Of the daily dose, 0.75% was excreted in urine as unchanged canagliflozin, 20% as the M7 metabolite and 10% as the M5 metabolite.

In Study DIA1007 in subjects with T2DM, paracetamol absorption was not delayed following canagliflozin indicating that canagliflozin did not alter gastric emptying time.

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

There was a 10% increase in canagliflozin AUC in mild and moderate hepatic impairment (Study DIA1013). The AUC for the M7 metabolite increased by 58% in mild hepatic impairment and 113% in moderate. The AUC for the M5 metabolite increased by 5% in mild hepatic impairment and 39% in moderate.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

There was no significant change in C_{max} with renal failure following a single 200 mg dose (Study DIA1003). AUC increased by 35% in moderate renal impairment and 17% in severe renal impairment. AUC for the M7 metabolite increased by 40% in mild renal impairment, 130% in moderate and 103% in severe. AUC for the M5 metabolite increased by 27% in mild renal impairment, 143% in moderate and 151% in severe. Haemodialysis was not effective in clearing canagliflozin.

In the population PK study the median dose-normalized AUC values were about 11%, 40%, and 29% higher in subjects with mild (60-89 mL/min/1.73 m^2), moderate (30-59 mL/min/1.73 m^2), and severe (15-29 mL/min/1.73 m^2) renal impairment, respectively, as compared to the normal renal function group (≥ 90 mL/min/1.73 m^2).

4.2.3.3. Pharmacokinetics according to age

In the population PK study once eGFR was accounted for there was no significant effect of age on clearance.

4.2.3.4. Pharmacokinetics related to genetic factors

In Study DIA1029, one subject was identified with the UGT1A9*3 allele who had the highest canagliflozin $AUC_{0-\infty}$ (40%) and C_{max} (47%) values compared to the mean canagliflozin $AUC_{0-\infty}$ and C_{max} values for subjects who did not carry the UGT1A9*3 allele (Study DIA1029). In Study DIA1048, there was one subject with the UGT1A9*3 allele who had the lowest concentrations of the M7 metabolite (Study DIA1048). This subject had the highest AUC for canagliflozin (40%

greater than the mean for the other study subjects) and the lowest CL/F (31% lower than the mean for the other study subjects).

In Study DIA1023, only one subject with the UGT1A9*3 variation was identified in the 100-mg dose group. On Day 1 and Day 7, plasma M7 AUC and C_{max} were two-fold lower while canagliflozin AUC was slightly elevated in this subject (14% to 23%) compared to the mean canagliflozin AUC for the other study subjects.

4.2.3.5. Pharmacokinetics in other special population / according to other population characteristic

In the population PK study there was no significant effect of gender or race on the clearance of canagliflozin.

PK parameters were similar in a population of Indian volunteers to Caucasian subjects (Study DIA1008).

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

4.2.4.1.1. Effects on canagliflozin PK by concurrent administration of other drugs

- The AUC and C_{max} of canagliflozin were decreased by 10% with concurrent administration of ethinyl estradiol 30 µg and levonorgestrel 150 µg, but there was no significant change in urinary glucose excretion (Study DIA1002).
- Hydrochlorothiazide did not have any significant effect on the AUC or C_{max} of canagliflozin: LS mean ratio (90% CI) 109.95 (105.17 to 113.12) % and 106.77 (98.91 to 115.25) % respectively (Study DIA1006).
- Metformin did not significantly alter canagliflozin AUC and C_{max}: mean ratio (90% CI) 109.76 (104.96 to 114.78) % and 105.17 (95.78 to 115.78) % respectively (Study DIA1028).
- Co-administration of rifampin reduced canagliflozin AUC by 50% and C_{max} by 28%: mean ratio (90% CI) 48.76 (43.69 to 54.43) % and 71.75 (61.13 to 84.21) % respectively (Study DIA1029). The AUC for the M7 metabolite was reduced by 32% but C_{max} increased by 31%. The AUC for the M5 metabolite increased by 5% and C_{max} increased by 60%.
- Ciclosporin when co-administered with canagliflozin increased canagliflozin AUC by 23% but did not significantly change C_{max}: mean ratio (90% CI) 122.98 (118.66 to 127.46) % and 100.81 (91.31 to 111.30) % respectively (Study DIA1031).
- Co-administration of hydrochlorothiazide increased canagliflozin AUC by 12% and C_{max} by 15%: mean ratio (90% CI) 112.24 (107.55 to 117.33) % and 114.86 (105.95 to 124.51) % respectively (Study DIA1034).
- In the population PK study there were no significant effects of UGT1A9 or UGT2B4 substrates on the clearance of canagliflozin.

4.2.4.1.2. Effects on the PK of other drugs by concurrent administration of canagliflozin

- The AUC and C_{max} of ethinyl estradiol and levonorgestrel were increased by approximately 10% and 20% respectively with concurrent administration of canagliflozin 200 mg (Study DIA1002).
- Canagliflozin had no significant effect on the PK of glyburide (CYP 2C9 substrate) (Study DIA1004).
- In Study DIA1006, canagliflozin did not have any significant effect on the AUC or C_{max} of hydrochlorothiazide: LS mean ratio (90% CI) 100.95 (96.17 to 105.97) % and 109.9 (99.70 to 119.36) % respectively (Study DIA1006). In Study DIA1034, canagliflozin did not

significantly alter the AUC or C_{max} of hydrochlorothiazide: mean ratio (90% CI) 99.46 (94.85 to 104.30) % and 93.93 (86.97 to 101.46) % respectively (Study DIA1034).

- Canagliflozin did not have any significant effect on the AUC or C_{max} of simvastatin: mean ratio (90% CI) 110.32 (93.65 to 129.96) % and 109.09 (90.68 to 131.25) % respectively (Study DIA1009).
- Canagliflozin increased the AUC of digoxin by approximately 20% and C_{max} by 36%: mean ratio (90% CI) 119.51 (112.02 to 127.51) % and 135.82 (120.85 to 152.64) % respectively (Study DIA1014).
- Canagliflozin did not alter the PK of warfarin (Study DIA1016). For s-warfarin the mean ratio (90% CI) for AUC was 106.67 (100.91 to 112.76) % and for C_{max} was 100.98 (90.32 to 112.89) %. For r-warfarin the mean ratio (90% CI) for AUC was 100.09 (95.85 to 104.52) % and for C_{max} was 102.96 (93.74 to 113.09) %.
- In Study DIA1028 canagliflozin increased metformin AUC by 20% but did not have a significant effect on C_{max}: mean ratio (90% CI) 121.23 (109.41 to 134.32) % respectively (Study DIA1028). However, in Study NAP1004 canagliflozin did not alter the PK of metformin: mean ratio (90% CI) 0.965 (0.819 to 1.137) for AUC and 0.856 (0.729 to 1.007) for C_{max} (Study NAP1004).
- Probenecid increased the AUC of canagliflozin by 21% and C_{max} by 13%: mean ratio (90% CI) 120.74 (116.37 to 125.27) % and 113.37 (100.37 to 128.06) % respectively (Study DIA1048). The AUC for the M7 metabolite was increased by 30% and C_{max} by 29%. The AUC for the M5 metabolite was increased by 46% and C_{max} by 29%.

4.3. Evaluator's overall conclusions on pharmacokinetics

The PK of canagliflozin are unlikely to pose any challenges in clinical practice. The PK of canagliflozin were linear at doses up to 800 mg. Excretion is a combination of biliary and renal excretion of the glucuronide metabolites. Renal clearance of parent canagliflozin was negligible. Less than 1% of the administered dose was recovered as unchanged drug in urine. Half-life was approximately 12 to 15 hours. Digoxin will require additional monitoring when used in conjunction with canagliflozin. Other than for digoxin, there were no clinically significant interactions identified.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

See Table 1 above.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.3. Mechanism of action

In Study DIA1025 there was a linear relationship between plasma glucose and UGE, when plasma glucose was greater that $RT_{glucose}$. Canagliflozin decreased the $RT_{glucose}$, but did not alter the relationship.

5.4. Pharmacodynamic effects

5.4.1.1. Primary pharmacodynamic effects

5.4.1.1.1. Healthy volunteers

Urinary glucose excretion was similar following fasted and fed administration, and for tablet and suspension (Study NAP1003). Urinary glucose excretion was not dose proportional in the 25 mg to 400 mg dose range (Study NAP1003). There was no significant difference between the dose levels in glucose AUC or C_{max}. Insulin AUC was increased with the 400 mg dose compared with the 25 mg and 200 mg dose levels.

In healthy Japanese males urinary glucose excretion was not dose proportional in the 25 mg to 200 mg dose range (Study TA-7284-03).

In healthy male volunteers, at oral dose levels in the range of 800 mg to 1600 mg, plasma glucose parameters were similar for canagliflozin and placebo (Study DIA1001). There was an increase in urine glucose excretion that was similar for all three dose levels that persisted until at least Day 4 post-dose.

Urinary glucose excretion was not dose proportional in the 200 mg to 300 mg dose range: UGE_{0-24} was similar, UGE_{24-48} but was 34% greater for the 300 mg dose and UGE_{48-72} was 43% greater for the 300 mg dose (Study DIA1008). Plasma glucose, insulin and C-peptide concentrations were similar for the two treatments.

UGE_{0-24}, when assessed in the dose range 10 mg to 800 mg daily, plateaued at the 400 mg dose level, at 65 g/day (Study NAP1001).

In healthy Japanese male volunteers, for single doses in the range 30 mg to 800 mg, UGE_{0-24} demonstrated a plateau at the 400 mg dose level at around 80 g/day (Study TA7284-01).

In a comparison of doses in the range 30 mg to 600 mg once daily and 300 mg twice daily, there was a dose dependent increase in UGE_{0-24} with the highest effect in the 300 mg twice daily group at 61.2 g/day (Study NAP1008). There was little difference between the 300 mg once daily and 600 mg once daily groups (47.0 g/day vs 50.4 g/day respectively). There were no consistent dose related effects on plasma glucose, insulin or C-peptide. The renal threshold for glucose decreased in a dose dependent manner with the lowest value being 56.96 with the 600 mg dose. There was a statistically significant decrease in GLP-1 for the 300 mg dose at Day 14.

In Study DIA1030 the renal threshold for glucose excretion was similar for single and multiple doses. After 5 days of treatment, the mean (SD) renal threshold was 82.1 (9.1) mg/dL for the 50 mg dose, 63.0 (20.1) mg/dL for the 100 mg and 47.0 (17.3) mg/dL for the 300 mg. UGE_{0-24} was also similar for single and multiple doses. Mean (SD) UGE_{0-24} following multiple dosing was 28.9 (9.9) g for the 50 mg dose, 44.6 (16.5) g for the 100 mg and 60.9 (18.7) g for the 300 mg. Mean plasma glucose was similar for all the dose levels.

Renal threshold for glucose excretion was similar for the same daily dose delivered as once daily or twice daily dosing (Study DIA1032). LS mean 59.16 mg/dL for twice daily compared with 60.27 mg/dL for once daily at the 100 mg dose, and 51.03 mg/dL for twice daily compared with 52.49 mg/dL for once daily at the 300 mg dose. Mean UGE_{0-24} was 52.77 g for twice daily compared with 48.62 g for once daily at the 100 mg dose, and 58.64 g for twice daily compared with 57.85 g for once daily at the 300 mg dose.

In Study DIA1022 canagliflozin delayed the absorption of oral glucose, but did not affect the overall absorption of glucose. This was proposed to be due to a transient inhibition of intestinal SGLT1. Plasma GIP concentrations in the canagliflozin group were approximately half those in the placebo, and plasma PYY concentrations were increased.

5.4.1.2. Renal failure

The urinary excretion of glucose following canagliflozin was decreased in subjects with renal impairment and in severe renal impairment canagliflozin had negligible effect on urinary glucose excretion. This supports the Sponsor's advice that "Canagliflozin is not recommended for use in patients with severe renal impairment (eGFR < 30 ml/min/1.73 m^2), end stage renal disease (ESRD), or in patients on dialysis as canagliflozin is not expected to be effective in these patient populations".

5.4.2. Secondary pharmacodynamic effects

Canagliflozin 300 mg did not have any effect on the HMG-CoA reductase inhibition of simvastatin (Study DIA1009).

Mean serum urate levels decreased from baseline after administration of canagliflozin alone by approximately 20% and in combination with probenecid by 60% (Study DIA1048).

Canagliflozin did not alter the PD of warfarin (Study DIA1016). The ratio (90% CI) for INR AUC was 100.33 (98.21 to 102.50) % and INR_{max} was 105.25 (99.23 to 111.64) %.

A thorough QT study conducted at the 300 mg (therapeutic) and 1200 mg (supratherapeutic) dose levels, administered as single oral doses, did not demonstrate any significant increase in QTc at either dose level, at any time point compared with placebo (Study DIA1010). At all time points the upper 97.5% CI for the difference in QTc (canagliflozin-placebo) was <10 ms. The positive control (moxifloxacin) did demonstrate prolongation of the QTc.

In Study DIA1011 a delayed photosensitivity response was demonstrated in 25% subjects with canagliflozin 300 mg daily and also with 300 mg twice daily; compared to 67% subjects treated with ciprofloxacin (positive control) and none with placebo (negative control). An immediate photosensitive response was elicited in 25% subject with canagliflozin 300 mg daily and 58% subjects with canagliflozin 300 mg twice daily compared to none with ciprofloxacin or placebo. The six subjects that developed an immediate response with canagliflozin were further studied in Study 1020. All six subjects had photosensitivity reactions at standard irradiance, two at ½ standard irradiance and none at 1/10 standard irradiance. The study report argues that: "Since subjects who had immediate photosensitivity with testing at standard irradiance (30-fold maximum natural light) following administration of canagliflozin, no longer have immediate photosensitivity when irradiance is reduced, but still exceeds maximum natural sunlight (by 3-fold or more), the immediate photosensitivity that was observed at standard irradiance is unlikely to be clinically relevant."

In Study DIA1019 a delayed photosensitivity response was demonstrated in 8% subjects at the canagliflozin 100 mg once daily dose, 17% subjects with canagliflozin 300 mg daily; compared to 67% subjects treated with ciprofloxacin (positive control) and 17% with placebo (negative control). An immediate photosensitive response was elicited in 25% subject with canagliflozin 300 mg daily and 8% ciprofloxacin or placebo; but none with canagliflozin 100 mg daily.

In Study NAP1005 there was no significant difference in phototoxicity index between canagliflozin and placebo, although the mean scores were between those of placebo and ciprofloxacin at the 335 +/- 30 nm wavelength: mean (SD) phototoxicity index 1.0 (0.37) for placebo, 1.57 (0.49) for ciprofloxacin, 1.2 (0.32) for canagliflozin 200 mg and 1.3 (0.35) for canagliflozin 400 mg as single doses.

In Study NAP1001 there were no apparent dose related changes in individual urinary amino acid excretion. However, the mean combined Z-scores on Day 1 in each canagliflozin dose level (from 10 mg to 800 mg) ranged from 2.23 to 3.69 compared with 0.0 in placebo ($p < 0.0001$).

In Study NAP1001 24-hour urinary NAG excretion was increased in the 200 mg daily and greater dose groups, in a dose dependent manner.

5.4.3. Pharmacodynamic effects in subjects with T2DM

In subjects with T2DM after 4 weeks of treatment mean (SD) UGE_{0-24} was 77.10 (32.25) g for 100 mg daily and 156.74 (40.92) g for 300 mg twice daily (Study DIA1007). Mean (SD) $RT_{glucose}$ was 104 (24) mg/dL for 100 mg daily and 77 (22) mg/dL for 300 mg twice daily. The mean (SD) change in FPG was -38.1 (22.7) mg/dL for the 100 mg daily group and -42.4 (28.6) mg/dL for the 300 mg twice daily. The mean (SD) change in HbA1c compared with placebo was -0.37 (0.22) % for the 100 mg daily group and -0.55 (0.22) % for the 300 mg twice daily. Hydrogen breath test was used to explore carbohydrate malabsorption following canagliflozin. There was no significant increase following canagliflozin administration. There was no significant effect on postprandial GLP-1 or PYY.

In Study DIA1023, mean plasma glucose was lowered in all three treatment groups compared with placebo, with the greatest effect in the 300 mg group: LS mean (SE) difference to placebo -42.21 (18.852) mg/dL for 50 mg, -48.72 (13.335) mg/dL for 100 mg and -57.26 (12.752) mg/dL for 300 mg. The change from baseline in renal threshold for glucose was also greatest in the 300 mg group: LS mean (SE) difference to placebo -119.7 (10.224) mg/dL for 50 mg, -145.6 (10.894) mg/dL for 100 mg and -150.3 (9.908) mg/dL for 300 mg. PKPD modeling estimated a maximum effect (in terms of the change in renal threshold for glucose) of 69%, an EC_{50} of 35.2 ng/mL and EC_{90} of 317 ng/mL.

In Study DIA1045 a comparison of canagliflozin 300 mg for two days, 300 mg/150 mg, 300 mg/placebo and placebo demonstrated better PD responses for the 300 mg two day regimen. The canagliflozin in 300 mg daily over 2 days regimen resulted in the greatest reductions in serum glucose and insulin concentrations. Total GLP-1 AUC_{0-2} was greater in the canagliflozin 300/300 group than in the placebo: mean (95% CI) difference 3.12 (1.26 to 4.98) pmol•hour/L. Plasma glucagon AUC_{0-2} was also greater in the 300/300 group compared with placebo: mean (95% CI) difference 18.44 (6.53 to 30.35) pmol•hour/L.

In Study NAP1002 doses of canagliflozin 30 mg, 100 mg, 300 mg and 400 mg once daily and 300 mg twice daily were evaluated. UGE_{0-24} was similar for Day 1 and Day 16, and decreased over a 3 day period once dosing was ceased. Maximum effect was for the 400 mg once daily dosing. The $RT_{glucose}$ was lowest in the 400 mg once daily group, with little difference between the 300 mg twice daily group. Mean plasma glucose at Day 16 was lowest in the 200 mg and 400 mg groups, with little difference between them: mean (SD) 165 (26.4) mg/dL for 200 mg daily and 168 (24.5) mg/dL for 400 mg daily. Fasting plasma glucose was lowest in the 300 mg twice daily group. Plasma insulin concentrations were decreased in all the active treatment groups.

In Study TA7284-02 in Japanese subjects, in the dose range 25 mg to 400 mg, the increase in UGE_{0-24} at Day 16 was greatest in the 100 mg group, with little difference between the 400 mg group.

5.5. Time course of pharmacodynamic effects

The effect on UGE persisted for 48 hours, with reduced effect during the second 24 hour period.

5.6. Relationship between drug concentration and PD effects

PKPD modelling was performed using a population approach. For $RT_{glucose}$ the estimates for the minimum achievable (RT_{Gmin}) in healthy volunteers was in the range 37.5 to 58.1 mg/dL. The EC_{50} for this effect was in the range 16.2 to 21.0 ng/mL. In subjects with T2DM the maximum change in $RT_{glucose}$ was 66.6% and the EC_{50} was 32.4 ng/mL. The covariate model using HbA1c as the PD outcome measure included effects for AHA at screening and baseline HbA1c. EC_{50} was 32.4 ng/mL. In subjects with no AHA at screening E_{max} was -0.94% and for those with AHA at screening -1.45%.

5.7. Genetic-, gender- and age-related differences in PD response

In the population PKPD model, there were no covariate effects described for gender, age or BMI.

5.8. Pharmacodynamic interactions

There was no significant change in urinary glucose excretion with concurrent administration of ethinyl estradiol 30 µg and levonorgestrel 150 µg despite a decrease in AUC and C_{max} of plasma canagliflozin 10% (Study DIA1002).

In combination with canagliflozin, there was decreased increased secretion (plasma AUC) with glyburide than when glyburide was administered alone (Study DIA1004). However, in these healthy volunteers the effect on plasma glucose was similar for the two treatments separately and in combination.

There was no significant change in urinary glucose excretion when metformin was added to canigliflozin (Study DIA1028).

Hydrochlorothiazide did not alter the effect of canagliflozin on urinary excretion of glucose (Study DIA1034).

5.9. Evaluator's overall conclusions on pharmacodynamics

The PD data supported the choice of the 100 mg and 300 mg dose levels used in the Phase 3 studies. The data also support the Sponsor's advice that canagliflozin has little effect in severe renal failure and should not be used in such patients. There was no demonstrated, clinically significant drug-drug interaction on PD.

6. Dosage selection for the pivotal studies

6.1. Dose ranging studies

6.1.1. Study DIA2001

Study DIA2001 was a randomised, double-blind, placebo-controlled, parallel-group, multicentre, dose-ranging study with seven treatment cohorts including an active reference arm. The study was conducted at 85 study sites in 13 countries from March 2008 to January 2009. The study included men and women between 18 and 65 years of age, inclusive, with a diagnosis of T2DM, with HbA1c levels ≥7% and ≤10.5%, who were receiving a stable daily dose of MET ≥1,500 mg/day, who had stable body weight and a BMI of 25 to 45 kg/m^2 (except for those of Asian descent who had a BMI of 24 to 45 kg/ m^2), with a serum creatinine concentration <137 µmol/L for men and <128 µmol/L for women.

The study treatments were:

1. Canagliflozin 50 mg once daily
2. Canagliflozin 100 mg once daily
3. Canagliflozin 200 mg once daily
4. Canagliflozin 300 mg once daily
5. Canagliflozin 300 mg twice daily
6. Sitagliptin 100 mg once daily
7. Placebo

The study subjects were randomised in a 1:1:1:1:1:1:1 ratio based on a computer-generated randomization schedule using IVRS.

The primary efficacy outcome measure was the change in HbA1c (%) from baseline through Week 12. The secondary efficacy outcome measures were:

- Change in HbA1c (%) from baseline to Weeks 6 and 9
- Change in FPG from baseline to Weeks 6 and 12
- Proportion of subjects with HbA1c <6.5% and <7.0% at Week 12
- Change in 7-point SMBG profiles from baseline to Weeks 6 and 12
- Rate of symptomatic hypoglycemia through Week 12
- Proportion of subjects and the time to protocol-specified discontinuation due to loss of glycaemic control
- Absolute change in body weight and percentage change in body weight from baseline to Weeks 3, 6, 9, and 12/ EOT visit
- Changes in fasting, overnight urinary glucose to creatinine ration from baseline to Weeks 3, 6, and 12

The exploratory evaluations were:

- Body weight
- Waist and hip circumference
- BMI
- Fasting lipid profile: triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol, and total cholesterol/HDL ratio
- Systolic blood pressure (SBP) and diastolic blood pressure (DBP)
- Fasting insulin and C-peptide levels
- Multidimensional Diabetes Questionnaire (MDQ) Section III: self-efficacy and outcome expectancies scales

The safety outcome measures included AEs, clinical laboratory tests, hypoglycaemic episodes, and urinary markers. Hypothesis tests were performed using an ANCOVA model with treatment and MMTT stratum as factors, and baseline HbA1c as a covariate.

There were 451 subjects randomised to treatment: 64 to 65 subjects per group. A total of 402 (89%) subjects completed. There were 236 (52%) males, 215 (48%) females, and the age range was 29 to 65 years. The treatment groups were similar in demographic characteristics.

For the primary efficacy outcome variable (change in HbA1c from baseline to Week 12) the mean (SD) was -0.22 (0.702) % for placebo, -0.79 (0.749) % for 50 mg once daily, -0.76 (0.992) % for 100 mg, -0.70 (0.720) % for 200 mg, -0.92 (0.695) % for 300 mg, -0.95 (0.704) % for 300 mg twice daily and -0.74 (0.615) % for sitagliptin. Over the 12 week period the change in HbA1c was similar for canagliflozin 300 mg once daily and 300 mg twice daily. The change in FPG was 0.2 (1.58) mmol/L for placebo, -0.9 (2.26) mmol/L for 50 mg, -1.4 (1.70) mmol/L for 100 mg, -1.5 (2.23) mmol/L for 200 mg, -1.4 (1.87) mmol/L for 300 mg, -1.3 (1.54) mmol/L for 300 mg twice daily and -0.7 (1.77) mmol/L for sitagliptin. The change in FPG over time was similar for the canagliflozin 300 mg once daily and 300 mg twice daily regimens. The proportion of subjects with HbA1c (%) values <7.0% at Week 12 LOCF was 42%, 53%, 61%, 72%, and 65% for canagliflozin 50 mg, 100 mg, 200 mg, and 300 mg once daily, and 300 mg twice daily treatment groups, respectively, compared to 34% for the placebo group and 65% for

sitagliptin. The proportion of subjects with HbA1c (%) values <6.5% at Week 12 LOCF was 19%, 27%, 27%, 42%, and 32% for canagliflozin 50 mg, 100 mg, 200 mg, and 300 mg once daily, and 300 mg twice daily treatment groups, respectively, compared to 13% for the placebo and 45% for sitagliptin. All the active treatment groups improved 7-point SMBG profiles. Hypoglycaemia was reported in one (2%) subject in the placebo group, none in the 50 mg, one (2%) in the 100 mg, four (6%) in the 200 mg, none in the 300 mg, two (3%) in the 300 mg twice daily and three (5%) in the sitagliptin. Mean (SD) change in body weight was: -1.1 (2.4) kg for placebo, -2.3 (2.8) kg for 50 mg, -2.6 (2.3) kg for 100 mg, -2.7 (3.0) kg for 200 mg, -3.4 (2.8) kg for 300 mg, -3.4 (2.6) kg for 300 mg twice daily and -0.6 (3.0) kg for placebo. The changes in hip and waist circumference reflected these changes. Urinary glucose/creatinine ratio increased in all the canagliflozin groups. There were no significant changes in fasting lipids in all of the groups. The mean changes in fasting serum insulin were -0.27, -3.67, -7.17, -11.85, and -13.83 pmol/L for canagliflozin at 50 mg, 100 mg, 200 mg, 300 mg, and 300 mg twice daily, respectively and 3.20 pmol/L for sitagliptin.

6.1.2. Study TA7284-04

Study TA7284-04 was a multicentre, randomised, placebo-controlled, double-blind, parallel-group comparative dose finding study. The study was conducted as a multicentre study in Japan from October 2009 to August 2010. The study included subjects with T2DM, aged ≥20 years and ≤80 years, with HbA1c ≥6.5% and ≤9.5%, who had undergone diet and exercise therapy for T2DM; and who had not used diabetes drugs for at least 8 weeks.

The study treatments were:

1: Canagliflozin 50 mg

2: Canagliflozin 100 mg

3: Canagliflozin 200 mg

4: Canagliflozin 300 mg

4: Placebo

The treatment duration was 12 weeks.

The primary efficacy outcome measure was the change in HbA1c to Week 12. The secondary endpoints were:

- Change and percentage change in fasting plasma glucose
- HbA1c <6.5% achievement rate, HbA1c <7.0% achievement rate
- Percentage of subjects experiencing hypoglycemia
- Change in urinary glucose/creatinine ratio
- Change in body weight
- Change in BMI
- Change in waist circumference
- Change in lipids (HDL-C, LDL-C, triglycerides, total cholesterol and LDL-C/HDL-C ratio)
- Change in blood pressure (SBP, DBP)
- Change in insulin, proinsulin and proinsulin/insulin ratio
- Changes in HOMA-R and HOMA-β
- Meal tolerance test (blood glucose, insulin, 2-hour urinary glucose excretion, plasma glucose $AUC_{0\text{-}2h}$, insulin $AUC_{0\text{-}2h}$, insulin $AUC_{0\text{-}2h}$/plasma glucose $AUC_{0\text{-}2h}$ ratio, Insulinogenic index)

The safety outcome measures were AEs, laboratory tests, vital signs, ECG, bone-related markers, renal function and hypoglycaemia.

There were 383 subjects were randomised and treated: 75 placebo, 82 in the 50 mg, 74 in the 100 mg, 77 in the 200 mg and 75 in the 300 mg. Twenty two subjects withdrew, four due to AE. There were 260 (68.1%) males and 122 (31.9%) females and the age range was 31 to 79 years. The treatment groups were similar in demographic and baseline characteristics.

At Week 12, the LS mean (95% CI) change in HbA1c compared to placebo was -0.72 (-0.88 to -0.55) for 50 mg, -0.90 (-1.07 to -0.74) for 100 mg, -0.90 (-1.07 to -0.73) for 200 mg and -0.99 (-1.15 to -0.82) for 300 mg. After 8 weeks of treatment the best response was in the 300 mg group. FBG decreased in a dose dependent manner with the greatest decrease occurring in the 300 mg group. The proportion of subjects with HbA1c <6.5% at Week 12 was 1.3% for placebo, 1.2% for 50 mg, 4.1% for 100 mg, 4.0% for 200 mg and 2.7% for 300 mg. The proportion of subjects with HbA1c <7.0% at Week 12 was 5.7% for placebo, 21.0% for 50 mg, 33.8% for 100 mg, 29.2% for 200 mg and 40.5% for 300 mg. The proportion of subjects that developed hypoglycaemia was 0% for placebo, 4.9% for 50 mg, 4.1% for 100 mg, 5.3% for 200 mg and 4.0% for 300 mg. Urinary glucose to creatinine ratio increased in a dose dependent manner. The mean (95% CI) change in body weight relative to placebo was -1.19 (-1.68 to -0.71) kg for 50 mg, -1.73 (-2.22 to -1.23) kg for 100 mg, -1.61 (-2.10 to -1.12) kg for 200 mg and -2.41 (-2.90 to -1.92) kg for 300 mg. The mean change in BMI was -0.31 kg/m^2 for placebo, -0.73 kg/m^2 for 50 mg, -0.93 kg/m^2 for 100 mg, -0.87 kg/m^2 for 200 mg and -1.17 kg/m^2 for 300 mg. The mean change in waist circumference was -0.6 cm for placebo, -1.6 cm for 50 mg, -1.8 cm for 100 mg, -1.8 cm for 200 mg and -2.2 cm for 300 mg. HDL-C increased in comparison with placebo: mean % change (95% CI) 4.29 (0.40 to 8.19) % for 50 mg, 7.48 (3.48 to 11.47) % for 100 mg, 8.92 (4.95 to 12.89) % for 200 mg and 8.21 (4.23 to 12.19) % for 300 mg. There were no other consistent changes in plasma lipids. SBP decreased relative to placebo: mean (95% CI) difference -4.6 (-7.9 to -1.3) mmHg for 50 mg, -5.9 (-9.3 to -2.6) mmHg for 100 mg, -8.1 (-11.4 to -4.8) mmHg for 200 mg and -7.5 (-10.9 to -4.2) mmHg for 300 mg. DBP also decreased relative to placebo in the 100 mg and above groups: mean (95% CI) difference -1.4 (-3.7 to 0.9) mmHg for 50 mg, -3.0 (-5.4 to -0.6) mmHg for 100 mg, -4.2 (-6.6 to -1.9) mmHg for 200 mg and -3.3 (-5.7 to -1.0) mmHg for 300 mg. Plasma insulin, proinsulin and insulin/proinsulin ratios all decreased in the canagliflozin groups relative to placebo. HOMA-R decreased and HOMA-β increased in the canagliflozin groups relative to placebo. There were also improvements in the meal tolerance test in the canagliflozin groups.

6.2. Evaluator's conclusion with regard dose selection

The dose finding studies supported the selection of the canagliflozin 100 mg and 300 mg dose levels used in the Phase 3 studies. There was a plateau in effects at the 300 mg dose level, and little difference between the 100 mg and 200 mg dose levels.

7. Clinical efficacy

7.1. Pivotal efficacy studies

7.1.1. Efficacy in combination with MET and SU

7.1.1.1. Study DIA3002

7.1.1.1.1. Study design, objectives, locations and dates

Study DIA3002 was a multicentre, randomised, double-blind, placebo-controlled, parallel-group, three-arm, study conducted to evaluate the efficacy, safety and tolerability of the addition of canagliflozin (100 mg daily and 300 mg daily) compared with placebo in subjects with T2DM

who were inadequately controlled with MET and a SU (Table 2). The study was conducted at 85 centres in 11 countries, including five centres in Australia, from April 2010 to September 2011.

Table 2. Summary of Study DIA3002

Study -investigator -coordinating centre centre(s) -report n°	Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Study DIA3002 (Module 5, Section 5.3.5.1) 85 centres in 11 countries, including 5 in Australia April 2010 to September 2011	Multicentre, randomised, double-blind, placebo-controlled, parallel-group, three-arm, study conducted to evaluate the efficacy, safety and tolerability of the addition of canagliflozin (100 mg daily and 300 mg daily) compared with placebo in subjects with T2DM who were inadequately controlled with MET and a SU.	469 randomised: 157 to 100 mg, 256 to 300 mg and 156 to placebo. All included in the mITT dataset. 28 (17.8%) in the 100 mg group, 27 (17.3%) in the 300 mg and 33 (21.2%) in the placebo discontinued. 239 (51.0%) males, 230 (49.0%) females age range 27 to 79 years. 84 (17.9%) aged ≥65 years.	Males or females, aged ≥18 and ≤80 years, with T2DM and currently treated with MET and an SU, meeting the following HbA1c eligibility criteria: On MET and an SU at protocol-specified doses for at least 8 weeks prior to screening, and with HbA1c ≤7.0% and ≤10.5% at screening visit, or On metformin and an SU, either or both at doses below protocol-specified with HbA1c ≥7.5% at screening and ≥7.0% and ≤10.5% at Week -2. The protocol specified dose of MET was ≥2000 mg per day, or ≥1500 mg per day if intolerant to a higher dose.	26 weeks	Canagliflozin 100 mg Canagliflozin 300 mg Oral administration once daily, before the first meal of the day Block randomised using IVRS/IWRS in 1:1:1 ratio, stratified by MET/SU dose and participation in FS-MMTT	Placebo All subjects continued on MET and SU at a stable dose during the study	The primary efficacy outcome measure was change in HbA1c. The secondary efficacy measures included: FPG Body weight SBP Fasting triglycerides Fasting HDL-C Safety outcome variables were AEs, laboratory tests, hypoglycaemic events, ECGs, vital signs, physical examinations and SMBG	The mean (SD) change from baseline in HbA1c was -0.92 (0.985) % for canagliflozin 100 mg, -1.13 (0.936) % for 300 mg and -0.20 (0.915) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.71 (-0.904 to -0.524) % for 100 mg and -0.92 (-1.114 to -0.732) % for 300 mg. The proportion of subjects with HbA1c <7.0% at Week 26 was 67 (43.2%) subjects for 100 mg, 86 (56.6%) for 300 mg and 27 (18.0%) for placebo (p <0.001). The proportion of subjects with HbA1c <6.5% at Week 26 was 29 (18.7%) subjects for 100 mg, 46 (30.2%) for 300 mg and nine (6.0%) for placebo. The mean (SD) change from baseline in FPG was -1.22 (2.743) mmol/L for canagliflozin 100 mg, -1.76 (2.232) mmol/L for 300 mg and 0.13 (2.769) mmol/L for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -1.24 (-1.747 to -0.728) mmol/L for 100 mg and -1.92 (-2.432 to -1.409) mmol/L for 300 mg.	TEAEs were reported in 90 (57.3%) subjects in the canagliflozin 100 mg group, 97 (62.2%) in the 300 mg and 100 (64.1%) in the placebo. There was a higher incidence of diarrhea in the canagliflozin 300 mg group than the other two groups (6% vs 3%); and a higher incidence of vaginal mycotic infections in the canagliflozin groups compared with placebo (5% vs 1%). There were no reported deaths. SAEs were reported in five (3.2%) subjects in the canagliflozin 100 mg group, six (3.8%) in the 300 mg and nine (5.8%) in the placebo. DAEs were reported in nine (5.7%) subjects in the canagliflozin 100 mg group, nine (5.8%) in the 300 mg and five (3.2%) in the placebo. Urogenital infections were more common reasons for discontinuation in the canagliflozin groups.

7.1.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Males or females, aged ≥18 and ≤80 years, with T2DM and currently treated with MET and an SU, meeting the following HbA1c eligibility criteria:
- On MET and an SU at protocol-specified doses for at least 8 weeks prior to screening, and with HbA1c ≤7.0% and ≤10.5% at screening visit, or
- On MET and an SU, either or both at doses below protocol-specified with HbA1c ≥7.5% at screening and ≥7.0% and ≤10.5% at Week -2

The protocol specified dose of MET was ≥2000 mg per day, or ≥1500 mg per day if intolerant to a higher dose.

The exclusion criteria included:

- Repeated (ie, two or more over a 1-week period) FPG and/or fasting SMBG measurements ≥15 mmol/L despite reinforcement of diet and exercise counselling
- History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
- On either a PPARγ agonist (eg, a thiazolidinedione [pioglitazone or rosiglitazone]), ongoing insulin therapy, another SGLT2 inhibitor, or any other AHA (including agents such as colesevelam and bromocriptine that have indications in some regions for treatment of T2DM) except as specified in the study inclusion criteria within 12 weeks
- Myocardial infarction, unstable angina, revascularization procedure (eg, stent or bypass graft surgery), or cerebrovascular accident within 3 months, or revascularization procedure is planned, or a history of New York Heart Association (NYHA) Class III-IV cardiac disease
- Findings on 12-lead ECG that required urgent diagnostic evaluation or intervention (eg, new clinically important arrhythmia or conduction disturbance)
- Uncontrolled hypertension (DBP ≥100 mm Hg or SBP ≥160 mmHg)
- ALT level >2xULN or total bilirubin >1.5xULN
- Estimated GFR <55 mL/min/1.73 m^2 (or <60 mL/min/1.73 m^2 if based upon restriction of MET use in the MET local label) or serum creatinine ≥124 µmol/L for men and ≥115 µmol/L for women

7.1.1.1.3. Study treatments

The study treatments were:

1: Canagliflozin 100 mg

2: Canagliflozin 300 mg

3: Placebo

Treatment duration was for 26 weeks. All subjects continued on MET and SU at a stable dose during the study. The treatments were administered orally, once daily, before the first meal of the day.

7.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure was change in HbA1c. The secondary efficacy measures included:

- FPG

- Body weight
- SBP
- Fasting triglycerides
- Fasting HDL-C

Additional efficacy outcome measures were:

- DBP
- Other fasting lipid levels (including LDL-C , total cholesterol, LDL-C/HDL-C ratio
- Use of rescue medication
- Time to initiation of rescue medication
- HOMA2%-B (calculated using FPG and C-peptide)
- Glucose, insulin, and C-peptide after the standard meal in the subset of subjects who underwent the FS-MMTT

The safety outcome variables were AEs, laboratory tests, hypoglycaemic events, ECGs, vital signs, physical examinations and SMBG.

7.1.1.1.5. Randomisation and blinding methods

The study was double blind and the treatments were indistinguishable. Subjects were block randomised using IVRS/IWRS in 1:1:1 ratio, stratified by MET/SU dose and participation in FS-MMTT.

7.1.1.1.6. Analysis populations

The analysis data sets were:

- mITT Analysis Set: All randomised subjects who took at least 1 dose of double-blind study drug
- Per-protocol (PP) Analysis Set: All mITT subjects who completed 26 weeks of treatment, were not initiated on rescue medication prior to the Week 26 visit, and had no major protocol deviations
- 26-week Completers' Analysis Set: All mITT subjects who completed 26 weeks
- Safety Analysis Set: as per the mITT analysis set

7.1.1.1.7. Sample size

The study was designed to test for superiority for the primary efficacy outcome measure at Week 26. Assuming a group difference for HbA1c of 0.5% between canagliflozin and placebo, and a common SD of 1.0% with respect to change in HbA1c, and using a 2-sample, 2-sided t-test with a type I error rate of 0.05, it was estimated that 85 randomised subjects per treatment group were required to achieve at least 90% power. The Sponsor increased this to 150 subjects per group in order to provide more data for safety and tolerability assessments.

7.1.1.1.8. Statistical methods

Hypothesis tests were performed using ANCOVA with treatment and stratification factors as fixed effects and HbA1c baseline value as a covariate. The hypothesis tests used the mITT data set. LOCF was used for imputing missing variables. To account for multiplicity, the hypothesis testing was conducted using a hierarchical/sequential approach, where the 100 mg dose level was tested only if the 300 mg was superior.

7.1.1.1.9. Participant flow

There were 469 subjects randomised: 157 to 100 mg, 256 to 300 mg and 156 to placebo. All of the subjects were included in the mITT dataset (and therefore the safety dataset). There were 28 (17.8%) subjects in the 100 mg group, 27 (17.3%) in the 300 mg and 33 (21.2%) in the placebo that discontinued.

7.1.1.1.10. Major protocol violations/deviations

The PP dataset included 126 (90.3%) subjects in the 100 mg group, 120 (76.9%) in the 300 mg and 102 (65.4%) in the placebo.

7.1.1.1.11. Baseline data

There were 239 (51.0%) males, 230 (49.0%) females and the age range was 27 to 79 years. There were 84 (17.9%) subjects aged ≥65 years. The treatment groups were similar in demographic characteristics (Table 3). The treatment groups were similar in anthropometric characteristics. The treatment groups were similar in baseline diabetes characteristics. The treatment groups were similar in baseline and concomitant medications. The treatment groups were similar in MET dose prior to and during the treatment period. The treatment groups were similar in SU use at baseline.

Table 3. Baseline Demographic Characteristics (Study DIA3002)

	Placebo (N=156)	CANA 100 mg (N=157)	CANA 300 mg (N=156)	CANA Total (N=313)	Total (N=469)
Sex, n (%)					
N	156	157	156	313	469
Male	76 (48.7)	76 (48.4)	87 (55.8)	163 (52.1)	239 (51.0)
Female	80 (51.3)	81 (51.6)	69 (44.2)	150 (47.9)	230 (49.0)
Age (Year)					
N	156	157	156	313	469
Category, n (%)					
<35	1 (0.6)	4 (2.5)	1 (0.6)	5 (1.6)	6 (1.3)
35 - <65	129 (82.7)	117 (74.5)	133 (85.3)	250 (79.9)	379 (80.8)
≥65	26 (16.7)	36 (22.9)	22 (14.1)	58 (18.5)	84 (17.9)
Mean (SD)	56.7 (8.36)	57.3 (10.47)	56.0 (8.95)	56.7 (9.75)	56.7 (9.30)
Median	57.0	59.0	56.0	58.0	58.0
Range	(31;79)	(27;79)	(34;78)	(27;79)	(27;79)
Race, n (%)					
N	156	157	156	313	469
White	128 (82.1)	132 (84.1)	127 (81.4)	259 (82.7)	387 (82.5)
Black or African American	10 (6.4)	5 (3.2)	11 (7.1)	16 (5.1)	26 (5.5)
Asian	2 (1.3)	2 (1.3)	0	2 (0.6)	4 (0.9)
American Indian or Alaska Native	0	2 (1.3)	2 (1.3)	4 (1.3)	4 (0.9)
Native Hawaiian or Other Pacific Islander	1 (0.6)	0	1 (0.6)	1 (0.3)	2 (0.4)
Multiple	1 (0.6)	0	2 (1.3)	2 (0.6)	3 (0.6)
Other	11 (7.1)	14 (8.9)	12 (7.7)	26 (8.3)	37 (7.9)
Not Reported	3 (1.9)	2 (1.3)	1 (0.6)	3 (1.0)	6 (1.3)
Ethnicity, n (%)					
N	156	157	156	313	469
Hispanic or Latino	44 (28.2)	32 (20.4)	33 (21.2)	65 (20.8)	109 (23.2)
Not Hispanic or Latino	112 (71.8)	124 (79.0)	123 (78.8)	247 (78.9)	359 (76.5)
Not Reported	0	1 (0.6)	0	1 (0.3)	1 (0.2)

Key: CANA=canagliflozin, N=total number of subjects, n=total number of subjects in subgroup, SD=standard deviation

7.1.1.1.12. Results for the primary efficacy outcome

Canagliflozin 300 mg and 100 mg were both superior to placebo (Table 4). The mean (SD) change from baseline in HbA1c was -0.92 (0.985) % for canagliflozin 100 mg, -1.13 (0.936) % for 300 mg and -0.20 (0.915) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.71 (-0.904 to -0.524) % for 100 mg and -0.92 (-1.114 to -0.732) % for 300 mg. There was no subgroup effect on efficacy.

Table 4. HbA1c: Change From Baseline to Week 26 (LOCF)

	Placebo (N=156)	CANA 100 mg (N=157)	CANA 300 mg (N=156)
HbA_{1c} (%)			
Value at Baseline			
N	150	155	152
Mean (SD)	8.12 (0.896)	8.13 (0.926)	8.13 (0.942)
Value at Week 26 LOCF			
N	150	155	152
Mean (SD)	7.93 (1.106)	7.21 (0.922)	7.01 (0.906)
Change from Baseline			
N	150	155	152
Mean (SD)	-0.20 (0.915)	-0.92 (0.985)	-1.13 (0.936)
LS Mean (SE)	-0.13 (0.075)	-0.85 (0.075)	-1.06 (0.076)
P-value(minus Placebo) [a]		<0.001	<0.001
Diff. of LS Means (SE)		-0.71 (0.097)	-0.92 (0.097)
95% CI [a]		(-0.904;-0.524)	(-1.114;-0.732)

[a] Pairwise comparison: p-values and CIs are based on the ANCOVA model with treatment, AHA adjustment period, and FS-MMTT as fixed effects, and baseline HbA_{1c} as a covariate.

Key: AHA=antihyperglycemic agent, ANCOVA=analysis of covariance, CANA=canagliflozin, CI=confidence interval, HbA_{1c}=hemoglobin A_{1c} (glycosylated hemoglobin), FS-MMTT=frequently sampled mixed-meal tolerance test, LOCF=last observation carried forward, LS=least squares, N=total number of subjects, SD=standard deviation, SE=standard error

7.1.1.1.13. Results for other efficacy outcomes

- The proportion of subjects with HbA1c <7.0% at Week 26 was 67 (43.2%) subjects for 100 mg, 86 (56.6%) for 300 mg and 27 (18.0%) for placebo (p <0.001).
- The proportion of subjects with HbA1c <6.5% at Week 26 was 29 (18.7%) subjects for 100 mg, 46 (30.2%) for 300 mg and nine (6.0%) for placebo.
- The mean (SD) change from baseline in FPG was -1.22 (2.743) mmol/L for canagliflozin 100 mg, -1.76 (2.232) mmol/L for 300 mg and 0.13 (2.769) mmol/L for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -1.24 (-1.747 to -0.728) mmol/L for 100 mg and -1.92 (-2.432 to -1.409) mmol/L for 300 mg.
- Glycaemic rescue was required for two (1.3%) subjects in the canagliflozin 100 mg group, three (1.9%) in the 300 mg and 20 (12.8%) in the placebo. The HR (95% CI) (canagliflozin compared to placebo) was 0.09 (0.02 to 0.41) for 100 mg and 0.14 (0.04 to 0.48) for 300 mg.
- The mean (SD) % change from baseline in body weight was -2.0 (2.8) % for canagliflozin 100 mg, -2.6 (2.8) % for 300 mg and -0.6 (3.7) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -1.4 (-2.1 to -0.7) % for 100 mg and -2.0 (-2.7 to -1.3) % for 300 mg.
- The mean (SD) change from baseline in BMI was -0.68 (0.976) kg/m^2 for canagliflozin 100 mg, -0.89 (1.032) kg/m^2 for 300 mg and -0.25 (0.102) kg/m^2 for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.40 (-0.656 to -0.139) kg/m^2 for 100 mg and -0.62 (-0.875 to -0.357) kg/m^2 for 300 mg.
- The mean (SD) change from baseline in waist circumference was -2.35 (4.759) cm for canagliflozin 100 mg, -3.56 (5.898) cm for 300 mg and -1.17 (7.719) cm for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.88 (-2.276 to 0.511) cm (not significant) for 100 mg and -2.12 (-3.519 to -0.729) cm for 300 mg.
- There was no significant difference between the groups in the change in SBP: mean (SD) change from baseline -4.63 (12.378) mmHg for canagliflozin 100 mg, -4.19 (13.818) mmHg for 300 mg and -2.25 (11.051) mmHg for placebo.

- There was no significant difference between the groups in the change in DBP: mean (SD) change from baseline -2.34 (7.952) mmHg for canagliflozin 100 mg, -2.03 (8.032) mmHg for 300 mg and -1.58 (6.953) mmHg for placebo.
- There was no significant difference between the groups in the change in HDL-C: mean (SD) change from baseline 6.4 (14.9) mmol/L for canagliflozin 100 mg, 7.6 (15.0) mmol/L for 300 mg and 2.9 (16.2) mmol/L for placebo.
- There was no significant difference between the groups in the change in triglycerides, cholesterol, LDL-C or LDL-C/HDL-C ratio.
- The mean (SD) change from baseline in HOMA2-%B was 15.58 (46.940) for canagliflozin 100 mg, 28.32 (62.130) for 300 mg and 0.61 (40.168) for placebo.

There was no significant difference in the ratio of C-peptide AUC to Glucose AUC during FS-MMTT, insulogenic index, β-cell glucose sensitivity, or insulin sensitivity between the treatment groups. Renal glucose excretion increased and renal glucose threshold decreased in the canagliflozin groups.

7.1.1.2. Study DIA3015

7.1.1.2.1. Study design, objectives, locations and dates

Study DIA3015 was a multicentre, randomised, double-blind, active-controlled, two- arm, parallel-group, study of treatment with once daily canagliflozin 300 mg or sitagliptin 100 mg (1:1 randomisation ratio) over 52 weeks in subjects with T2DM (Table 5). The study was conducted at 140 centres in 17 countries from June 2010 to March 2012.

Table 5. Summary of Study DIA3015

Study -investigator -coordinating centre centre(s) -report n°	Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Study DIA3015 (Module 5, Section 5.3.5.1) 140 centres in 17 countries June 2010 to March 2012	Multicentre, randomised, double-blind, active-controlled, two- arm, parallel-group, study of treatment with once daily canagliflozin 300 mg or sitagliptin 100 mg (1:1 randomisation ratio) over 52 weeks in subjects with T2DM	1672 screened, 756 randomised: 378 to canagliflozin 300 mg and 378 to sitagliptin 100 mg. There were 123 (32.5%) subjects in the canagliflozin group and 168 (44.4%) in the sitagliptin that discontinued. 239 (51.0%) males, 230 (49.0%) females, age range 27 to 79 years. 84 (17.9%) subjects aged ≥65 years.	Male or female ≥18 years of age with T2DM and currently treated with MET (≥2,000 mg/day or ≥1,500 mg/day if intolerant of higher dose) and an SU for at least 8 weeks and HbA1c ≥7.0% and ≤10.5% or MET and an SU, either or both at doses below protocol-specified with HbA1c ≥7.5% at screening and ≥7.0% and ≥10.5% at Week -2.	52 weeks	Canagliflozin 300 mg daily Treatment duration was for 52 weeks. All subjects continued on MET and SU at a stable dose during the study. The treatments were administered orally, once daily, before the first meal of the day. No other AHAs were allowed during the study.	Sitagliptin 100 mg daily	The primary efficacy outcome measure was change in HbA1c. The secondary efficacy measures included: FPG Body weight SBP Fasting triglycerides Fasting HDL-C Safety outcome variables were AEs, laboratory tests, hypoglycaemic events, ECGs, vital signs, physical examinations and SMBG	Canagliflozin 300 mg was superior to sitagliptin 100 mg. The mean (SD) change from baseline in HbA1c was -1.0 (0.940) % for canagliflozin and -0.63 (1.022) % for sitagliptin. The LS mean (95% CI) difference (canagliflozin-sitagliptin) was -0.37 (-0.500 to -0.250) %. The proportion of subjects with HbA1c <7.0% at Week 52 was 178 (47.6%) subjects for canagliflozin and 129 (35.3%) for sitagliptin; OR (95% CI) 1.80 (1.30 to 2.48).Mean (SD) change from baseline in FPG was -1.72 (2.452) mmol/L for canagliflozin 300 mg and -0.19 (2.881) mmol/L sitagliptin. The LS mean (95% CI) difference (canagliflozin-sitaliptin) was -1.34 (-1.658 to -1.012) mmol/L.	TEAEs were reported in 289 (76.7%) subjects in the canagliflozin group and 293 (77.5%) in the sitagliptin. Treatment related TEAEs were reported in 128 (34.0%) subjects in the canagliflozin group and 105 (27.8%) in the sitagliptin. There were two deaths in the canagliflozin group. SAEs were reported in 24 (6.4%) subjects in the canagliflozin group and 21 (5.6%) in the sitagliptin. DAEs were reported in 20 (5.3%) subjects in the canagliflozin group and eleven (2.9%) in the sitagliptin.

7.1.1.2.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female ≥18 years of age with T2DM
- Currently treated with MET (≥2,000 mg/day or ≥1,500 mg/day if intolerant of higher dose) and an SU for at least 8 weeks and HbA1c ≥7.0% and ≤10.5% or MET and an SU, either or both at doses below protocol-specified with HbA1c ≥7.5% at screening and ≥7.0% and ≥10.5% at Week -2.

The exclusion criteria were the same as for Section 7.1.1.1.2.

7.1.1.2.3. Study treatments

The study treatments were:

1: Canagliflozin 300 mg

2: Sitagliptin 100 mg

Treatment duration was for 52 weeks. All subjects continued on MET and SU at a stable dose during the study. The treatments were administered orally, once daily, before the first meal of the day. No other AHAs were allowed during the study.

7.1.1.2.4. Efficacy variables and outcomes

As per Section 7.1.1.1.4.

7.1.1.2.5. Randomisation and blinding methods

The study was double blind and the treatments were indistinguishable. Subjects were block randomised using IVRS/IWRS in 1:1 ratio, stratified by HbA1c at Week -2 and participation in FS-MMTT.

7.1.1.2.6. Analysis populations

As per Section 7.1.1.1.6.

7.1.1.2.7. Sample size

The study was designed to test for non-inferiority for the primary efficacy outcome measure (change in HbA1c) at Week 52. The sample size calculation used a margin of non-inferiority of 0.3%, assumed a group difference for HbA1c of 0.0% between canagliflozin and placebo, and a common SD of 1.0% with respect to change in HbA1c, and using a 2-sample, one-sided t-test with a type I error rate of 0.025, it was estimated that 234 randomised subjects per treatment group were required to achieve at least 90% power. Assuming a drop-out rate of 35%, the final sample size calculation was 360 subjects per treatment group.

7.1.1.2.8. Statistical methods

As per Section 7.1.1.1.8.

7.1.1.2.9. Participant flow

There were 1672 subjects screened and 756 were randomised to treatment: 378 to canagliflozin 300 mg and 378 to sitagliptin 100 mg. One subject in the canagliflozin group was not dosed and was excluded from mITT dataset (and therefore the safety dataset). There were 123 (32.5%) subjects in the canagliflozin group and 168 (44.4%) in the sitagliptin that discontinued.

7.1.1.2.10. Major protocol violations/deviations

The PP dataset included 247 (65.3%) subjects in the canagliflozin group and 207 (54.8%) in the sitagliptin.

7.1.1.2.11. Baseline data

There were 239 (51.0%) males, 230 (49.0%) females and the age range was 27 to 79 years. There were 84 (17.9%) subjects aged ≥65 years. The treatment groups were similar in demographic and anthropometric characteristics (Table 6). The treatment groups were similar in baseline diabetes characteristics. The treatment groups were similar in MET dose prior to and during the treatment period. There were six (2%) subjects in the canagliflozin group and seven (2%) in the sitagliptin that had a dose change in MET during the study. The treatment groups were similar in SU use at baseline and during the treatment period. There were 32 (8%) subjects in the canagliflozin group and 40 (11%) in the sitagliptin that had a dose change in SU during the study.

Table 6. Baseline Demographic Characteristics (Study DIA3015)

	CANA 300 mg (N=377)	Sita 100 mg (N=378)	Total (N=755)
Sex, n (%)			
N	377	378	755
Male	207 (54.9)	215 (56.9)	422 (55.9)
Female	170 (45.1)	163 (43.1)	333 (44.1)
Age (Years)			
N	377	378	755
Category, n (%)			
<35	5 (1.3)	5 (1.3)	10 (1.3)
35 - <65	299 (79.3)	302 (79.9)	601 (79.6)
≥65	73 (19.4)	71 (18.8)	144 (19.1)
Mean (SD)	56.6 (9.62)	56.7 (9.30)	56.7 (9.46)
Median	57.0	57.0	57.0
Range	(30;91)	(21;85)	(21;91)
Race, n (%)			
N	377	378	755
White	245 (65.0)	240 (63.5)	485 (64.2)
Black or African American	43 (11.4)	45 (11.9)	88 (11.7)
Asian	67 (17.8)	65 (17.2)	132 (17.5)
American Indian or Alaska Native	0	1 (0.3)	1 (0.1)
Native Hawaiian or other Pacific Islander	1 (0.3)	3 (0.8)	4 (0.5)
Multiple	12 (3.2)	17 (4.5)	29 (3.8)
Other	7 (1.9)	6 (1.6)	13 (1.7)
Unknown	1 (0.3)	0	1 (0.1)
Not reported	1 (0.3)	1 (0.3)	2 (0.3)
Ethnicity, n (%)			
N	377	378	755
Hispanic or Latino	79 (21.0)	80 (21.2)	159 (21.1)
Not Hispanic or Latino	298 (79.0)	296 (78.3)	594 (78.7)
Not reported	0	1 (0.3)	1 (0.1)
Unknown	0	1 (0.3)	1 (0.1)
Baseline Weight (kg)			
N	377	378	755
Mean (SD)	87.4 (23.22)	89.1 (23.17)	88.3 (23.20)
Median	84.0	85.7	85.3
Range	(46;161)	(38;157)	(38;161)
Baseline BMI (kg/m²)			
N	377	378	755
Category, n (%)			
<30	182 (48.3)	173 (45.8)	355 (47.0)
≥30	195 (51.7)	205 (54.2)	400 (53.0)
Mean (SD)	31.5 (6.93)	31.7 (6.89)	31.6 (6.91)
Median	30.2	30.6	30.4
Range	(19;55)	(16;64)	(16;64)

Key BMI=body mass index, CANA=canagliflozin; N=total number of subjects, n=total number of subjects in subgroup, SD=standard deviation; Sita=sitagliptin

7.1.1.2.12. Results for the primary efficacy outcome

Canagliflozin 300 mg was superior to sitagliptin 100 mg (Table 7). The mean (SD) change from baseline in HbA1c was -1.0 (0.940) % for canagliflozin and -0.63 (1.022) % for sitagliptin. The LS mean (95% CI) difference (canagliflozin-sitagliptin) was -0.37 (-0.500 to -0.250) %. Effect was not demonstrated in the African American subgroup.

Table 7. HbA1c: Change From Baseline to Week 52 – LOCF (Study DIA3015)

	CANA 300 mg (N=377)	Sita 100 mg (N=378)
HbA_{1c} (%)		
Value at baseline		
N	374	365
Mean (SD)	8.12 (0.910)	8.13 (0.916)
Value at Week 52 LOCF		
N	374	365
Mean (SD)	7.12 (0.875)	7.50 (1.083)
Change from baseline		
N	374	365
Mean (SD)	-1.00 (0.940)	-0.63 (1.022)
LS mean (SE)	-1.03 (0.048)	-0.66 (0.049)
Diff. of LS means (SE)(minus Sita 100 mg)	-0.37 (0.064)	
95% CI [a]	(-0.500;-0.250)	

[a] Treatment comparison: CI is based on the ANCOVA model with treatment, glycemic control (whether HbA_{1c} ≥9%), FS-MMTT, and baseline HbA_{1c} in the model.

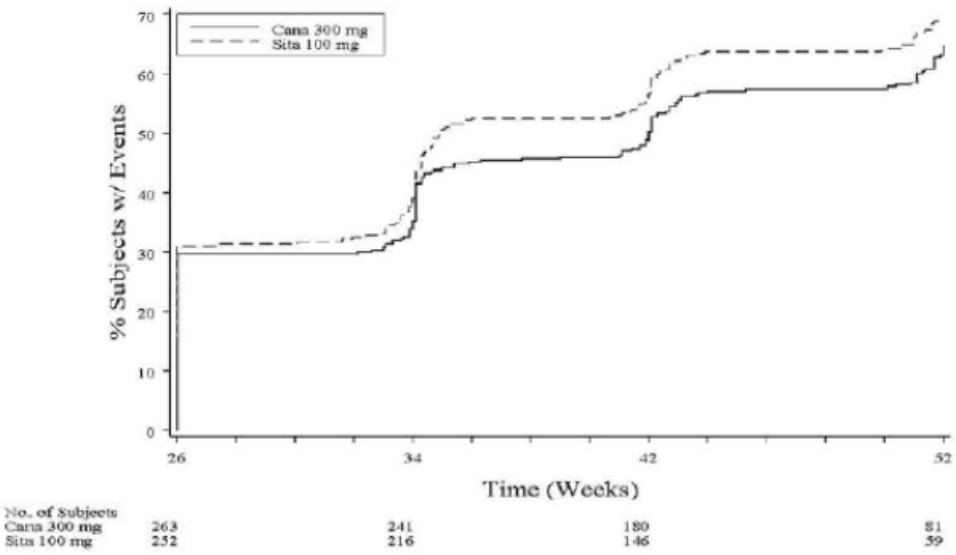
KEY: ANCOVA=analysis of covariance, CANA=canagliflozin, CI=confidence interval; Diff=difference, FS-MMTT=frequently-sampled mixed-meal tolerance test, HbA1c=glycosylated hemoglobin, LOCF=last observation carried forward, LS=least-squares, , N=total number of subjects; SD=standard deviation; SE=standard error, Sita=sitagliptin

7.1.1.2.13. Results for other efficacy outcomes

- The proportion of subjects with HbA1c <7.0% at Week 52 was 178 (47.6%) subjects for canagliflozin and 129 (35.3%) for sitagliptin; OR (95% CI) 1.80 (1.30 to 2.48).
- The proportion of subjects with HbA1c <6.5% at Week 52 was 84 (22.5%) subjects for canagliflozin and 69 (18.9%) for sitagliptin; OR (95% CI) 1.27 (0.87 to 1.86).
- The mean (SD) change from baseline in FPG was -1.72 (2.452) mmol/L for canagliflozin 300 mg and -0.19 (2.881) mmol/L sitagliptin. The LS mean (95% CI) difference (canagliflozin-sitaliptin) was -1.34 (-1.658 to -1.012) mmol/L.
- Glycaemic withdrawal criteria were met for 40 (10.6%) subjects in the canagliflozin group and 85 (22.5%) in the sitagliptin.
- The mean (SD) % change from baseline in body weight was -2.6 (3.7) % for canagliflozin and -0.2 (3.6) % for sitagliptin. The LS mean (95% CI) difference (canagliflozin-sitagliptin) was -2.8 (-3.3 to -2.2) %.
- The mean (SD) change from baseline in BMI was -0.84 (1.263) kg/m^2 for canagliflozin and 0.03 (1.170) kg/m^2 for sitagliptin. The LS mean (95% CI) difference (canagliflozin-sitagliptin) was -0.88 (-1.049 to -0.704) kg/m^2.
- The mean (SD) change from baseline in waist circumference was -1.95 (4.856) cm for canagliflozin and -0.16 (4.894) cm for sitagliptin. The LS mean (95% CI) difference (canagliflozin- sitagliptin) was -1.87 (-2.568 to -1.178) cm.
- SBP decreased in the canagliflozin group relative to sitagliptin: mean (SD) change from baseline -5.67 (12.694) mmHg for canagliflozin and 0.70 (13.900) mmHg for sitagliptin.

- DBP decreased in the canagliflozin group relative to sitagliptin: mean (SD) change from baseline -3.28 (8.104) mmHg for canagliflozin and -0.32 (8.358) mmHg for sitagliptin.
- Serum HDL-C increased in the canagliflozin group relative to sitagliptin: mean (SD) % change from baseline 8.2 (16.9) % for canagliflozin and 1.3 (17.2) % for sitagliptin.
- Serum cholesterol increased in the canagliflozin group relative to sitagliptin: mean (SD) % change from baseline 6.2 (21.8) % for canagliflozin and 2.6 (19.1) % for sitagliptin.
- Serum LDL-C increased in the canagliflozin group relative to sitagliptin: mean (SD) % change from baseline 10.2 (36.1) % for canagliflozin and 5.5 (33.8) % for sitagliptin.
- There was no significant difference between the groups in the change in triglycerides or LDL-C/HDL-C ratio.
- The mean (SD) change from baseline in HOMA2-%B was 22.77 (40.872) for canagliflozin and 8.50 (51.232) for sitagliptin. There was no significant difference between the groups in serum proinsulin/insulin ratio. Proinsulin/ C-peptide ratio decreased in the canagliflozin group relative to sitagliptin: LS mean difference (95% CI) (canagliflozin-sitagliptin) -4.3 (-7.66 to -0.99) pmol/nmol.
- In initial responders, time to relapse was greater in the canagliflozin group (Figure 1).

Figure 1. Time to Develop an Increase in HbA1c of at Least 0.3% from Week 26 through Week 52 in Subjects With a Decrease from Baseline in HbA1c of At Least 0.4% at Week 26 (mITT) (Study DIA3015)



In the FS-MMTT group glucose AUC and 2 hour postprandial glucose decreased to a greater extent in the canagliflozin group relative to sitagliptin. LS mean difference (95% CI) (canagliflozin-sitagliptin) -4.42 (-6.497 to -2.341) mmol/L•h and -1.41 (-2.176;-0.643) mmol/L respectively.

7.1.2. Efficacy as add-on therapy in moderate renal failure

7.1.2.1. Study DIA3004

7.1.2.1.1. Study design, objectives, locations and dates

Study DIA3004 was a multicentre, randomised, double-blind, placebo-controlled, parallel-group, three-arm study to evaluate the efficacy, safety, and tolerability of the addition of canagliflozin (100 mg daily and 300 mg daily) compared with placebo in subjects with T2DM

who were inadequately controlled on their current diabetes treatment regimen (Table 8). The study was conducted at 89 centres in 19 countries, including three centres in Australia, from March 2010 to December 2011. The report covers the first 26 weeks of a planned total duration of 52 weeks.

Table 8. Summary of Study DIA3004

Study -investigator -coordinating centre centre(s) -report n°	Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Study DIA3004 (Module 5, Section 5.3.5.1) 89 centres in 19 countries, including 3 centres in Australia March 2010 to December 2011	Multicentre, randomised, double-blind, placebo-controlled, parallel-group, three-arm study to evaluate the efficacy, safety, and tolerability of the addition of canagliflozin (100 mg daily and 300 mg daily) compared with placebo in subjects with T2DM who were inadequately controlled on their current diabetes treatment regimen	910 subjects screened, 272 randomised: 90 to 100 mg, 91 to 300 mg and 91 to placebo. There were 15 (16.7%) subjects in the 100 mg group, seven (7.7%) in the 300 mg and 13 (14.3%) in the placebo that discontinued. 163 (60.6%) males, 106 (39.4%) females, age range 39 to 96 years.	Males or females with T2DM, ≥25 years of age HbA1c ≥7.0% to ≤10.5% Moderate renal impairment, as defined by eGFR values ≥28 and ≤55 mL/min/1.73m^2 at the prescreening or screening visit, and ≥30 and <50 mL/min/1.73m2 at the Week -2 visit, with generally stable renal function, as demonstrated by ≤25% decline in eGFR at Week-2 relative to the (pre)screening visit value	26 Weeks (eventual duration 52 weeks)	Canagliflozin 100 mg Canagliflozin 300 mg Oral administration once daily, before the first meal of the day Block randomised using IVRS/IWRS in 1:1:1 ratio,	Placebo All subjects continued on baseline AHA agents	The primary efficacy outcome measure was change in HbA1c. The secondary efficacy measures included: FPG Body weight SBP Fasting triglycerides Fasting HDL-C Safety outcome variables were AEs, laboratory tests, hypoglycaemic events, ECGs, vital signs, physical examinations, SMBG; and renal safety measures	The mean (SD) change from baseline in HbA1c was -0.37 (0.873) % for canagliflozin 100 mg, -0.52 (0.813) % for 300 mg and -0.13 (0.880) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.30 (-0.529 to -0.066) % (p = 0.012) for 100 mg and -0.40 (-0.635 to -0.174) % for 300 mg (p <0.001). The proportion of subjects with HbA1c <7.0% at Week 26 greater in the 300 mg group compared to placebo (p = 0.017): 24 (27.3%) subjects for 100 mg, 29 (32.6%) for 300 mg and 15 (17.2%) for placebo. The proportion of subjects with HbA1c <6.5% at Week 26 was seven (8.0%) subjects for 100 mg, eight (9.0%) for 300 mg and three (3.4%) for placebo. The mean (SD) change from baseline in FPG was -1.16 (2.661) mmol/L for canagliflozin 100 mg, -0.64 (2.951) mmol/L for 300 mg and 0.03 (3.234) mmol/L for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.85 (-1.579 to -0.128) mmol/L (0 = 0.021) for 100 mg and -0.67 (-1.405 to 0.056) mmol/L (p = 0.070) for 300 mg.	TEAEs were reported in 70 (77.8%) subjects in the canagliflozin 100 mg group, 66 (74.2%) in the 300 mg group and 66 (73.3%) in the placebo. There were two deaths: one in the canagliflozin 100 mg group and one in the placebo. SAEs were reported in ten (11.2%) subjects in the canagliflozin 100 mg group, nine (10.0%) in the 300 mg group and twelve (13.3%) in the placebo. DAEs were reported in three (3.3%) subjects in the canagliflozin 100 mg group, two (2.2%) in the 300 mg group and five (5.6%) in the placebo.

7.1.2.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Males or females with T2DM, ≥25 years of age
- HbA1c ≥7.0% to ≤10.5%
- Moderate renal impairment, as defined by eGFR values ≥28 and ≤55 mL/min/1.73m^2 at the pre-screening or screening visit, and ≥30 and <50 mL/min/1.73m^2 at the Week -2 visit, with generally stable renal function, as demonstrated by ≤25% decline in eGFR at Week-2 relative to the (pre)screening visit value

The exclusion criteria were similar to those in Section 7.1.1.1.2 but included:

- Ongoing eating disorder or significant weight loss or weight gain within 12 weeks before the screening visit, defined as an increase or decrease of 5% in body weight
- Renal disease that required treatment with immunosuppressive therapy or a history of dialysis or renal transplant
- Presence of nephrotic syndrome, or inflammatory renal disease
- Subject is likely to require dialysis or transplantation during participation in the study
- Haemoglobin concentration <100 g/L

7.1.2.1.3. Study treatments

The study treatments were:

1: Canagliflozin 100 mg

2: Canagliflozin 300 mg

3: Placebo

Treatment duration was for 26 weeks. All subjects continued on their AHA a stable dose during the study. The treatments were administered orally, once daily, before the first meal of the day.

7.1.2.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure was change in HbA1c. The secondary efficacy measures included:

- FPG
- Body weight
- SBP
- Fasting triglycerides
- Fasting HDL-C
- Additional efficacy outcome measures were:
- DBP
- Other fasting lipid levels (including LDL-C , total cholesterol, LDL-C/HDL-C ratio
- Use of rescue medication
- Time to initiation of rescue medication

The safety outcome variables were AEs, laboratory tests, hypoglycaemic events, ECGs, vital signs, physical examinations, SMBG and renal safety evaluations.

7.1.2.1.5. Randomisation and blinding methods

Randomisation similar to Section 7.1.1.1.5, with stratification by presence/absence of ASCVD.

7.1.2.1.6. Analysis populations

As per Section 7.1.1.1.6.

7.1.2.1.7. Sample size

The study was designed to test for superiority for the primary efficacy outcome measure at Week 26. Assuming a group difference of 0.5% between the canagliflozin and placebo group, and a common SD of 0.85% with respect to change in HbA1c, and using a 2-sample, 2-sided t-test with a type I error rate of 0.05, it was estimated that 61 randomised subjects per group would be required to achieve at least 90% power. The Sponsor increased the sample size to 80 subjects per group to obtain additional safety data.

7.1.2.1.8. Statistical methods

As per Section 7.1.1.1.8.

7.1.2.1.9. Participant flow

There were 910 subjects screened and 272 were randomised: 90 to 100 mg, 91 to 300 mg and 91 to placebo). Two subjects in the 300 mg group and one in the placebo were not dosed and were excluded from the analysis sets. There were 15 (16.7%) subjects in the 100 mg group, seven (7.7%) in the 300 mg and 13 (14.3%) in the placebo that discontinued.

7.1.2.1.10. Major protocol violations/deviations

The PP dataset included 68 (75.6%) subjects in the 100 mg group, 78 (85.7%) in the 300 mg and 75 (82.4%) in the placebo.

7.1.2.1.11. Baseline data

There were 163 (60.6%) males, 106 (39.4%) females and the age range was 39 to 96 years. There were 186 (69.1%) subjects aged ≥65 years. The treatment groups were similar in demographic characteristics and anthropometric characteristics (Table 9). The treatment groups were similar in baseline diabetes characteristics. The treatment groups were similar in AHA treatment at baseline, with around 74% treated with insulin, 30% treated with SU and only four subjects with biguanides.

Table 9. Baseline Demographic and Anthropometric Characteristics (mITT) (Study DIA3004)

	Placebo (N=90)	CANA 100 mg (N=90)	CANA 300 mg (N=89)	CANA Total (N=179)	Total (N=269)
Sex, n (%)					
N	90	90	89	179	269
Male	57 (63.3)	58 (64.4)	48 (53.9)	106 (59.2)	163 (60.6)
Female	33 (36.7)	32 (35.6)	41 (46.1)	73 (40.8)	106 (39.4)
Age (Years)					
N	90	90	89	179	269
Category, n (%)					
35 - < 65	27 (30.0)	24 (26.7)	32 (36.0)	56 (31.3)	83 (30.9)
≥ 65	63 (70.0)	66 (73.3)	57 (64.0)	123 (68.7)	186 (69.1)
Mean (SD)	68.2 (8.40)	69.5 (8.20)	67.9 (8.24)	68.7 (8.23)	68.5 (8.28)
Median	69.0	70.0	66.0	68.0	69.0
Range	(45;96)	(39;85)	(46;90)	(39;90)	(39;96)
Race, n (%)					
N	90	90	89	179	269
White	78 (86.7)	71 (78.9)	66 (74.2)	137 (76.5)	215 (79.9)
Black or African American	0	3 (3.3)	2 (2.2)	5 (2.8)	5 (1.9)
Asian	7 (7.8)	9 (10.0)	11 (12.4)	20 (11.2)	27 (10.0)
American Indian or Alaska Native	0	0	1 (1.1)	1 (0.6)	1 (0.4)
Native Hawaiian or Other Pacific Islander	1 (1.1)	0	1 (1.1)	1 (0.6)	2 (0.7)
Other	3 (3.3)	7 (7.8)	8 (9.0)	15 (8.4)	18 (6.7)
Unknown	1 (1.1)	0	0	0	1 (0.4)
Ethnicity, n (%)					
N	90	90	89	179	269
Hispanic or Latino	3 (3.3)	7 (7.8)	11 (12.4)	18 (10.1)	21 (7.8)
Not Hispanic or Latino	84 (93.3)	80 (88.9)	76 (85.4)	156 (87.2)	240 (89.2)
Not Reported	3 (3.3)	0	0	0	3 (1.1)
Unknown	0	3 (3.3)	2 (2.2)	5 (2.8)	5 (1.9)
Baseline Weight (kg)					
N	90	90	89	179	269
Mean (SD)	92.8 (17.42)	90.5 (18.41)	90.2 (18.09)	90.3 (18.20)	91.2 (17.95)
Median	91.8	89.3	88.8	89.0	89.9
Range	(54;135)	(43;144)	(62;130)	(43;144)	(43;144)
Baseline BMI (kg/m²)					
N	90	90	89	179	269
Category, n (%)					
< 30	29 (32.2)	26 (28.9)	32 (36.0)	58 (32.4)	87 (32.3)
≥ 30	61 (67.8)	64 (71.1)	57 (64.0)	121 (67.6)	182 (67.7)
Mean (SD)	33.1 (6.45)	32.4 (5.54)	33.4 (6.46)	32.9 (6.02)	33.0 (6.15)
Median	31.9	32.5	32.9	32.8	32.2
Range	(18,52)	(19;48)	(20;55)	(19;55)	(18;55)

7.1.2.1.12. Results for the primary efficacy outcome

Canagliflozin 300 mg and 100 mg were both superior to placebo (Table 10). The mean (SD) change from baseline in HbA1c was -0.37 (0.873) % for canagliflozin 100 mg, -0.52 (0.813) % for 300 mg and -0.13 (0.880) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.30 (-0.529 to -0.066) % (p = 0.012) for 100 mg and -0.40 (-0.635 to -0.174) % for 300 mg (p <0.001). There was no subgroup analysis.

Table 10. Change from Baseline to Week 26 for Primary and Secondary Efficacy Endpoints (LOCF), mITT dataset (Study DIA3004)

	CANA 100 mg (Placebo-Subtracted)		CANA 300 mg (Placebo-Subtracted)	
Endpoints	Mean (95% CI)	p-value	Mean (95% CI)	p-value
HbA_{1c} Change (%)	-0.30 (-0.529;-0.066)	0.012	-0.40 (-0.635; -0.174)	<0.001
FPG Change (mmol/L)	-0.85 (-1.579;-0.128)	0.021	-0.67 (-1.405; 0.056)	0.070[a]
Achieving 7% HbA_{1c} target[b]	10.03 (-2.20; 22.30)	0.227	15.34 (2.79; 27.91)	0.017
Body Weight Percent Change(%)[c]	-1.6 (-2.3;-0.8)	<0.001	-1.8 (-2.6; -1.0)	<0.001
Systolic BP Change (mmHg)[c]	-5.73 (-9.545;-1.912)	0.003	-6.12 (-9.959; -2.280)	0.002
HDL-C Percent Change (%)[c]	2.5 (-1.9;7.0)	0.264	1.5 (-3.0; 5.9)	0.513
Triglycerides Percent Change (%)[c]	-1.7 (-13.8; 10.5)	0.785	3.9 (-8.1; 15.9)	0.521

[a] Canagliflozin 300 mg did not achieve statistical significance with respect to the change from baseline in FPG, no further statistical testing was conducted.

[b] For the proportion of patients achieving 7% HbA_{1c} target, p-value is based on logistic regression with terms for treatment and stratification factors and adjusting for the baseline Hb_{A1c} and baseline eGFR as covariates.

[c] Secondary endpoints (body weight, systolic BP, HDL-C, and triglycerides) were not pre-specified hypotheses

Key: AHA= antihyperglycemic agent, ANCOVA=analysis of covariance, BP=blood pressure, CI=confidence interval, CV=cardiovascular, eGFR=estimated glomerular filtration rate, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, FPG=fasting plasma glucose, LOCF=last observation carried forward

Note: For continuous endpoints, the least squares mean is presented with associated p-values and CI based on ANCOVA models with terms for treatment and stratification factors (AHA washout, Atherosclerotic CV Disease History) and adjusting for the corresponding baseline value and baseline eGFR value (only for HbA_{1c}, FPG, and body weight) as covariates.

7.1.2.1.13. Results for other efficacy outcomes

The efficacy endpoints are summarised in Table 10.

- The proportion of subjects with HbA1c <7.0% at Week 26 greater in the 300 mg group compared to placebo (p = 0.017): 24 (27.3%) subjects for 100 mg, 29 (32.6%) for 300 mg and 15 (17.2%) for placebo.
- The proportion of subjects with HbA1c <6.5% at Week 26 was seven (8.0%) subjects for 100 mg, eight (9.0%) for 300 mg and three (3.4%) for placebo.
- The mean (SD) change from baseline in FPG was -1.16 (2.661) mmol/L for canagliflozin 100 mg, -0.64 (2.951) mmol/L for 300 mg and 0.03 (3.234) mmol/L for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.85 (-1.579 to -0.128) mmol/L (p = 0.021) for 100 mg and -0.67 (-1.405 to 0.056) mmol/L (p = 0.070) for 300 mg.
- Glycaemic rescue was required for four (4.4%) subjects in the canagliflozin 100 mg group, three (3.4%) in the 300 mg and 13 (14.4%) in the placebo. The HR (95% CI) (canagliflozin compared to placebo) was 0.30 (0.10 to 0.93) for 100 mg and 0.22 (0.06 to 0.77) for 300 mg.
- The mean (SD) % change from baseline in body weight was -1.3 (2.8) % for canagliflozin 100 mg, -1.5 (2.9) % for 300 mg and 0.2 (2.3) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -1.6 (-2.3 to -0.8) % for 100 mg and -1.8 (-2.6 to -1.0) % for 300 mg.
- The mean (SD) change from baseline in BMI was -0.42 (0.896) kg/m^2 for canagliflozin 100 mg, -0.50 (1.020) kg/m^2 for 300 mg and 0.05 (0.801) kg/m^2 for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.49 (-0.752 to -0.226) kg/m^2 for 100 mg and -0.58 (-0.845 to -0.317) kg/m^2 for 300 mg.
- There was a significant decrease in SBP in the canagliflozin groups: mean (SD) change from baseline -5.98 (14.766) mmHg for canagliflozin 100 mg, -6.77 (13.041) mmHg for 300 mg and 1.49 (14.954) mmHg for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -5.73 (-9.545 to -1.912) mmHg for 100 mg and -6.12 (-9.959 to -2.280) mmHg for 300 mg.

- There was no significant difference between the groups in the change in DBP: mean (SD) change from baseline -1.94 (8.507) mmHg for canagliflozin 100 mg, -3.76 (7.764) mmHg for 300 mg and -0.90 (8.449) mmHg for placebo.
- There was no significant difference between the groups in the change in HDL-C: mean (SD) change from baseline 3.7 (15.4) mmol/L for canagliflozin 100 mg, 2.1 (16.7) mmol/L for 300 mg and 1.4 (11.6) mmol/L for placebo.
- There was no significant difference between the groups in the change in triglycerides, cholesterol, LDL-C or LDL-C/HDL-C ratio.

7.1.3. Efficacy as monotherapy

7.1.3.1. Study DIA3005

7.1.3.1.1. Study design, objectives, locations and dates

Study DIA3005 was a multicentre, randomised, double-blind, placebo-controlled, three-arm, parallel-group study that evaluated the efficacy, safety and tolerability of canagliflozin monotherapy in subjects with T2DM who were inadequately controlled with diet and exercise (Table 11). The study was conducted at 90 sites in 17 countries from February 2010 to August 2011.

Table 11. Summary of Study DIA3005

Study -investigator -coordinating centre centre(s) -report n°	Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Study DIA3005 (Module 5, Section 5.3.5.1) 90 sites in 17 countries February 2010 to August 2011	Multicentre, randomised, double-blind, placebo-controlled, three-arm, parallel-group study that evaluated the efficacy, safety and tolerability of canagliflozin monotherapy in subjects with T2DM who were inadequately controlled with diet and exercise.	1,667 screened, 587 randomised: 196 to 100 mg, 197 to 300 mg and 194 to placebo. 23 (11.7%) in the 100 mg group, 22 (11.2%) 300 mg and 32 (16.5%) placebo discontinued. 326 (55.8%) females, 258 (44.2%) males, age range 24 to 79 years. In the high glycaemic substudy there were 91 subjects: 49 (53.8%) females, 42 (46.2%) males, age range of 27 to 78 years	Males or females ≥18 and ≤80 years of age with T2DM who met one of the two following criteria: Not on an AHA at screening (off for at least 12 weeks) with HbA1c ≥7.0% and ≤10.0%, OR on an oral AHA in monotherapy (except a PPARγ agonist) or on low-dose combination therapy with metformin (≤1,000 mg) and SU (at ≤50% of maximally effective doses) with HbA1c ≥6.5% and ≤9.5% at screening and had a Week -2 (after the 8-week diet and exercise and AHA washout period) HbA1c ≥7.0% and ≤10.0% and FPG <15 mmol/L. For the High Glycaemic Substudy subjects were required to have HbA1c >10% and ≤12% at screening or at Week -1 visit after the 8-week washout period and FPG ≤19.4 mmol/L	26 weeks (total planned duration 52 weeks)	Canagliflozin 100 mg Canagliflozin 300 mg Oral administration once daily, before the first meal of the day Block randomised using IVRS/IWRS in 1:1:1 ratio,	Placebo After 26 weeks, switched to Sitagliptin 100 mg daily No other AHA treatment	The primary efficacy outcome measure was change in HbA1c. The secondary efficacy measures included: FPG Postprandial glucose Body weight SBP Fasting triglycerides Fasting HDL-C Safety outcome variables were AEs, laboratory tests, hypoglycaemic events, ECGs, vital signs, physical examinations, SMBG, and renal safety measures	The mean (SD) change from baseline in HbA1c was -0.79 (0.906) % for canagliflozin 100 mg, -1.03 (0.863) % for 300 mg and 0.14 (1.057) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.91 (-1.088 to -0.729) % for 100 mg and -1.16 (-1.342 to -0.985) % for 300 mg. HbA1c <7.0% at Week 26 in 85 (44.5%) subjects for 100 mg, 121 (62.4%) for 300 mg and 39 (20.6%) for placebo (p <0.001). HbA1c <6.5% at Week 26 in 34 (17.8%) subjects for 100 mg, 55 (28.4%) for 300 mg and ten (5.3%) for placebo. Mean (SD) change from baseline in FPG was -1.59 (2.236) mmol/L for canagliflozin 100 mg, -2.02 (2.146) mmol/L for 300 mg and 0.57 (2.151) mmol/L for placebo (p <0.001).	TEAEs were reported in 118 (60.5%) subjects in the canagliflozin 100 mg group, 118 (59.9%) in the 300 mg and 94 (49.0%) in the placebo. There were two deaths: one in the canagliflozin 100 mg group and one in the placebo. SAEs were reported in eight (4.1%) subjects in the canagliflozin 100 mg group, two (1.0%) in the 300 mg and four (2.1%) in the placebo. DAEs were reported in six (3.1%) subjects in the canagliflozin 100 mg group, four (2.0%) in the 300 mg and two (1.0%) in the placebo.

7.1.3.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Males or females ≥18 and ≤80 years of age with T2DM who met one of the two following criteria:
- Not on an AHA at screening (off for at least 12 weeks) with HbA1c ≥7.0% and ≤10.0%, or
- On an oral AHA in monotherapy (except a PPARγ agonist) or on low-dose combination therapy with metformin (≤1,000 mg) and SU (at ≤50% of maximally or near-maximally effective doses) with HbA1c ≥6.5% and ≤9.5% at screening and had a Week -2 (after the 8-week diet and exercise and AHA washout period) HbA1c ≥7.0% and ≤10.0% and FPG <15 mmol/L
- For the High Glycaemic Substudy subjects were required to have HbA1c >10% and ≤12% at screening or at Week -1 visit after the 8-week washout period and a FPG value ≤19.4 mmol/L at the Week -1 visit

The exclusion criteria were as for Section 7.1.1.1.2 with the addition of:

- Fasting C-peptide <0.7 ng/mL in subjects for whom the investigator could not reasonably exclude T1DM based upon clinical evaluation (eg, young age at onset, new onset diabetes and/or negative family history of T2DM and/or lower range BMI)
- eGFR <50 mL/min/1.73 m^2

7.1.3.1.3. Study treatments

The study treatments were:

1: Canagliflozin 100 mg

2: Canagliflozin 300 mg

3: Placebo

Treatment duration was for 26 weeks (but the total planned study duration was for 52 weeks). After 26 weeks the placebo subjects were to be switched to sitagliptin 100 mg once daily. Other AHA agents were not permitted during the study. The treatments were administered orally, once daily, before the first meal of the day.

7.1.3.1.4. Efficacy variables and outcomes

As for Section 7.1.1.1.4 with the addition of the secondary efficacy outcome measure:

2-hour PPG after a standardized meal for the MMTT

7.1.3.1.5. Randomisation and blinding methods

As for Section 7.1.1.1.5.

7.1.3.1.6. Analysis populations

As or Section 7.1.1.1.6.

7.1.3.1.7. Sample size

As for Section 7.1.1.1.7.

7.1.3.1.8. Statistical methods

As for Section 7.1.1.1.8.

7.1.3.1.9. Participant flow

A total of 1,667 subjects were screened, and 587 subjects were randomised to the main study: 196 to 100 mg, 197 to 300 mg and 194 to placebo. There were 91 subjects randomised to the high glycaemic substudy. Two subjects in the placebo group and one in the canagliflozin 100 mg were not dosed and were excluded from the mITT dataset (and therefore the safety dataset). There were 23 (11.7%) subjects in the 100 mg group, 22 (11.2%) in the 300 mg and 32 (16.5%) in the placebo that discontinued.

7.1.3.1.10. Major protocol violations/deviations

The PP dataset included 166 (84.7%) subjects in the 100 mg group, 171 (86.8%) in the 300 mg and 121 (62.4%) in the placebo.

7.1.3.1.11. Baseline data

There were 326 (55.8%) females, 258 (44.2%) males and the age range was 24 to 79 years. There were 118 (20.2%) subjects aged ≥65 years. The treatment groups were similar in demographic and anthropometric characteristics (Table 12). The treatment groups were similar in baseline diabetes characteristics. There were 303 (51.9%) subjects that were not on AHA at screening.

Table 12. Baseline Demographic and anthropometric Characteristics (Main Study) (Study DIA3005)

	Placebo (N=192)	CANA 100 Mg (N=195)	CANA 300 Mg (N=197)	CANA Total (N=392)	Total (N=584)
Sex, n (%)					
N	192	195	197	392	584
Male	88 (45.8)	81 (41.5)	89 (45.2)	170 (43.4)	258 (44.2)
Female	104 (54.2)	114 (58.5)	108 (54.8)	222 (56.6)	326 (55.8)
Age (years)					
N	192	195	197	392	584
Category, n (%)					
<35	8 (4.2)	7 (3.6)	6 (3.0)	13 (3.3)	21 (3.6)
35 - <65	142 (74.0)	149 (76.4)	154 (78.2)	303 (77.3)	445 (76.2)
≥65	42 (21.9)	39 (20.0)	37 (18.8)	76 (19.4)	118 (20.2)
Mean (SD)	55.7 (10.88)	55.1 (10.83)	55.3 (10.17)	55.2 (10.49)	55.4 (10.61)
Median	57.0	55.0	56.0	56.0	56.0
Range	(24;78)	(26;78)	(25;79)	(25;79)	(24;79)
Race, n (%)					
N	192	195	197	392	584
White	134 (69.8)	124 (63.6)	137 (69.5)	261 (66.6)	395 (67.6)
Black or African American	9 (4.7)	18 (9.2)	14 (7.1)	32 (8.2)	41 (7.0)
Asian	29 (15.1)	27 (13.8)	29 (14.7)	56 (14.3)	85 (14.6)
American Indian or Alaska Native	2 (1.0)	1 (0.5)	2 (1.0)	3 (0.8)	5 (0.9)
Other	17 (8.9)	24 (12.3)	15 (7.6)	39 (9.9)	56 (9.6)
Unknown	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Not reported	1 (0.5)	0	0	0	1 (0.2)
Ethnicity, n (%)					
N	192	195	197	392	584
Hispanic or Latino	60 (31.3)	63 (32.3)	57 (28.9)	120 (30.6)	180 (30.8)
Not Hispanic or Latino	132 (68.8)	131 (67.2)	139 (70.6)	270 (68.9)	402 (68.8)
Unknown	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.3)
Baseline Weight (kg)					
N	192	195	197	392	584
Mean (SD)	87.6 (19.45)	85.8 (21.41)	86.9 (20.48)	86.4 (20.93)	86.8 (20.44)
Median	85.5	83.8	85.0	84.3	84.6
Range	(46;142)	(46;157)	(43;155)	(43;157)	(43;157)
Baseline BMI (kg/m²)					
N	192	195	197	392	584
Category, n (%)					
<30	87 (45.3)	92 (47.2)	87 (44.2)	179 (45.7)	266 (45.5)
≥30	105 (54.7)	103 (52.8)	110 (55.8)	213 (54.3)	318 (54.5)
Mean (SD)	31.8 (6.16)	31.3 (6.55)	31.7 (6.02)	31.5 (6.29)	31.6 (6.24)
Median	31.1	30.6	31.4	30.9	31.0
Range	(18;53)	(20;61)	(19;49)	(19;61)	(18;61)

In the high glycaemic substudy there were 91 subjects, including 49 (53.8%) females, 42 (46.2%) males, with an age range of 27 to 78 years. This was a separate group to the main study. Of these subjects, 70 (76.9%) had not been on AHA at screening.

7.1.3.1.12. Results for the primary efficacy outcome

Canagliflozin 300 mg and 100 mg were both superior to placebo (Table 13). The mean (SD) change from baseline in HbA1c was -0.79 (0.906) % for canagliflozin 100 mg, -1.03 (0.863) % for 300 mg and 0.14 (1.057) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.91 (-1.088 to -0.729) % for 100 mg and -1.16 (-1.342 to -0.985) % for 300 mg. There was no subgroup effect on efficacy.

Table 13. HbA1c: Change From Baseline to Week 26 (Main Study) – LOCF (Study DIA3005)

	Placebo (N=192)	CANA 100 mg (N=195)	CANA 300 mg (N=197)
Blood HbA_{1c} (%)			
Value at baseline			
N	189	191	194
Mean (SD)	7.97 (0.955)	8.06 (0.959)	8.01 (0.988)
Value at Week 26 LOCF			
N	189	191	194
Mean (SD)	8.11 (1.391)	7.27 (1.030)	6.98 (0.980)
Change from baseline			
N	189	191	194
Mean (SD)	0.14 (1.057)	-0.79 (0.906)	-1.03 (0.863)
LS Mean (SE)	0.14 (0.065)	-0.77 (0.065)	-1.03 (0.064)
P value(minus placebo) [a]		<0.001	<0.001
Diff. of LS means (SE)		-0.91 (0.091)	-1.16 (0.091)
95% CI [a]		(-1.088;-0.729)	(-1.342;-0.985)

[a] Pairwise comparison: p values and CIs were based on an ANCOVA model with treatment, AHA washout, and FS-MMTT as factors and baseline HbA_{1c} as covariate.

Key: AHA=antihyperglycemic agent, ANCOVA=analysis of covariance, CANA=canagliflozin, CI=confidence interval; Diff=difference, FS-MMTT=frequently sampled mixed-meal tolerance test, HbA_{1c}=glycosylated hemoglobin A1c, LOCF=last observation carried forward, mITT=modified intent-to-treat, N=total number of subjects; SD=standard deviation; SE=standard error

7.1.3.1.13. Results for other efficacy outcomes

- The proportion of subjects with HbA1c <7.0% at Week 26 was 85 (44.5%) subjects for 100 mg, 121 (62.4%) for 300 mg and 39 (20.6%) for placebo (p <0.001).
- The proportion of subjects with HbA1c <6.5% at Week 26 was 34 (17.8%) subjects for 100 mg, 55 (28.4%) for 300 mg and ten (5.3%) for placebo.
- The mean (SD) change from baseline in FPG was -1.59 (2.236) mmol/L for canagliflozin 100 mg, -2.02 (2.146) mmol/L for 300 mg and 0.57 (2.151) mmol/L for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -1.97 (-2.343 to -1.597) mmol/L for 100 mg and -2.41 (-2.776 to -2.034) mmol/L for 300 mg (p <0.001).
- Postprandial glucose was lower in the canagliflozin groups at 1 hour and 2 hours. Glucose AUC in the MMTT was also lower.
- Glycaemic rescue was required for five (2.6%) subjects in the canagliflozin 100 mg group, four (2.0%) in the 300 mg and 44 (22.9%) in the placebo. The HR (95% CI) (canagliflozin compared to placebo) was 0.09 (0.04 to 0.23) for 100 mg and 0.07 (0.03 to 0.20) for 300 mg.
- The mean (SD) % change from baseline in body weight was -2.8 (3.4) % for canagliflozin 100 mg, -3.9 (3.3) % for 300 mg and -0.6 (3.2) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -2.2 (-2.9 to -1.6) % for 100 mg and -3.3 (-4.0 to -2.6) % for 300 mg.
- The mean (SD) change from baseline in BMI was -0.88 (1.084) kg/m^2 for canagliflozin 100 mg, -1.26 (1.206) kg/m^2 for 300 mg and -0.20 (1.006) kg/m^2 for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.71 (-0.923 to -0.490) kg/m^2 for 100 mg and -1.07 (-1.285 to -0.854) kg/m^2 for 300 mg.
- The mean (SD) change from baseline in waist circumference was -2.01 (4.740) cm for canagliflozin 100 mg, -2.75 (4.672) cm for 300 mg and -1.00 (3.787) cm for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -1.13 (-2.029 to -0.236) cm for 100 mg and -1.79 (-2.690 to -0.895) cm for 300 mg.
- There was a significant decrease in SBP in the canagliflozin groups relative to placebo: mean (SD) change from baseline -3.14 (10.524) mmHg for canagliflozin 100 mg, -5.52 (12.480) mmHg for 300 mg and 0.19 (12.072) mmHg for placebo (p <0.001).

- There was a significant decrease in DBP in the canagliflozin groups relative to placebo: mean (SD) change from baseline -1.57 (6.986) mmHg for canagliflozin 100 mg, -2.57 (7.952) mmHg for 300 mg and 0.09 (7.396) mmHg for placebo.
- HDL-C increased in the canagliflozin groups relative to placebo: mean (SD) change from baseline 10.8 (21.7) mmol/L for canagliflozin 100 mg, 10.6 (18.3) mmol/L for 300 mg and 5.3 (17.2) mmol/L for placebo ($p < 0.001$).
- Triglycerides decreased in the canagliflozin 300 mg group relative to placebo: mean (SD) change from baseline 3.5 (51.2) mmol/L for canagliflozin 100 mg, -1.3 (45.1) mmol/L for 300 mg and 6.3 (43.1) mmol/L for placebo ($p = 0.035$).
- There was no consistent significant difference between the groups in the change in cholesterol, LDL-C or LDL-C/HDL-C ratio or FFA.
- The mean (SD) change from baseline in HOMA2-%B was 11.24 (25.727) for canagliflozin 100 mg, 20.47 (22.201) for 300 mg and -3.28 (26.866) for placebo.
- C-peptide AUC to Glucose AUC increased in the canagliflozin groups relative to placebo: mean (SD) change from baseline 26.75 (59.185) for canagliflozin 100 mg, 35.33 (48.538) for 300 mg and -20.0 (53.660).
- β-cell glucose sensitivity and insulin sensitivity both increased in the canagliflozin groups relative to placebo. There was no significant change in insulogenic index, between the treatment groups.
- Renal glucose excretion increased and renal glucose threshold decreased in the canagliflozin groups.
- The comparison of the canagliflozin groups in the high glycaemic substudy indicates little difference between the doses.

7.1.4. Efficacy in Combination with MET

7.1.4.1. Study DIA3006

7.1.4.1.1. Study design, objectives, locations and dates

Study DIA3006 multicentre, randomised, double-blind, four-arm, parallel-group, global multicentre study, conducted to evaluate the efficacy, safety, and tolerability of canagliflozin in subjects with T2DM who were inadequately controlled with metformin immediate release (IR) monotherapy (Table 14). The Study was conducted at 169 centres in 22 countries from April 2010 to October 2011. The study involved a stabilisation phase on MET prior to randomisation.

Table 14. Summary of Study DIA3006

Study -investigator -coordinating centre centre(s) -report n°	Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Study DIA3006 (Module 5, Section 5.3.5.1) 169 centres in 22 countries April 2010 to October 2011	Multicentre, randomised, double-blind, four-arm, parallel-group, global multicentre study, conducted to evaluate the efficacy, safety, and tolerability of canagliflozin in subjects with T2DM who were inadequately controlled with metformin immediate release (IR) monotherapy	2,883 screened, 1,284 randomised: 368 to 100 mg, 367 to 300 mg, 366 to sitagliptin and 183 to placebo. 46 (12.5%) subjects in 100 mg group, 44 (12.0%) in 300 mg, 47 (12.8%) in sitagliptin and 28 (15.3%) in placebo discontinued. 679 (52.9%) females, 605 (47.1%) males, age range 21 to 79 years. 206 (16.0%) aged ≥65 years	Male or female ≥18 and ≤80 years of age with T2DM who met one of the following four criteria: On MET IR monotherapy at ≥2000 mg/day or ≥1500 mg/day, if unable to tolerate a higher dose for at least 8 weeks before screening and had an HbA1c of ≥7.0% and ≤10.5% at screening, or able to transition to this from other MET regimens FPG <15 mmol/L Center fasting fingerstick glucose of ≥6.1 and <15 mmol/L	26 weeks (total duration 52 weeks)	Canagliflozin 100 mg Canagliflozin 300 mg Oral administration once daily, before the first meal of the day Block randomised using IVRS/IWRS in 1:1:1 ratio,	Placebo Sitagliptin 100 mg daily After 26 weeks, placebo subjects switched to Sitagliptin 100 mg daily for the reaminder of the study Stable dose of MET throughout the treatment phase. No other AHA treatment	The primary efficacy outcome measure was change in HbA1c. The secondary efficacy measures included: FPG Postprandial glucose Body weight SBP Fasting triglycerides Fasting HDL-C Safety outcome variables were AEs, laboratory tests, hypoglycaemic events, ECGs, vital signs, physical examinations, SMBG; and renal safety	The mean (SD) change from baseline in HbA1c was -0.81 (0.650) % for canagliflozin 100 mg, -0.98 (0.885) % for 300 mg, -0.84 (0.835) for sitagliptin and 0.20 (0.895) % for placebo. The LS mean (95% CI) difference (active-placebo) was -0.62 (-0.758 to -0.481) % for 100 mg and -0.77 (-0.914 to -0.636) % for 300 mg ($p < 0.001$) and -0.66 (-0.795 to -0.516) % for sitagliptin. The proportion of subjects with HbA1c <7.0% at Week 26 was 166 (45.5%) subjects for 100 mg, 208 (57.8%) for 300 mg, 193 (54.5%) for sitagliptin and 54 (29.8%) for placebo ($p < 0.001$ for canagliflozin placebo comparison). The proportion of subjects with HbA1c <6.5% at Week 26 was 75 (20.5%) subjects for 100 mg, 96 (26.7%) for 300 mg, 96 (27.1%) for sitagliptin and 21 (11.6%) for placebo. The mean (SD) change from baseline in FPG was -1.43 (2.054) mmol/L for canagliflozin 100 mg, -2.13 (2.190) mmol/L for 300 mg, -1.04 (2.227) for sitagliptin and 0.35 (2.622) mmol/L for placebo (Table 7.4.1.1.6).	TEAEs were reported in 225 (61.1%) subjects in the canagliflozin 100 mg group, 204 (55.6%) in the 300 mg, 199 (54.4%) in the sitagliptin and 104 (56.8%) in the placebo. There was one death in the canagliflozin 300 mg group and one in the placebo. SAEs were reported in twelve (3.3%) subjects in the canagliflozin 100 mg group, ten (2.7%) in the 300 mg, eight (2.2%) in the sitagliptin and four (2.2%) in the placebo. DAEs were reported in 18 (4.9%) subjects in the canagliflozin 100 mg group, twelve (3.3%) in the 300 mg, seven (1.9%) in the sitagliptin and seven (3.8%) in the placebo.

7.1.4.1.2. Inclusion and exclusion criteria

- Male or female ≥18 and ≤80 years of age with T2DM who met one of the following four criteria:
  - On MET IR monotherapy at the stable protocol-specified dose (≥2000 mg/day or ≥1500 mg/day, if unable to tolerate a higher dose) for at least 8 weeks before screening and had an HbA1c of ≥7.0% and ≤10.5% at screening, or
  - On metformin XR monotherapy at the protocol-specified dose with an HbA1c of ≥7.0% and ≤10.5% at screening and had a Week -2 visit HbA1c of ≥7.0% and ≤10.5%, after at least 8 weeks on the stable protocol-specified dose of metformin IR, or
  - On metformin monotherapy (IR or XR) at a dose <2,000 mg/day with an HbA1c of ≥7.5% and ≤11.0% at screening and had a Week -2 visit HbA1c of ≥7.0% and ≤10.5%, after at least 8 weeks on the stable protocol-specified dose of metformin IR, or
  - On metformin (IR or XR) in combination with an SU with an HbA1c of ≥6.5% and ≤9.5% at screening and had a Week -2 visit HbA1c of ≥7.0% and ≤10.5%, after at least 8 weeks on the stable protocol-specified dose of metformin IR
- FPG <15 mmol/L
- Centre fasting fingerstick glucose of ≥6.1 mmol/L and <15 mmol/L

The exclusion criteria were the same as for Section 7.1.1.1.2.

7.1.4.1.3. Study treatments

The study treatments were:

1: Canagliflozin 100 mg

2: Canagliflozin 300 mg

3: Sitagliptin 100 mg

4: Placebo

Treatment duration was for 26 weeks (but the total planned study duration was for 52 weeks). After 26 weeks the placebo subjects were to be switched to sitagliptin 100 mg once daily. Subjects remained on stable dose of MET throughout the treatment phase but other AHA agents were not permitted during the study. The treatments were administered orally, once daily, before the first meal of the day.

7.1.4.1.4. Efficacy variables and outcomes

As for Section 7.1.1.1.4 with the addition of the secondary efficacy outcome measure:

- 2-hour PPG after a standardized meal for the MMTT

7.1.4.1.5. Randomisation and blinding methods

Randomisation in the ratio 2:2:2:1 for 100 mg/300 mg/ sitagliptin/ placebo using IVRS, and stratified by MET or MET/SU at baseline. Treatments were double blind.

7.1.4.1.6. Analysis populations

As for Section 7.1.1.1.6.

7.1.4.1.7. Sample size

The sample size calculation was based on a test of superiority in comparison with placebo at Week 26, and a non-inferiority comparison with sitagliptin at Week 52. The comparison with placebo assumed a group difference of 0.5% between canagliflozin and placebo group, and a common standard deviation of 1.0% with respect to the change in HbA1c, and using a 2-sample,

2-sided t-test with type I error rate of 0.05, it was estimated that 86 subjects per treatment group will be required to achieve 90% power to demonstrate the superiority of canagliflozin over placebo. For the test of non-inferiority, a non-inferiority margin of 0.3% was used for comparisons of canagliflozin with sitagliptin after 52 weeks of treatment. Assuming a discontinuation rate of 35% at Week 52, with a 2:2:2:1 treatment assignment ratio for canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin 100 mg, or placebo, it was estimated that 360 subjects was required in each of the three active treatment groups and approximately 180 subjects in the placebo group.

7.1.4.1.8. Statistical methods

As for Section 7.1.1.1.8.

7.1.4.1.9. Participant flow

A total of 2,883 subjects were screened, and 1,284 were randomised to treatment: 368 to 100 mg, 367 to 300 mg, 366 to sitagliptin and 183 to placebo. All randomised subjects were included in the mITT dataset (and therefore the safety dataset). There were 46 (12.5%) subjects in the 100 mg group, 44 (12.0%) in the 300 mg, 47 (12.8%) in the sitagliptin and 28 (15.3%) in the placebo that discontinued prior to Week 26.

7.1.4.1.10. Major protocol violations/deviations

The PP dataset included 313 (85.1%) subjects in the 100 mg group, 320 (87.2%) in the 300 mg, 297 (81.1%) in the sitagliptin and 130 (71.0%) in the placebo.

7.1.4.1.11. Baseline data

There were 679 (52.9%) females, 605 (47.1%) males and the age range was 21 to 79 years. There were 206 (16.0%) subjects aged ≥65 years. The treatment groups were similar in demographic and anthropometric characteristics (Table 15). The treatment groups were similar in baseline diabetes characteristics. MET dose at baseline was similar for the four treatment groups. For the majority of subjects (99%) the MET dose was unchanged throughout the study.

Table 15. Baseline Demographic and Anthropometric Characteristics (Study DIA3006)

	Placebo (N=183)	CANA 100 mg (N=368)	CANA 300 mg (N=367)	CANA Total (N=735)	Sita 100 mg (N=366)	Total (N=1284)
Sex, n (%)						
N	183	368	367	735	366	1284
Male	94 (51.4)	174 (47.3)	165 (45.0)	339 (46.1)	172 (47.0)	605 (47.1)
Female	89 (48.6)	194 (52.7)	202 (55.0)	396 (53.9)	194 (53.0)	679 (52.9)
Age (Years)						
N	183	368	367	735	366	1284
Category, n (%)						
<35	5 (2.7)	5 (1.4)	4 (1.1)	9 (1.2)	5 (1.4)	19 (1.5)
35 -<65	141 (77.0)	309 (84.0)	305 (83.1)	614 (83.5)	304 (83.1)	1059 (82.5)
≥65	37 (20.2)	54 (14.7)	58 (15.8)	112 (15.2)	57 (15.6)	206 (16.0)
Mean (SD)	55.3 (9.76)	55.5 (9.38)	55.3 (9.19)	55.4 (9.28)	55.5 (9.55)	55.4 (9.42)
Median	57.0	56.0	56.0	56.0	56.0	56.0
Range	(26;73)	(27;78)	(21;79)	(21;79)	(33;79)	(21;79)
Race, n (%)						
N	183	368	367	735	366	1284
White	129 (70.5)	252 (68.5)	256 (69.8)	508 (69.1)	264 (72.1)	901 (70.2)
Black or African American	3 (1.6)	16 (4.3)	13 (3.5)	29 (3.9)	13 (3.6)	45 (3.5)
Asian	30 (16.4)	51 (13.9)	60 (16.3)	111 (15.1)	41 (11.2)	182 (14.2)
American Indian or Alaska Native	5 (2.7)	6 (1.6)	5 (1.4)	11 (1.5)	8 (2.2)	24 (1.9)
Native Hawaiian or Other Pacific Islander	1 (0.5)	0	0	0	0	1 (0.1)
Multiple	0	0	1 (0.3)	1 (0.1)	0	1 (0.1)
Other	15 (8.2)	43 (11.7)	32 (8.7)	75 (10.2)	40 (10.9)	130 (10.1)
Ethnicity, n (%)						
N	183	368	367	735	366	1284
Hispanic or Latino	53 (29.0)	104 (28.3)	109 (29.7)	213 (29.0)	107 (29.2)	373 (29.0)
Not Hispanic or Latino	130 (71.0)	264 (71.7)	257 (70.0)	521 (70.9)	257 (70.2)	908 (70.7)
Not Reported	0	0	0	0	1 (0.3)	1 (0.1)
Unknown	0	0	1 (0.3)	1 (0.1)	1 (0.3)	2 (0.2)
Baseline Weight (kg)						
N	183	368	367	735	366	1284
Mean (SD)	86.6 (22.42)	88.8 (22.21)	85.4 (20.84)	87.1 (21.59)	87.7 (21.60)	87.2 (21.70)
Median	84.0	86.0	82.0	84.1	84.8	84.2
Range	(45;218)	(40;188)	(47;168)	(40;188)	(41;185)	(40;218)
Baseline BMI (kg/m²)						
N	183	368	366	734	366	1283
Category, n (%)						
< 30	89 (48.6)	145 (39.4)	172 (46.9)	317 (43.1)	159 (43.4)	565 (44.0)
≥ 30	94 (51.4)	223 (60.6)	194 (52.9)	417 (56.7)	207 (56.6)	718 (55.9)
Mean (SD)	31.1 (6.06)	32.4 (6.40)	31.4 (6.30)	31.9 (6.37)	32.0 (6.06)	31.8 (6.24)
Median	30.1	31.6	30.4	31.0	31.6	30.9
Range	(20;69)	(19;58)	(18;73)	(18;73)	(19;60)	(18;73)

7.1.4.1.12. Results for the primary efficacy outcome

At Week 26 canagliflozin 300 mg and 100 mg were both superior to placebo but no formal comparison was performed with sitagliptin (Table 16). The mean (SD) change from baseline in HbA1c was -0.81 (0.650) % for canagliflozin 100 mg, -0.98 (0.885) % for 300 mg, -0.84 (0.835) for sitagliptin and 0.20 (0.895) % for placebo. The LS mean (95% CI) difference (active-placebo) was -0.62 (-0.758 to -0.481) % for 100 mg and -0.77 (-0.914 to -0.636) % for 300 mg ($p < 0.001$) and -0.66 (-0.795 to -0.516) % for sitagliptin. There was no subgroup effect on efficacy.

Table 16. HbA1c: Changes from Baseline to Week 26 – LOCF (Study DIA3006)

	Placebo (N=183)	CANA 100 mg (N=368)	CANA 300 mg (N=367)	Sita 100 mg (N=366)
Blood HbA_{1c} (%)				
Value at Baseline				
N	181	365	360	354
Mean (SD)	7.96 (0.896)	7.94 (0.879)	7.95 (0.931)	7.92 (0.875)
Value at Week 26 LOCF				
N	181	365	360	354
Mean (SD)	7.76 (1.216)	7.13 (0.861)	6.98 (0.819)	7.08 (0.970)
Change from Baseline				
N	181	365	360	354
Mean (SD)	-0.20 (0.895)	-0.81 (0.850)	-0.98 (0.885)	-0.84 (0.835)
LS Mean (SE)	-0.17 (0.060)	-0.79 (0.044)	-0.94 (0.044)	-0.82 (0.044)
P-value(minus Placebo)[a]		<0.001	<0.001	
Diff. of LS Means (SE)[b]		-0.62 (0.071)	-0.77 (0.071)	-0.66 (0.071)
95% CI[a]		(-0.758;-0.481)	(-0.914;-0.636)	(-0.795;-0.516)

CANA=canagliflozin, Sita=sitagliptin, HbA_{1c}=glycosylated hemoglobin, LOCF=last observation carried forward, SD=standard deviation, SE=standard error

[a] Pairwise comparison: p-values and CIs are based on the ANCOVA model with treatment, metformin monotherapy or metformin + SU, and baseline HbA_{1c}.

[b] Placebo-subtracted change from baseline in LS Means.

7.1.4.1.13. Results for other efficacy outcomes

- The proportion of subjects with HbA1c <7.0% at Week 26 was 166 (45.5%) subjects for 100 mg, 208 (57.8%) for 300 mg, 193 (54.5%) for sitagliptin and 54 (29.8%) for placebo (p <0.001 for canagliflozin placebo comparison).
- The proportion of subjects with HbA1c <6.5% at Week 26 was 75 (20.5%) subjects for 100 mg, 96 (26.7%) for 300 mg, 96 (27.1%) for sitagliptin and 21 (11.6%) for placebo.
- The mean (SD) change from baseline in FPG was -1.43 (2.054) mmol/L for canagliflozin 100 mg, -2.13 (2.190) mmol/L for 300 mg, -1.04 (2.227) for sitagliptin and 0.35 (2.622) mmol/L for placebo. The LS mean (95% CI) difference (active-placebo) was -1.65 (-1.986 to -1.323) mmol/L for 100 mg and -2.23 (-2.567 to -1.901) mmol/L for 300 mg (p <0.001 for canagliflozin placebo comparison) and -1.26 (-1.593 to -0.927) for sitagliptin.
- 2-hour postprandial glucose was lower than placebo in the canagliflozin and sitagliptin groups.
- Glycaemic rescue was required for six (1.6%) subjects in the canagliflozin 100 mg group, one (0.3%) in the 300 mg, 23 (6.3%) in the sitagliptin and 27 (14.8%) in the placebo. The HR (95% CI) (canagliflozin compared to placebo) was 0.10 (0.04 to 0.24) for 100 mg, 0.02 (0.0 to 0.12) for 300 mg, and 0.39 (0.22 to 0.68) for sitagliptin.
- The mean (SD) % change from baseline in body weight was -3.5 (3.8) % for canagliflozin 100 mg, -3.9 (3.6) % for 300 mg, -1.0 (3.2) for sitagliptin and -1.0 (3.2) % for placebo. The LS mean (95% CI) difference (active-placebo) was -2.5 (-3.1 to -1.9) % for 100 mg, -2.9 (-3.5 to -2.3) % for 300 mg, an -0.0 (-0.6 to 0.6) for sitagliptin.
- The mean (SD) change from baseline in BMI was -1.15 (1.254) kg/m^2 for canagliflozin 100 mg, -1.22 (1.202) kg/m^2 for 300 mg, -0.33 (1.042) kg/m^2 for sitagliptin and -0.31 (1.012) kg/m^2 for placebo. The LS mean (95% CI) difference (active-placebo) was -0.79 (-0.990 to -0.589) kg/m^2 for 100 mg, -0.90 (-1.100 to -0.699) kg/m^2 for 300 mg and -0.33 (-0.190 to 0.212) kg/m^2 for sitagliptin.
- The mean (SD) change from baseline in waist circumference was -2.09 (4.102) cm for canagliflozin 100 mg, -2.11 (4.099) cm for 300 mg, -0.46 (3.816) cm for sitagliptin and -0.97

(3.694) cm for placebo. The LS mean (95% CI) difference (active-placebo) was -1.02 (-1.732 to -0.310) cm for 100 mg, -1.16 (-1.873 to -0.446) cm for 300 mg and 0.56 (-0.150 to 1.280) cm for sitagliptin.

- There was a significant decrease in SBP in the canagliflozin groups relative to placebo: mean (SD) change from baseline -3.51 (12.693) mmHg for canagliflozin 100 mg, -5.00 (12.187) mmHg for 300 mg, -1.45 (11.432) mmHg for sitagliptin and 1.86 (11.913) mmHg for placebo ($p < 0.001$ for the comparisons between canagliflozin and placebo).
- There was a significant decrease in DBP in the canagliflozin groups relative to placebo: mean (SD) change from baseline -2.00 (7.990) mmHg for canagliflozin 100 mg, -1.98 (7.916) mmHg for 300 mg, -0.80 (7.828) mmHg for sitagliptin and 0.46 (7.685) mmHg for placebo.
- HDL-C increased in the canagliflozin groups relative to placebo: mean (SD) change from baseline 10.3 (18.5) mmol/L for canagliflozin 100 mg, 11.7 (18.6) mmol/L for 300 mg, 5.1 (15.8) mmol/L for sitagliptin and 4.2 (15.0) mmol/L for placebo ($p < 0.001$ for the comparison between canagliflozin and placebo).
- There was no significant change in triglycerides.
- Mean serum cholesterol increased in the canagliflozin groups relative to placebo: mean (95% CI) % difference 4.4 (1.3 to 7.4) % for 100 mg and 6.0 (3.0 to 9.1) % for 300 mg.
- Mean serum LDL-C increased in the canagliflozin groups relative to placebo: mean (95% CI) % difference 7.9 (2.4 to 13.5) % for 100 mg and 12.2 (6.6 to 17.8) % for 300 mg.
- The mean (SD) change from baseline in HOMA2-%B was 14.08 (24.238) for canagliflozin 100 mg, 17.18 (24.450) for 300 mg, 12.48 (22.716) for sitagliptin and 1.67 (28.267) for placebo.

7.1.4.2. Study DIA3009

7.1.4.2.1. Study design, objectives, locations and dates

Study DIA3009 was a multicentre, randomised, double-blind, three-arm, parallel-group, active-controlled study conducted to evaluate the efficacy, safety and tolerability of the addition of canagliflozin (100 mg daily and 300 mg daily) compared with glimepiride in subjects with T2DM with inadequate glycaemic control on a maximally effective dose of metformin (Table 17). The study was conducted at 157 centres in 19 countries from August 2009 to December 2011.

Table 17. Summary of Study DIA3009

Study -investigator -coordinating centre centre(s) -report n°	Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Study DIA3009)Module 5, Section 5.3.5.1) 157 centres in 19 countries August 2009 to December 2011	Multicentre, randomised, double-blind, three-arm, parallel-group, active-controlled study conducted to evaluate the efficacy, safety and tolerability of the addition of canagliflozin compared with glimepiride in subjects with T2DM with inadequate glycaemic control on a maximally effective dose of MET.	3316 subjects screened, 1452 randomised: 483 to 100 mg, 485 to 300 mg and 484 to glimepiride. 88 (18.1%) subjects in the 100 mg group, 105 (21.6%) in the 300 mg and 96 (19.8%) glimepiride discontinued. 756 (52.1%) males, 694 (47.9%) females, age range was 22 to 80 years. 243 (16.8%) subjects aged ≥65 years	Male or female ≥18 and ≤80 years of age with T2DM and currently treated with MET, meeting the following HbA1c eligibility criteria: on MET monotherapy at time of randomisation at a stable protocol specified dose (≥2000 mg/day, or ≥1500 mg/day, if unable to tolerate a higher dose) with a HbA1c of ≥7.0% and ≤9.5%,	104 weeks	Canagliflozin 100 mg Canagliflozin 300 mg Treatments were administered orally, once daily before the first meal of the day. Subjects continued on MET at their stable dose. No other AHAs were allowed during the study.	Glimepiride, titrated in the dose range 1 mg to 8 mg per day	HbA1c. Body weight Hypoglycemia SDP and DBP FPG Waist circumference and BMI Use of rescue medication Time to initiation of rescue medication Fasting serum lipid profile Fasting proinsulin, insulin, and HOMA2-%B Body composition Safety outcome variables were AEs, laboratory tests, hypoglycaemic events, ECGs, vital signs, physical examinations, SMBG	Canagliflozin 300 mg was superior to glimepiride but canagliflozin 100 mg was not. The mean (SD) change from baseline in HbA1c to Week 52 was -0.78 (0.820) % for canagliflozin 100 mg, -0.89 (0.831) % for 300 mg and -0.79 (0.947) % for glimepiride. The LS mean (95% CI) difference (canagliflozin-glimepiride) was -0.01 (-0.109 to 0.085) % for 100 mg and -0.12 (-0.217 to -0.023) % for 300 mg. Proportion of subjects with HbA1c <7.0% at Week 26 was 256 (53.6%) subjects for 100 mg, 285 (60.1%) for 300 mg and 264 (55.8%) for glimepiride. Greater decrease in FPG in both canagliflozin groups than with glimepiride. The mean (SD) change from baseline in FPG was -1.40 (1.929) mmol/L for canagliflozin 100 mg, -1.50 (2.159) mmol/L for 300 mg and -1.07 (2.587) mmol/L for glimepiride (Table 7.4.1.2.6). The LS mean (95% CI) difference (canagliflozin-glimepiride) was -0.33 (-0.557 to -0.110) mmol/L for 100 mg and -0.50 (-0.731 to -0.284) mmol/L for 300 mg.	TEAEs were reported in 310 (64.2%) subjects in the canagliflozin 100 mg group, 332 (68.5%) in the 300 mg and 326 (67.6%) in the glimepiride. Treatment related TEAEs were reported in 118 (24.4%) subjects in the canagliflozin 100 mg group, 145 (29.9%) in the 300 mg and 109 (22.6%) in the glimepiride. There were four deaths: two (0.4%) in the canagliflozin 300 mg group and two (0.4%) in the glimepiride. SAEs were reported in 24 (5.0%) subjects in the canagliflozin 100 mg group, 25 (5.2%) in the 300 mg and 38 (7.9%) in the glimepiride. There was no apparent pattern to the SAEs. DAEs were reported in 25 (5.2%) subjects in the canagliflozin 100 mg group, 32 (6.6%) in the 300 mg and 18 (5.8%) in the glimepiride.

7.1.4.2.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female ≥18 and ≤80 years of age with T2DM and currently treated with metformin, meeting the following HbA1c eligibility criteria:
  - On MET monotherapy at a stable protocol specified dose (≥2000 mg/day, or ≥1500 mg/day, if unable to tolerate a higher dose) for at least 12 weeks and has an HbA1c of ≥7.0% and ≤9.5%, or
  - On MET monotherapy at a dose <2,000 mg/day with an HbA1c of ≥7.5% and ≤10.0% at screening and has a Week -2 visit HbA1c of ≥7.0% and ≤9.5%, after at least 10 weeks on a stable protocol-specified dose of MET, or
  - On MET at a stable protocol specified dose in combination with one other oral non-thiazolidinedione (TZD) AHA with an HbA1c of ≥6.5% and ≤9.0% at screening and has a Week -2 visit HbA1c of ≥7.0% and ≤9.5%, after discontinuing the AHA and on a stable protocol-specified dose of MET at least 10 weeks, or
  - On MET at a dose <2,000 mg/day in combination with one other oral non-TZD AHA with an HbA1c of ≥6.5% and ≤9.0% at screening and had a Week -2 visit HbA1c of ≥7.0% and ≤9.5%, after discontinuing the AHA and on a stable protocol-specified dose of MET at least 10 weeks

The exclusion criteria were similar to those in Section 7.1.1.1.2 with the addition of:

- History of more than one severe hypoglycaemic episode, defined as an episode that requires the help of another person, or resulting in seizure, or loss of consciousness, within 6 months
- History of an ongoing eating disorder or significant weight loss or weight gain, defined as an increase or decrease of 5% in body weight (based on subject report) within 3 months
- Have taken TZD therapy in the past 16 weeks before screening

7.1.4.2.3. Study treatments

The study treatments were:

1: Canagliflozin 100 mg

2: Canagliflozin 300 mg

3: Glimepiride, titrated in the dose range 1 mg to 8 mg per day

Treatments were administered orally, once daily before the first meal of the day. Subjects continued on MET at their stable dose. No other AHAs were allowed during the study. Treatment duration was 104 weeks.

7.1.4.2.4. Efficacy variables and outcomes

The primary efficacy outcome measure was change in HbA1c. The secondary efficacy outcome measures were:

- Body weight
- Hypoglycaemia events
- Durability of glycaemic control (as measured by a longitudinal profile of HbA1c)

Additional efficacy measures included:

- SDP and DBP
- FPG

- Waist circumference and BMI
- Use of rescue medication
- Time to initiation of rescue medication
- Fasting serum lipid profile (triglycerides, LDL-C, HDL-C, total cholesterol, the ratio of LDL-C to HDL-C)
- Fasting proinsulin, insulin, and HOMA2-%B
- Body composition (measured using DXA and abdominal CT scan)

The safety outcome variables were AEs, laboratory tests, hypoglycaemic events, ECGs, vital signs, physical examinations and SMBG.

7.1.4.2.5. Randomisation and blinding methods

The study was double blind and the treatments were indistinguishable. Subjects were block randomised using IVRS in 1:1:1 ratio, stratified by MET dose and discontinuation of additional AHA prior to screening.

7.1.4.2.6. Analysis populations

As per Section 7.1.1.1.6.

7.1.4.2.7. Sample size

The sample size calculation was based on a test of non-inferiority between canagliflozin and glimepiride. The calculation used a non-inferiority margin of 0.3%, assumed a group difference of 0.0% and a common standard deviation of 1.0% with respect to change in HbA1c, and using a 2-sample, 1-sided t-test with Type I error rate of 0.0125 it was estimated that 277 randomised subjects per group would be required to complete the Week 52 visit to achieve 90% power in the PP analysis. Assuming a discontinuation rate of 35% in 52 weeks approximately 427 subjects per treatment group (a total of 1,281 subjects) would be required.

7.1.4.2.8. Statistical methods

Hypothesis tests were performed using an ANCOVA model with treatment and stratification factors (whether or not a subject underwent the MET dose stabilization/ AHA washout period prior to run-in, and country) as fixed effects and HbA1c baseline value as covariate, based on the mITT analysis set. Imputation of missing variables was performed using LOCF.

7.1.4.2.9. Participant flow

A total of 3316 subjects were screened and 1452 were randomised: 483 to 100 mg, 485 to 300 mg and 484 to glimepiride. Two subjects in the glimepiride group were not dosed and were excluded from the mITT dataset (and therefore the safety dataset). There were 88 (18.1%) subjects in the 100 mg group, 105 (21.6%) in the 300 mg and 96 (19.8%) in the glimepiride that discontinued.

7.1.4.2.10. Major protocol violations/deviations

The PP dataset included 361 (74.7%) subjects in the 100 mg group, 357 (73.6%) in the 300 mg and 336 (69.4%) in the glimepiride.

7.1.4.2.11. Baseline data

There were 756 (52.1%) males, 694 (47.9%) females and the age range was 27 to 79 years. There were 243 (16.8%) subjects aged ≥65 years. The treatment groups were similar in demographic and anthropometric characteristics (Table 18). The treatment groups were similar in baseline diabetes characteristics. The treatment groups were similar in MET dose prior to and during the treatment period. Twenty (1%) subjects had their MET dose changed during the study.

Table 18. Baseline Demographic and Anthropometric Characteristics (Study DIA3009)

	CANA 100 mg (N=483)	CANA 300 mg (N=485)	CANA Total (N=968)	Glimepiride (N=482)	Total (N=1450)
Sex, n (%)					
N	483	485	968	482	1450
Male	252 (52.2)	241 (49.7)	493 (50.9)	263 (54.6)	756 (52.1)
Female	231 (47.8)	244 (50.3)	475 (49.1)	219 (45.4)	694 (47.9)
Age (Years)					
N	483	485	968	482	1450
Category, n (%)					
< 35	7 (1.4)	7 (1.4)	14 (1.4)	6 (1.2)	20 (1.4)
35 - < 65	390 (80.7)	404 (83.3)	794 (82.0)	393 (81.5)	1187 (81.9)
≥65	86 (17.8)	74 (15.3)	160 (16.5)	83 (17.2)	243 (16.8)
Mean (SD)	56.4 (9.49)	55.8 (9.17)	56.1 (9.33)	56.3 (9.01)	56.2 (9.22)
Median	57.0	56.0	56.0	57.0	57.0
Range	(22;79)	(26;80)	(22;80)	(28;79)	(22;80)
Race, n (%)					
N	483	485	968	482	1450
White	323 (66.9)	333 (68.7)	656 (67.8)	322 (66.8)	978 (67.4)
Black Or African-American	20 (4.1)	19 (3.9)	39 (4.0)	22 (4.6)	61 (4.2)
Asian	99 (20.5)	92 (19.0)	191 (19.7)	93 (19.3)	284 (19.6)
American Indian Or Alaska Native	1 (0.2)	0	1 (0.1)	2 (0.4)	3 (0.2)
Native Hawaiian Or Other Pacific Islander	0	0	0	1 (0.2)	1 (0.1)
Multiple	7 (1.4)	9 (1.9)	16 (1.7)	11 (2.3)	27 (1.9)
Other	33 (6.8)	32 (6.6)	65 (6.7)	31 (6.4)	96 (6.6)
Ethnicity, n (%)					
N	483	485	968	482	1450
Hispanic Or Latino	86 (17.8)	80 (16.5)	166 (17.1)	76 (15.8)	242 (16.7)
Not Hispanic Or Latino	395 (81.8)	404 (83.3)	799 (82.5)	403 (83.6)	1202 (82.9)
Not Reported	1 (0.2)	1 (0.2)	2 (0.2)	1 (0.2)	3 (0.2)
Unknown	1 (0.2)	0	1 (0.1)	2 (0.4)	3 (0.2)
Baseline Weight (kg)					
N	483	485	968	482	1450
Mean (SD)	86.9 (20.06)	86.6 (19.48)	86.7 (19.76)	86.5 (19.82)	86.6 (19.78)
Median	85.5	84.0	85.0	86.0	85.5
Range	(46;148)	(44;167)	(44;167)	(42;149)	(42;167)
Baseline BMI (kg/m²)					
N	483	485	968	482	1450
Category, n (%)					
< 30	215 (44.5)	224 (46.2)	439 (45.4)	234 (48.5)	673 (46.4)
≥30	268 (55.5)	261 (53.8)	529 (54.6)	248 (51.5)	777 (53.6)
Mean (SD)	31.0 (5.29)	31.2 (5.39)	31.1 (5.34)	30.9 (5.54)	31.0 (5.41)
Median	30.6	30.4	30.6	30.2	30.4
Range	(20;45)	(20;47)	(20;47)	(21;46)	(20;47)
Baseline Waist Circumference (cm)					
N	479	481	960	478	1438
Mean (SD)	103.0 (13.08)	103.7 (13.54)	103.4 (13.31)	102.9 (13.27)	103.2 (13.29)
Median	103.0	102.0	102.0	102.0	102.0
Range	(70;150)	(71;155)	(70;155)	(52;145)	(52;155)

7.1.4.2.12. Results for the primary efficacy outcome

Canagliflozin 300 mg was superior to glimepiride but canagliflozin 100 mg was not (Table 19). The mean (SD) change from baseline in HbA1c to Week 52 was -0.78 (0.820) % for canagliflozin 100 mg, -0.89 (0.831) % for 300 mg and -0.79 (0.947) % for glimepiride. The LS mean (95% CI) difference (canagliflozin-glimepiride) was -0.01 (-0.109 to 0.085) % for 100 mg and -0.12 (-0.217 to -0.023) % for 300 mg. The treatment benefit of canagliflozin 300 mg is of doubtful clinical significance. There was no subgroup effect on efficacy.

Table 19. HbA1c: Change From Baseline to Week 52 – LOCF (Study DIA3009)

	CANA 100 mg (N=483)	CANA 300 mg (N=485)	Glimepiride (N=482)
HbA_{1c} (%)			
Value at Baseline			
N	478	474	473
Mean (SD)	7.78 (0.787)	7.79 (0.779)	7.83 (0.795)
Value at Week 52 LOCF			
N	478	474	473
Mean (SD)	7.00 (0.769)	6.90 (0.806)	7.04 (0.984)
Change from Baseline			
N	478	474	473
Mean (SD)	-0.78 (0.820)	-0.89 (0.831)	-0.79 (0.947)
LS Mean (SE)	-0.82 (0.039)	-0.93 (0.039)	-0.81 (0.039)
Diff. of LS Means (SE)(minus Glimepiride)	-0.01 (0.050)	-0.12 (0.050)	
95% CI (a)	(-0.109;0.085)	(-0.217;-0.023)	

(a) Pairwise comparison: CIs are based on the ANCOVA model with treatment, AHA adjustment period, country and baseline HbA_{1c}. Difference from glimepiride in the change from baseline in LS means.

7.1.4.2.13. Results for other efficacy outcomes

- The proportion of subjects with HbA1c <7.0% at Week 26 was 256 (53.6%) subjects for 100 mg, 285 (60.1%) for 300 mg and 264 (55.8%) for glimepiride (not significant).
- The proportion of subjects with HbA1c <6.5% at Week 26 was 122 (25.5%) subjects for 100 mg, 145 (30.6%) for 300 mg and 145 (30.7%) for glimepiride.
- There was a greater decrease in FPG in both canagliflozin groups than with glimepiride. The mean (SD) change from baseline in FPG was -1.40 (1.929) mmol/L for canagliflozin 100 mg, -1.50 (2.159) mmol/L for 300 mg and -1.07 (2.587) mmol/L for glimepiride. The LS mean (95% CI) difference (canagliflozin- glimepiride) was -0.33 (-0.557 to -0.110) mmol/L for 100 mg and -0.50 (-0.731 to -0.284) mmol/L for 300 mg.
- Glycaemic rescue was less likely for the canagliflozin groups. Glycaemic rescue was required for 32 (6.6%) subjects in the canagliflozin 100 mg group, 24 (4.9%) in the 300 mg and 51 (10.6%) in the glimepiride. The HR (95% CI) (canagliflozin compared to placebo) was 0.58 (0.37 to 0.91) for 100 mg and 0.45 (0.28 to 0.74) for 300 mg.
- The mean (SD) % change from baseline in body weight was -4.0 (4.1) % for canagliflozin 100 mg, -4.4 (4.2) % for 300 mg and 1.2 (4.1) % for glimepiride. The LS mean (95% CI) difference (canagliflozin-glimepiride) was -5.2 (-5.7 to -4.7) % for 100 mg and -5.7 (-6.2 to -5.1) % for 300 mg.
- The mean (SD) change from baseline in BMI was -1.23 (1.321) kg/m^2 for canagliflozin 100 mg, -1.38 (1.363) kg/m^2 for 300 mg and 0.35 (1.294) kg/m^2 for glimepiride. The LS mean (95% CI) difference (canagliflozin-glimepiride) was -1.58 (-1.742 to -1.412) kg/m^2 for 100 mg and -1.72 (-1.885 to -1.555) kg/m^2 for 300 mg.
- The mean (SD) change from baseline in waist circumference was -2.79 (5.257) cm for canagliflozin 100 mg, -3.08 (4.869) cm for 300 mg and 0.32 (4.908) cm for glimepiride. The LS mean (95% CI) difference (canagliflozin-glimepiride) was -3.12 (-3.747 to -2.493) cm for 100 mg and -3.34 (-3.969 to -2.713) cm for 300 mg.
- Using DXA body composition analysis, relative to glimepiride, in the canagliflozin groups there was a decrease in total fat, region % total fat, total lean measurement, and tissue % total fat. However there was no significant difference between the groups using CT scan analysis.

- There was a significant decrease in SBP in the canagliflozin groups relative to glimepiride: mean (SD) change from baseline -3.88 (11.999) mmHg for canagliflozin 100 mg, -5.17 (13.314) mmHg for 300 mg and -0.14 (13.449) mmHg for glimepiride. The LS mean (95% CI) difference (canagliflozin-glimepiride) was -3.48 (-4.881 to -2.072) mmHg for 100 mg and -4.76 (-6.166 to -3.358) mmHg for 300 mg.
- There was a significant decrease in DBP in the canagliflozin groups relative to glimepiride: mean (SD) change from baseline -1.87 (8.302) mmHg for canagliflozin 100 mg, -2.81 (8.053) mmHg for 300 mg and -0.28 (8.578) mmHg for glimepiride. The LS mean (95% CI) difference (canagliflozin-glimepiride) was -1.70 (-2.618 to -0.775) mmHg for 100 mg and -2.39 (-3.316 to -1.473) mmHg for 300 mg.
- HDL-C increased in the canagliflozin groups relative to glimepiride: mean (SD) change from baseline 7.3 (16.8) mmol/L for canagliflozin 100 mg, 8.5 (16.6) mmol/L for 300 mg and -0.2 (14.9) mmol/L for glimepiride. The LS mean (95% CI) difference (canagliflozin-glimepiride) was 7.5 (5.6 to 9.5) mmol/L for 100 mg and 8.6 (6.7 to 10.6) mmol/L for 300 mg.
- Triglycerides decreased in the canagliflozin groups relative to glimepiride: mean (SD) change from baseline -3.0 (44.9) mmol/L for canagliflozin 100 mg, 2.9 (51.8) mmol/L for 300 mg and 11.7 (51.2) mmol/L for glimepiride. The LS mean (95% CI) difference (canagliflozin-glimepiride) was -13.2 (-19.4 to -7.0) mmol/L for 100 mg and -7.2 (-13.4 to -1.0) mmol/L for 300 mg.
- Relative to glimepiride there was an increase in mean cholesterol and LDL-C in the canagliflozin 300 mg group, but not significant difference in LDL-C/ HDL-C ratio.
- The mean (SD) change from baseline in HOMA2-%B was 10.20 (27.354) for canagliflozin 100 mg, 12.57 (24.266) for 300 mg and 18.82 (36.718) for glimepiride.
- Hypoglycaemia was reported in 27 (5.6%) subjects in the canagliflozin 100 mg group, 24 (4.9%) in the 300 mg and 165 (34.2%) in the glimepiride. The OR (95% CI) for hypoglycaemia, canagliflozin compared to glimepiride, was 0.10 (0.06 to 0.16) for 100 mg ($p < 0.001$) and 0.09 (0.05 to 0.14) for 300 mg ($p < 0.001$).
- Durability of effect, as measured by time to an increase in HbA1c of 0.3% in responders was greater for the canagliflozin 300 mg group than either 100 mg or glimepiride.

7.1.5. Efficacy in older subjects

7.1.5.1. Study DIA3010

7.1.5.1.1. Study design, objectives, locations and dates

Study DIA3010 was a multicentre, randomised, double-blind, placebo-controlled, parallel-group, three-arm study conducted to evaluate the efficacy, safety and tolerability of the addition of canagliflozin (100 mg daily and 300 mg daily) in older subjects with T2DM inadequately controlled on their current diabetes treatment regimen (Table 20). The study was conducted at 90 centres in 17 countries, including three in Australia from April 2010 to November 2011. The study was intended to be of 110 weeks duration and data for the first 26 weeks were presented.

Table 20. Summary of Study DIA3010

Study -investigator -coordinating centre centre(s) -report n°	Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Study DIA3010 (Module 5, Section 5.3.5.1) 90 centres in 17 countries, including three in Australia April 2010 to November 2011	Multicentre, randomised, double-blind, placebo-controlled, parallel-group, three-arm study conducted to evaluate the efficacy, safety and tolerability of the addition of canagliflozin (100 mg daily and 300 mg daily) in older subjects with T2DM inadequately controlled on their current diabetes treatment regimen.	1902 screened, 716 randomised: 241 to 100 mg, 236 to 300 mg and 239 to placebo. 15 (6.2%) subjects in the 100 mg group, 27 (11.4%) in the 300 mg and 40 (16.7%) placebo discontinued. 306 (55.5%) males, 318 (44.5%) females, age range 55 to 80 years. 273 (38.2%) subjects aged ≥65 years	Male or female ≥55 to ≤80 years of age with T2DM; women must be at least 3 years postmenopausal HbA1c ≥7.0% to ≤10.0% at screening (or at Week -2, if HbA1c obtained more than 3 weeks prior to Week -2 visit), and Not currently on AHA therapy (off for at least 12 weeks) or on a stable regimen of AHA(s) in monotherapy or on combination therapy, with any approved agent (including MET, SU, DPP-4 inhibitor, AGI, GLP-1 analogue, or insulin for at least 12 weeks; or pioglitazone for at least 6 months) FPG <15 mmol/L Fasting fingerstick glucose of ≥6.1 mmol/L and <15 mmol/L BMI ≥20 to ≤40 kg/m^2	Approximately 110 weeks	Canagliflozin 100 mg Canagliflozin 300 mg Once daily oral administration prior to the first meal of the day Subjects were allowed to take other AHAs during the study	Placebo Randomised 1:1:1	HbA1c. Body weight Hypoglycemia SDP and DBP FPG Waist circumference and BMI Use of rescue medication Time to initiation of rescue medication Fasting serum lipid profile Fasting proinsulin, insulin, Bone mineral density, Body composition Safety outcome variables were AEs, laboratory tests, hypoglycaemic events, ECGs, vital signs, physical examinations, SMBG	Canagliflozin 300 mg and 100 mg were both superior to placebo. The mean (SD) change from baseline in HbA1c was -0.64 (0.747) % for canagliflozin 100 mg, -0.74 (0.753) % for 300 mg and -0.07 (0.922) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.57 (-0.708 to -0.436) % for 100 mg and -0.70 (-0.841 to -0.566) % for 300 mg. The mean (SD) change from baseline in FPG was -1.29 (1.959) mmol/L for canagliflozin 100 mg, -1.17 (2.015) mmol/L for 300 mg and 0.26 (2.631) mmol/L for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -1.41 (-1.756 to -1.071) mmol/L for 100 mg and -1.54 (-1.884 to -1.192) mmol/L for 300 mg.	TEAEs were reported in 174 (72.2%) subjects in the canagliflozin 100 mg group, 184 (78.0%) in the 300 mg and 174 (73.4%) in the placebo. There were no deaths reported. SAEs were reported in ten (4.1%) subjects in the canagliflozin 100 mg group, eight (3.4%) in the 300 mg and twelve (5.1%) in the placebo. DAEs were reported in five (2.1%) subjects in the canagliflozin 100 mg group, 17 (7.2%) in the 300 mg and ten (4.2%) in the placebo.

7.1.5.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female ≥55 to ≤80 years of age with T2DM; women must be at least 3 years postmenopausal
- HbA1c ≥7.0% to ≤10.0% at screening (or at Week -2, if HbA1c obtained more than 3 weeks prior to Week -2 visit)
- Not currently on AHA therapy (off for at least 12 weeks) or on a stable regimen of AHA(s) in monotherapy or on combination therapy, with any approved agent (including MET, SU, DPP-4 inhibitor, AGI, GLP-1 analogue, or insulin for at least 12 weeks; or pioglitazone for at least 6 months
- FPG <15 mmol/L
- Fasting fingerstick glucose of ≥6.1 mmol/L and <15 mmol/L
- BMI ≥20 to ≤40 kg/m^2

The exclusion criteria were similar to those in Section 7.1.1.1.2 but also included:

- Use of a bisphosphonate within 12 months prior to screening or expected to receive treatment with bisphosphonate during the study period
- On medication treatment for osteoporosis (eg, estrogen replacement, selective estrogen receptor modulator therapy, or calcitonin), not on a stable regimen
- T-score <-2.5 at any site in a subject not currently on treatment for osteoporosis
- Parathyroid hormone (eg, teriparatide) or denosumab treatment within 12 months before screening
- Severe vitamin D deficiency with serum 25-hydroxy-vitamin D level ≤10 ng/mL at screening or within 12 months prior to screening
- Hypercalcemia
- Conditions that interfere with accurate measurement of BMD (eg, severe scoliosis, spine degenerative disease, spinal fusion or metal implants, bilateral hip replacement or other surgery resulting in metal implants in both hips)
- Non-healed fracture, or any fracture within 12 months of screening
- Acquired or inherited bone disorders that may confound assessment of bone density or bone turnover (eg, Paget's disease, osteomalacia, osteopetrosis, osteogenesis imperfect) or elevation of ALP >1.5xULN

7.1.5.1.3. Study treatments

The study treatments were:

1: Canagliflozin 100 mg

2: Canagliflozin 300 mg

3: Placebo

Treatment duration was for approximately 110 weeks. Subjects continued their AHAs at randomisation at the same dose levels during the study. The treatments were administered orally, once daily, before the first meal of the day.

7.1.5.1.4. Efficacy variables and outcomes

The efficacy outcome measures were the same as for Section 7.1.1.1.4, but also included as secondary outcome measures:

- Body composition endpoints
- Bone mineral density

The safety outcome variables were AEs, laboratory tests, hypoglycaemic events, ECGs, vital signs, physical examinations and SMBG.

7.1.5.1.5. Randomisation and blinding methods

The study was double blind and the treatments were indistinguishable. Subjects were block randomised using IVRS/IWRS in 1:1:1 ratio, stratified by T-score of lumbar spine and whether the subjects was taking a PPARγ agent (pioglitazone).

7.1.5.1.6. Analysis populations

As per Section 7.1.1.1.6.

7.1.5.1.7. Sample size

As per Section 7.1.1.1.7.

7.1.5.1.8. Statistical methods

As per Section 7.1.1.1.8.

7.1.5.1.9. Participant flow

There were 1902 subjects screened and 716 were randomised to treatment: 241 to 100 mg, 236 to 300 mg and 239 to placebo. Two subjects in the placebo group were not dosed and were excluded from the mITT dataset (and therefore the safety dataset). There were 15 (6.2%) subjects in the 100 mg group, 27 (11.4%) in the 300 mg and 40 (16.7%) in the placebo that discontinued.

7.1.5.1.10. Major protocol violations/deviations

The PP dataset included 210 (90.9%) subjects in the 100 mg group, 206 (87.3%) in the 300 mg and 171 (71.5%) in the placebo.

7.1.5.1.11. Baseline data

There were 306 (55.5%) males, 318 (44.5%) females and the age range was 55 to 80 years. There were 273 (38.2%) subjects aged ≥65 years. Other than a lower proportion of females in the placebo group (39.7% compared with 47.0% in the canagliflozin groups) the treatment groups were similar in demographic and anthropometric characteristics (Table 21). The treatment groups were similar in baseline diabetes characteristics . The study subjects were on a broad range of concomitant AHA during the study, with a similar pattern between the treatment groups.

Table 21. Baseline Demographic and Anthropometric Characteristics (Study DIA3010)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)	CANA Total (N=477)	Total (N=714)
Sex, n (%)					
N	237	241	236	477	714
Male	143 (60.3)	124 (51.5)	129 (54.7)	253 (53.0)	396 (55.5)
Female	94 (39.7)	117 (48.5)	107 (45.3)	224 (47.0)	318 (44.5)
Age (Years)					
N	237	241	236	477	714
Category, n (%)					
35 - < 65	151 (63.7)	141 (58.5)	149 (63.1)	290 (60.8)	441 (61.8)
≥65	86 (36.3)	100 (41.5)	87 (36.9)	187 (39.2)	273 (38.2)
Mean (SD)	63.2 (6.21)	64.3 (6.46)	63.4 (5.99)	63.9 (6.24)	63.6 (6.24)
Median	62.0	63.0	62.0	63.0	63.0
Range	(55;80)	(55;80)	(55;79)	(55;80)	(55;80)
Race, n (%)					
N	237	241	236	477	714
White	185 (78.1)	194 (80.5)	173 (73.3)	367 (76.9)	552 (77.3)
Black or African American	20 (8.4)	18 (7.5)	19 (8.1)	37 (7.8)	57 (8.0)
Asian	21 (8.9)	15 (6.2)	25 (10.6)	40 (8.4)	61 (8.5)
American Indian or Alaska Native	0	4 (1.7)	1 (0.4)	5 (1.0)	5 (0.7)
Native Hawaiian or Other Pacific Islander	0	2 (0.8)	1 (0.4)	3 (0.6)	3 (0.4)
Multiple	1 (0.4)	0	2 (0.8)	2 (0.4)	3 (0.4)
Other	10 (4.2)	8 (3.3)	14 (5.9)	22 (4.6)	32 (4.5)
Not Reported	0	0	1 (0.4)	1 (0.2)	1 (0.1)
Ethnicity, n (%)					
N	237	241	236	477	714
Hispanic or Latino	33 (13.9)	37 (15.4)	34 (14.4)	71 (14.9)	104 (14.6)
Not Hispanic or Latino	203 (85.7)	203 (84.2)	201 (85.2)	404 (84.7)	607 (85.0)
Not Reported	0	0	1 (0.4)	1 (0.2)	1 (0.1)
Unknown	1 (0.4)	1 (0.4)	0	1 (0.2)	2 (0.3)
Baseline Weight (kg)					
N	237	241	236	477	714
Mean (SD)	91.1 (17.52)	88.4 (15.57)	88.8 (17.09)	88.6 (16.33)	89.5 (16.76)
Median	89.4	88.2	87.9	88.1	88.8
Range	(58;150)	(54;141)	(50;150)	(50;150)	(50;150)
Baseline Height (cm)					
N	237	241	236	477	714
Mean (SD)	168.9 (9.83)	167.5 (10.34)	167.7 (10.29)	167.6 (10.30)	168.1 (10.16)
Median	169.5	167.6	167.0	167.3	168.0
Range	(142;193)	(146;195)	(143;193)	(143;195)	(142;195)
Baseline BMI (kg/m²)					
N	237	241	236	477	714
Category, n (%)					
< 30	87 (36.7)	90 (37.3)	93 (39.4)	183 (38.4)	270 (37.8)
≥30	150 (63.3)	151 (62.7)	143 (60.6)	294 (61.6)	444 (62.2)
Mean (SD)	31.8 (4.76)	31.4 (4.41)	31.5 (4.56)	31.5 (4.48)	31.6 (4.57)
Median	31.7	31.2	31.4	31.3	31.4
Range	(20;43)	(22;41)	(22;42)	(22;42)	(20;43)
Baseline Waist Circumference (cm)					
N	235	238	230	468	703
Mean (SD)	106.2 (12.93)	105.5 (12.15)	105.2 (13.06)	105.4 (12.59)	105.7 (12.70)
Median	105.0	104.0	105.0	104.1	104.5
Range	(74;142)	(75;140)	(56;137)	(56;140)	(56;142)

7.1.5.1.12. Results for the primary efficacy outcome

Canagliflozin 300 mg and 100 mg were both superior to placebo (Table 22). The mean (SD) change from baseline in HbA1c was -0.64 (0.747) % for canagliflozin 100 mg, -0.74 (0.753) % for 300 mg and -0.07 (0.922) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.57 (-0.708 to -0.436) % for 100 mg and -0.70 (-0.841 to -0.566) % for 300 mg. There was no subgroup effect on efficacy.

Table 22. Summary: Change from Baseline to Week 26 for Primary and Secondary Efficacy Endpoints (LOCF) (Study 28431754-DIA3010: Modified Intent-to-Treat Analysis Set)

Endpoints	CANA 100 mg (Placebo-Subtracted) Mean (95% CI)	p-value[a]	CANA 300 mg (Placebo-Subtracted) Mean (95% CI)	p-value[a]
HbA_{1c} Change (%)	-0.57 (-0.708; -0.436)	<0.001	-0.70 (-0.841; -0.566)	<0.001
Achieving <7.0% HbA_{1c} target (%)	19.7 (10.7; 28.7)	<0.001	30.5 (21.5; 39.5)	<0.001
FPG Change (mmol/L)	-1.41 (-1.756; -1.071)	<0.001	-1.54 (-1.884; -1.192)	<0.001
Body Weight Percent Change (%)	-2.3 (-2.8; -1.7)	<0.001	-3.0 (-3.5; -2.4)	<0.001
Systolic BP Change (mmHg)	-4.63 (-6.854; -2.401)	<0.001	-7.89 (-10.14; -5.641)	<0.001
HDL-C Percent Change (%)	5.3 (2.6; 7.9)	<0.001	4.7 (2.0; 7.4)	<0.001
Triglycerides Percent Change (%)	-4.8 (-12.1; 2.5)	0.193	0.7 (-6.6; 8.1)	0.842

[a] Nominal p-value.

Key: ANCOVA=analysis of covariance, BP=blood pressure CI=confidence interval, HbA1c=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, FPG=fasting plasma glucose.

Note 1: For continuous endpoints, the least squares mean is presented with associated p-value and CI based on ANCOVA models with terms for treatment and stratification factors and adjusting for the baseline value as a covariate.

Note 2: For the proportion of patients achieving 7.0% HbA_{1c} target, CI of the difference in proportion is based on normal approximation to binomial distribution with continuity correction; p-value is based on a logistic regression with terms for treatment and stratification factors and adjusting for the baseline value as a covariate.

7.1.5.1.13. Results for other efficacy outcomes

- The proportion of subjects with HbA1c <7.0% at Week 26 was 114 (47.7%) subjects for 100 mg, 134 (58.5%) for 300 mg and 65 (28.0%) for placebo (p <0.001).
- The proportion of subjects with HbA1c <6.5% at Week 26 was 45 (18.8%) subjects for 100 mg, 68 (29.7%) for 300 mg and 14 (6.0%) for placebo.
- The mean (SD) change from baseline in FPG was -1.29 (1.959) mmol/L for canagliflozin 100 mg, -1.17 (2.015) mmol/L for 300 mg and 0.26 (2.631) mmol/L for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -1.41 (-1.756 to -1.071) mmol/L for 100 mg and -1.54 (-1.884 to -1.192) mmol/L for 300 mg.
- Glycaemic rescue was required for five (2.1%) subjects in the canagliflozin 100 mg group, one (0.4%) in the 300 mg and 26 (11.0%) in the placebo. The HR (95% CI) (canagliflozin compared to placebo) was 0.17 (0.06 to 0.44) for 100 mg and 0.04 (0.00 to 0.26) for 300 mg.
- The mean (SD) % change from baseline in body weight was -2.7 (3.2) % for canagliflozin 100 mg, -3.4 (3.4) % for 300 mg and -0.5 (2.6) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -2.3 (-2.8 to -1.7) % for 100 mg and -3.0 (-3.5 to -2.4) % for 300 mg.
- The mean (SD) change from baseline in BMI was -0.86 (1.008) kg/m^2 for canagliflozin 100 mg, -1.09 (1.062) kg/m^2 for 300 mg and -0.15 (0.804) kg/m^2 for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.72 (-0.890 to -0.545) kg/m^2 for 100 mg and -0.95 (-1.123 to -0.773) kg/m^2 for 300 mg.
- The mean (SD) change from baseline in waist circumference was -2.02 (4.402) cm for canagliflozin 100 mg, -2.60 (4.965) cm for 300 mg and -0.54 (4.213) cm for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -1.47 (-2.307 to -0.624) cm for 100 mg and -2.11 (-2.961 to -1.262) cm for 300 mg.
- SBP decreased relative to placebo: mean (SD) change from baseline -3.96 (13.333) mmHg for canagliflozin 100 mg, -7.47 (14.648) mmHg for 300 mg and 0.30 (13.155) mmHg for placebo (p <0.001).
- DBP also decreased relative to placebo: mean (SD) change from baseline -1.97 (7.599) mmHg for canagliflozin 100 mg, -3.48 (8.034) mmHg for 300 mg and -0.49 (7.679) mmHg for placebo.
- There was a significant increase in HDL-C in the canagliflozin groups: mean (SD) % change from baseline 7.9 (15.2) % for canagliflozin 100 mg, 7.8 (15.3) % for 300 mg and 2.2 (13.0)

% for placebo. There was an increase in total cholesterol in the canagliflozin groups: mean (SD) change from baseline 6.0 (22.5) % for canagliflozin 100 mg, 8.4 (17.7) % for 300 mg and 2.3 (20.3) %for placebo. There was a significant increase in LDL-C in the canagliflozin groups: mean (SD) % change from baseline 12.9 (48.3) % for canagliflozin 100 mg, 14.3 (34.8) % for 300 mg and 5.4 (34.8) % for placebo.

- In both canagliflozin groups there was a decrease in total fat, total lean measurement and the tissue % total fat, relative to placebo.

7.1.6. Efficacy in combination with MET and Pioglitazone

7.1.6.1. Study DIA3012

7.1.6.1.1. Study design, objectives, locations and dates

Study DIA3012 was a multicentre, Phase 3, randomised, double-blind, placebo controlled, parallel group, three-arm study, of canagliflozin (100 mg daily and 300 mg daily) compared with placebo in subjects with T2DM who were inadequately controlled with MET and pioglitazone (Table 23). The study was conducted in 74 centres in 11 countries from April 2010 to November 2011. The intended study duration is 52 weeks and the results of the first 26 weeks were submitted.

Table 23. Summary of Study DIA3012

Study -investigator -coordinating centre centre(s) -report n°	Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Study DIA3012 (Module 5, Section 5.3.5.1) 74 centres in 11 countries April 2010 to November 2011	Multicentre Phase 3 randomised, double-blind, placebo controlled, parallel group, three-arm study, of canagliflozin (100 mg daily and 300 mg daily) compared with placebo in subjects with T2DM who were inadequately controlled with MET and pioglitazone.	877 screened, 344 randomised: 115 to 100 mg, 114 to 300 mg and 115 to placebo. There were nine (7.8%) subjects in the 100 mg group, 13 (11.4%) in the 300 mg and 24 (20.9%) in the placebo that discontinued. 216 (63.2%) males, 126 (36.8%) females, age range was 27 to 78 years. 93 (27.2%) subjects aged ≥65 years.	Male or female ≥18 and ≤80 years of age with T2DM who met one of the following five criteria: On dual MET ≥2,000 mg per day or ≥1,500 mg per day, if unable to tolerate a higher dose; and pioglitazone 30 mg or 45 mg per day; or able to transition to this combination with a HbA1c of ≥7.0% and ≤10.5%; FPG <15 mmol/L; site fasting fingerstick glucose of ≥6.1 mmol/L and <15 mmol/L on Day 1	26 weeks (with 26 week extension reported separately)	Canagliflozin 100 mg Canagliflozin 300 mg Oral administration once daily, before the first meal of the day Block randomised using IVRS/IWRS in 1:1:1 ratio,	Placebo After 26 weeks, placebo subjects switched to Sitagliptin 100 mg daily for the reaminder of the study Stable dose of MET and pioglitazone throughout the treatment phase. No other AHA treatment	The primary efficacy outcome measure was change in HbA1c. The secondary efficacy measures included: FPG Postprandial glucose Body weight SBP Fasting triglycerides Fasting HDL-C HOMA-2%B Safety outcome variables were AEs, laboratory tests, hypoglycaemic events, ECGs, vital signs, physical examinations, and SMBG	Canagliflozin 300 mg and 100 mg were both superior to placebo. The mean (SD) change from baseline in HbA1c was -0.92 (0.802) % for canagliflozin 100 mg, -1.00 (0.806) % for 300 mg and -0.30 (0.860) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.62 (-0.811 to -0.437) % for 100 mg and -0.76 (-0.951 to -0.575) % for 300 mg. Proportion of subjects with HbA1c <7.0% at Week 26 was 53 (46.9%) subjects for 100 mg, 72 (64.3%) for 300 mg and 37 (32.5%) for placebo. Mean (SD) change from baseline in FPG was -1.63 (2.005) mmol/L for canagliflozin 100 mg, -1.86 (1.980) mmol/L for 300 mg and 0.12 (1.885) mmol/L for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -1.63 (-2.050 to -1.208) mmol/L for 100 mg and -1.98 (-2.405 to -1.562) mmol/L for 300 mg.	TEAEs were reported in 67 (59.3%) subjects in the canagliflozin 100 mg group, 75 (65.8%) in the 300 mg and 74 (64.3%) in the placebo. There were no deaths reported during the first 26 weeks of the study. SAEs were reported in three (2.7%) subjects in the canagliflozin 100 mg group, four (3.5%) in the 300 mg and five (4.3%) in the placebo. DAEs were reported in three (2.7%) subjects in the canagliflozin 100 mg group, five (4.4%) in the 300 mg and six (5.2%) in the placebo.

7.1.6.1.2. Inclusion and exclusion criteria

The inclusion criteria included

- Male or female ≥18 and ≤80 years of age with T2DM who met one of the following five criteria:
  - On dual combination MET and pioglitazone, both agents at protocol-specified doses (MET ≥2,000 mg per day or ≥1,500 mg per day, if unable to tolerate a higher dose; and pioglitazone 30 mg or 45 mg per day) with a HbA1c of ≥7.0% and ≤10.5%, or
  - On dual combination MET and pioglitazone with either agent at a dose below protocol-specified, with an HbA1c of ≥7.5% and ≤11.0% at screening, and has an HbA1c of ≥7.0% and ≤10.5% at Week -2, after at least 8 weeks on stable protocol-specified doses of MET and pioglitazone, or
  - On dual combination metformin and rosiglitazone, with an HbA1c of ≥7.0% and ≤10.5% at screening, and has an HbA1c of ≥7.0% and ≤10.5% at Week -2, after at least 8 weeks on stable protocol-specified doses of MET and pioglitazone, or
  - On a PPARγ agent (pioglitazone or rosiglitazone) in dual combination with another oral AHA, with an HbA1c of ≥7.0% and ≤10.5% at screening, and has an HbA1c of ≥7.0% and ≤10.5% at Week -2, after at least 8 weeks on stable protocol-specified doses of MET and pioglitazone, or
  - On metformin, a PPARγ agent (pioglitazone or rosiglitazone), and an SU (or meglitinide) or a DPP-4 inhibitor in triple combination therapy with an HbA1c of ≥6.5% and ≤9.5% at screening, and has an HbA1c of ≥7.0% and ≤10.5% at Week -2, after at least 8 weeks on stable protocol-specified doses of MET and pioglitazone
- FPG <15 mmol/L at Week -2.
- Site fasting fingerstick glucose of ≥6.1 mmol/L and <15 mmol/L on Day 1

The exclusion criteria were similar to those for Section 7.1.1.1.2 with the addition of:

- Ongoing eating disorder or significant weight loss or weight gain within 12 weeks, defined as an increase or decrease of 5% in body weight based upon clinic-based measurement or, if not available, subject report

7.1.6.1.3. Study treatments

The study treatments were:

1: Canagliflozin 100 mg

2: Canagliflozin 300 mg

3: Placebo

Treatment duration was for 52 weeks, with the Sponsor submitting data for the first 26 weeks. All subjects continued on MET and pioglitazone at a stable dose during the study. The treatments were administered orally, once daily, before the first meal of the day.

7.1.6.1.4. Efficacy variables and outcomes

The outcome measures were the same as for Section 7.1.1.1.4.

7.1.6.1.5. Randomisation and blinding methods

The study was double blind and the treatments were indistinguishable. Subjects were block randomised using IVRS/IWRS in 1:1:1 ratio, stratified by whether the subjects were transitioned to MET or pioglitazone; and by pioglitazone dose at baseline.

7.1.6.1.6. Analysis populations

As per Section 7.1.1.1.6.

7.1.6.1.7. Sample size

As per Section 7.1.1.1.7.

7.1.6.1.8. Statistical methods

As per Section 7.1.1.1.8.

7.1.6.1.9. Participant flow

There were 877 subjects screened and 344 were randomised to treatment: 115 to 100 mg, 114 to 300 mg and 115 to placebo. Two subjects in the canagliflozin 100 mg group were not dosed and were excluded from the mITT dataset (and therefore the safety dataset). There were nine (7.8%) subjects in the 100 mg group, 13 (11.4%) in the 300 mg and 24 (20.9%) in the placebo that discontinued.

7.1.6.1.10. Major protocol violations/deviations

The PP dataset included 103 (89.6%) subjects in the 100 mg group, 101 (88.6%) in the 300 mg and 78 (67.8%) in the placebo.

7.1.6.1.11. Baseline data

There were 216 (63.2%) males, 126 (36.8%) females and the age range was 27 to 78 years. There were 93 (27.2%) subjects aged ≥65 years. The treatment groups were similar in demographic and anthropometric characteristics (Table 24). The treatment groups were similar in baseline diabetes characteristics. The treatment groups were similar in MET dose prior to and during the treatment period. The treatment groups were similar in pioglitazone dose during the study.

Table 24. Baseline Demographic and Anthropometric Characteristics (Study DIA3012)

	Placebo (N=115)	CANA 100 mg (N=113)	CANA 300 mg (N=114)	CANA Total (N=227)	Total (N=342)
Sex, n (%)					
N	115	113	114	227	342
Male	76 (66.1)	77 (68.1)	63 (55.3)	140 (61.7)	216 (63.2)
Female	39 (33.9)	36 (31.9)	51 (44.7)	87 (38.3)	126 (36.8)
Age (Years)					
N	115	113	114	227	342
Category, n (%)					
< 35	0	1 (0.9)	1 (0.9)	2 (0.9)	2 (0.6)
35 - <65	83 (72.2)	82 (72.6)	82 (71.9)	164 (72.2)	247 (72.2)
≥65	32 (27.8)	30 (26.5)	31 (27.2)	61 (26.9)	93 (27.2)
Mean (SD)	58.3 (9.56)	56.7 (10.36)	57.0 (10.19)	56.9 (10.25)	57.4 (10.03)
Median	58.0	56.0	57.5	57.0	57.0
Range	(38;78)	(27;76)	(32;77)	(27;77)	(27;78)
Race, n (%)					
N	115	113	114	227	342
White	79 (68.7)	83 (73.5)	90 (78.9)	173 (76.2)	252 (73.7)
Black or African American	6 (5.2)	4 (3.5)	10 (8.8)	14 (6.2)	20 (5.8)
Asian	21 (18.3)	23 (20.4)	11 (9.6)	34 (15.0)	55 (16.1)
Multiple	0	0	1 (0.9)	1 (0.4)	1 (0.3)
Other	9 (7.8)	3 (2.7)	2 (1.8)	5 (2.2)	14 (4.1)
Ethnicity, n (%)					
N	115	113	114	227	342
Hispanic or Latino	18 (15.7)	14 (12.4)	22 (19.3)	36 (15.9)	54 (15.8)
Not Hispanic or Latino	97 (84.3)	96 (85.0)	90 (78.9)	186 (81.9)	283 (82.7)
Not Reported	0	1 (0.9)	2 (1.8)	3 (1.3)	3 (0.9)
Unknown	0	2 (1.8)	0	2 (0.9)	2 (0.6)
Baseline Weight (kg)					
N	115	113	114	227	342
Mean (SD)	93.8 (22.41)	94.2 (22.24)	94.4 (25.85)	94.3 (24.07)	94.1 (23.49)
Median	90.9	90.5	91.4	91.0	91.0
Range	(54;186)	(52;154)	(50;196)	(50;196)	(50;196)
Baseline BMI (kg/m²)					
N	115	113	114	227	342
Category, n (%)					
<30	42 (36.5)	45 (39.8)	46 (40.4)	91 (40.1)	133 (38.9)
≥30	73 (63.5)	68 (60.2)	68 (59.6)	136 (59.9)	209 (61.1)
Mean (SD)	32.5 (6.39)	32.3 (6.15)	32.8 (7.69)	32.6 (6.95)	32.6 (6.76)
Median	31.6	31.5	31.0	31.1	31.2
Range	(21;58)	(20;48)	(20;68)	(20;68)	(20;68)

7.1.6.1.12. Results for the primary efficacy outcome

Canagliflozin 300 mg and 100 mg were both superior to placebo (Table 25). The mean (SD) change from baseline in HbA1c was -0.92 (0.802) % for canagliflozin 100 mg, -1.00 (0.806) % for 300 mg and -0.30 (0.860) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.62 (-0.811 to -0.437) % for 100 mg and -0.76 (-0.951 to -0.575) % for 300 mg. There was no subgroup effect on efficacy.

Table 25. HbA1c: Change from Baseline to Week 26 – LOCF (Study DIA3012)

	Placebo (N=115)	CANA 100 mg (N=113)	CANA 300 mg (N=114)
Blood HbA_{1c} (%)			
Value at Baseline			
N	114	113	112
Mean (SD)	8.00 (1.010)	7.99 (0.940)	7.84 (0.911)
Value at Week 26 LOCF			
N	114	113	112
Mean (SD)	7.69 (1.146)	7.06 (0.737)	6.84 (0.803)
Change from Baseline			
N	114	113	112
Mean (SD)	-0.30 (0.860)	-0.92 (0.802)	-1.00 (0.806)
LS Mean (SE)	-0.26 (0.069)	-0.89 (0.069)	-1.03 (0.070)
P-value(minus Placebo)[a]		<0.001	<0.001
Diff. of LS Means (SE)		-0.62 (0.095)	-0.76 (0.096)
95% CI[a]		(-0.811;-0.437)	(-0.951;-0.575)

[a] Pairwise comparison: p-values and CIs are based on the ANCOVA model with treatment, AHA adjustment, Pioglitazone dose (30/45 mg) and baseline HbA_{1c}.

7.1.6.1.13. Results for other efficacy outcomes

- The proportion of subjects with HbA1c <7.0% at Week 26 was 53 (46.9%) subjects for 100 mg (p = 0.007 vs placebo), 72 (64.3%) for 300 mg (p <0.001) and 37 (32.5%) for placebo.
- The proportion of subjects with HbA1c <6.5% at Week 26 was 18 (15.9%) subjects for 100 mg, 36 (32.1%) for 300 mg and 13 (11.4%) for placebo.
- The mean (SD) change from baseline in FPG was -1.63 (2.005) mmol/L for canagliflozin 100 mg, -1.86 (1.980) mmol/L for 300 mg and 0.12 (1.885) mmol/L for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -1.63 (-2.050 to -1.208) mmol/L for 100 mg and -1.98 (-2.405 to -1.562) mmol/L for 300 mg.
- The mean (SD) change from baseline in HOMA2-%B was 15.69 (20.711) for canagliflozin 100 mg, 18.62 (18.951) for 300 mg and 1.25 (14.785) for placebo (p <0.001).
- Glycaemic rescue was required for one (0.9%) subject in the canagliflozin 100 mg group, none in the 300 mg and 14 (12.2%) in the placebo. The HR (95% CI) (canagliflozin compared to placebo) was 0.06 (0.01 to 0.48) for 100 mg and 0.0 (not calculable) for 300 mg.
- The mean (SD) % change from baseline in body weight was -2.8 (3.2) % for canagliflozin 100 mg, -3.8 (3.8) % for 300 mg and -0.1 (3.0) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -2.7 (-3.6 to -1.8) % for 100 mg and -3.7 (-4.6 to -2.8) % for 300 mg.
- The mean (SD) change from baseline in BMI was -0.91 (1.060) kg/m^2 for canagliflozin 100 mg, -1.27 (1.282) kg/m^2 for 300 mg and -0.05 (1.019) kg/m^2 for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.86 (-1.155 to -0.574) kg/m^2 for 100 mg and -1.21 (-1.503 to -0.920) kg/m^2 for 300 mg.
- The mean (SD) change from baseline in waist circumference was -2.63 (10.027) cm for canagliflozin 100 mg, -2.46 (5.510) cm for 300 mg and 0.29 (8.684) cm for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -2.96 (-5.119 to -0.799) cm for 100 mg and -2.70 (-4.846 to -0.557) cm for 300 mg.
- SBP decreased relative to placebo: mean (SD) change from baseline -5.13 (11.843) mmHg for canagliflozin 100 mg, -4.62 (11.925) mmHg for 300 mg and -1.67 (10.738) mmHg for placebo (p <0.05).

- DBP also decreased relative to placebo: mean (SD) change from baseline -2.83 (7.263) mmHg for canagliflozin 100 mg, -3.52 (8.311) mmHg for 300 mg and -1.18 (8.283) mmHg for placebo.
- There was a significant increase in HDL-C in the canagliflozin groups: mean (SD) % change from baseline 7.4 (14.7) % for canagliflozin 100 mg, 8.0 (14.9) % for 300 mg and 2.6 (13.5) % for placebo. There was a significant decrease in triglycerides in the canagliflozin groups: mean (SD) % change from baseline 3.4 (41.4) % for canagliflozin 100 mg, -1.0 (34.3) % for 300 mg and 15.9 (52.0) % for placebo. There was an increase in total cholesterol in the canagliflozin groups: mean (SD) change from baseline 4.5 (15.5) % for canagliflozin 100 mg, 7.1 (17.4) % for 300 mg and 0.9 (18.2) %for placebo. There was a significant increase in LDL-C in the canagliflozin groups: mean (SD) % change from baseline 7.9 (26.1) % for canagliflozin 100 mg, 13.0 (29.7) % for 300 mg and -0.9 (25.1) % for placebo. There was no significant difference in LDL-C/HDL-C ratio.

7.2. Supportive efficacy data

7.2.1. Other efficacy studies

7.2.1.1. Study DIA3008

Study DIA3008 was a long-term cardiovascular safety study. It was a Phase 3, randomised, double-blind, placebo-controlled, three parallel-group study to evaluate the safety, tolerability, and CV risk with canagliflozin plus standard of care relative to placebo plus standard of care in subjects with T2DM, on a wide range of current AHAs, who had either a history or high risk of CV disease. The study was conducted at 369 centres in 24 countries, including 17 in Australia from November 2009 to September 2011. The study included males or females with a diagnosis of T2DM with HbA1c level ≥7.0% to ≤10.5% at screening and, at screening, could be either (1) not on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent; eg, SU, MET, pioglitazone, AGI, GLP-1 analog, DPP-4 inhibitor, or insulin; history or high risk of CV disease defined on the basis of either (1) age ≥30 years with documented symptomatic atherosclerotic CV disease, or (2) age ≥50 years with two or more risk factors for CV disease determined at the screening visit.

The study treatments were:

1: Canagliflozin 100 mg

2: Canagliflozin 300 mg

3: Placebo

Subjects were randomised 1:1:1. Treatments were administered once daily orally prior to the first meal of the day. Planned treatment duration was for a minimum of 4 years. Subjects were allowed to take other AHAs during the study.

Although the study was primarily designed as a safety study, limited efficacy data were provided that related to subjects comedicated with insulin or SU for the canagliflozin 100 mg and 300 mg doses. The efficacy outcome variables were: HbA1c, body weight, FPG, HbA1c targets, SBP, HDL-C and triglycerides. Formal hypothesis tests were not performed and the statistical analysis was the within treatment change from baseline. Safety outcome variables were AEs, laboratory tests, hypoglycaemic events, ECGs, vital signs, physical examinations, and SMBG.

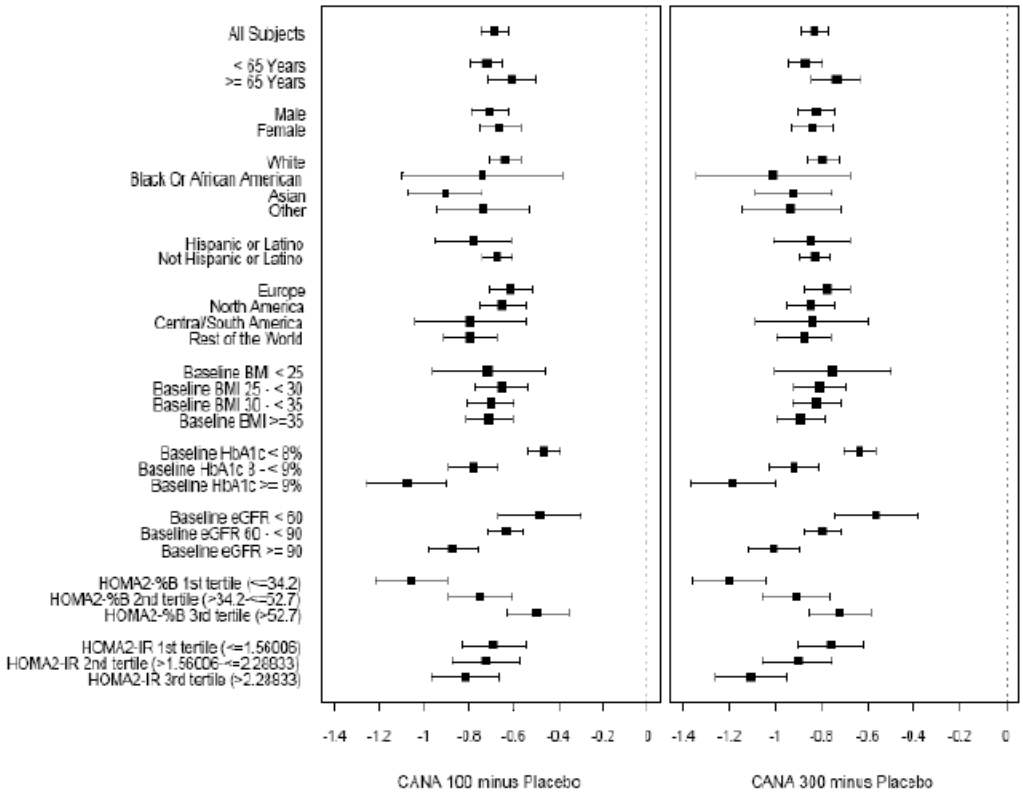
There were 7691 subjects screened, and 4330 subjects were randomised: 1445 to canagliflozin 100 mg, 1443 to 300 mg and 1442 to placebo. There was discontinuation in 188 (13.0%) subjects in the 100 mg group, 216 (15.0%) in the 300 mg and 246 (17.1%) in the placebo. There were 2860 (66.1%) males, 1467 (33.9%) females, and the age range was 32 to 87 years. The treatment groups were similar in demographic and anthropometric characteristics. The

treatment groups were similar in baseline diabetes characteristics. There were 342 subjects comedicated with SU and 2074 with insulin. For each of the strata of insulin or SU treatment the efficacy appeared to be slightly better for canagliflozin 300 mg than canagliflozin 100 mg.

7.3. Analyses performed across trials (pooled analyses and meta-analyses)

The Integrated Analysis of Efficacy examined the effects of demographic, anthropometric and baseline characteristics upon efficacy. There were no effects of age, gender, race or baseline BMI (Figure 2). However, efficacy was greater for subjects with poorer control at baseline, as measured by HbA1c.

Figure 2. HbA1c (%) by Subgroup: Placebo-Subtracted LS Mean Change (95% CI) From Baseline at Primary Assessment Timepoint - Pooled Placebo-Controlled Studies (ISE Phase 3 Studies: Modified Intent-to-Treat Analysis Set)



7.4. Evaluator's conclusions on clinical efficacy

For the primary efficacy outcome variable used in the pivotal studies (change from baseline in HbA1c):

- Efficacy as Monotherapy
  - Canagliflozin 300 mg and 100 mg were both superior to placebo over 26 weeks (Study DIA3005, Table 11). The mean (SD) change from baseline in HbA1c was -0.79 (0.906) % for canagliflozin 100 mg, -1.03 (0.863) % for 300 mg and 0.14 (1.057) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.91 (-1.088 to -0.729) % for 100 mg and -1.16 (-1.342 to -0.985) % for 300 mg. There was no subgroup effect on efficacy. Half of the subjects were "treatment naïve".

- Efficacy in Combination with MET
  - Over 26 weeks canagliflozin 300 mg and 100 mg were both superior to placebo but no formal comparison was performed with sitagliptin (Study DIA3006, Table 14). The mean (SD) change from baseline in HbA1c was -0.81 (0.650) % for canagliflozin 100 mg, -0.98 (0.885) % for 300 mg, -0.84 (0.835) for sitagliptin and 0.20 (0.895) % for placebo. The LS mean (95% CI) difference (active-placebo) was -0.62 (-0.758 to -0.481) % for 100 mg and -0.77 (-0.914 to -0.636) % for 300 mg ($p < 0.001$) and -0.66 (-0.795 to -0.516) % for sitagliptin. There was no subgroup effect on efficacy.
  - Canagliflozin 300 mg was superior to glimepiride, but canagliflozin 100 mg was not, over 52 weeks of treatment (Study DIA3009, Table 17). The mean (SD) change from baseline in HbA1c to Week 52 was -0.78 (0.820) % for canagliflozin 100 mg, -0.89 (0.831) % for 300 mg and -0.79 (0.947) % for glimepiride. The LS mean (95% CI) difference (canagliflozin-glimepiride) was -0.01 (-0.109 to 0.085) % for 100 mg and -0.12 (-0.217 to -0.023) % for 300 mg. The treatment benefit of canagliflozin 300 mg is of doubtful clinical significance. There was no subgroup effect on efficacy.
- Efficacy in combination with MET and SU:
  - Canagliflozin 300 mg and 100 mg were both superior to placebo over 26 weeks (Study DIA3002, Table 2). The mean (SD) change from baseline in HbA1c was -0.92 (0.985) % for canagliflozin 100 mg, -1.13 (0.936) % for 300 mg and -0.20 (0.915) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.71 (-0.904 to -0.524) % for 100 mg and -0.92 (-1.114 to -0.732) % for 300 mg. There was no subgroup effect on HbA1c.
  - Canagliflozin 300 mg was superior to sitagliptin 100 mg over 52 weeks (Study DIA3015, Table 5). The mean (SD) change from baseline in HbA1c was -1.0 (0.940) % for canagliflozin and -0.63 (1.022) % for sitagliptin. The LS mean (95% CI) difference (canagliflozin-sitagliptin) was -0.37 (-0.500 to -0.250) %. Effect was not demonstrated in the African American subgroup.
- Efficacy in combination with MET and Pioglitazone
  - Canagliflozin 300 mg and 100 mg were both superior to placebo (Study DIA3012, Table 23). The mean (SD) change from baseline in HbA1c was -0.92 (0.802) % for canagliflozin 100 mg, -1.00 (0.806) % for 300 mg and -0.30 (0.860) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.62 (-0.811 to -0.437) % for 100 mg and -0.76 (-0.951 to -0.575) % for 300 mg. There was no subgroup effect on efficacy.
- Efficacy as Add-On Therapy in Moderate Renal Failure
  - Canagliflozin 300 mg and 100 mg were both superior to placebo over 26 weeks (Study DIA3004, Table 8). The mean (SD) change from baseline in HbA1c was -0.37 (0.873) % for canagliflozin 100 mg, -0.52 (0.813) % for 300 mg and -0.13 (0.880) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.30 (-0.529 to -0.066) % ($p = 0.012$) for 100 mg and -0.40 (-0.635 to -0.174) % for 300 mg ($p < 0.001$).
- Efficacy in Older Subjects
  - Canagliflozin 300 mg and 100 mg were both superior to placebo over 26 weeks (Study DIA3010, Table 20). The mean (SD) change from baseline in HbA1c was -0.64 (0.747) % for canagliflozin 100 mg, -0.74 (0.753) % for 300 mg and -0.07 (0.922) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.57 (-0.708 to -0.436) % for 100 mg and -0.70 (-0.841 to -0.566) % for 300 mg. There was no subgroup effect on efficacy.

- Efficacy in combination with insulin:
  - Although efficacy was demonstrated for canagliflozin in comparison with placebo, this was in a selected population, in an 18 week substudy and where formal hypothesis testing had not been planned.

The glycaemic secondary efficacy outcome measures (HbA1c targets and FPG) were all supportive of the primary outcome. There were consistent decreases in body weight, BMI and waist circumference that were clinically and statistically significant. However, it is not clear that these changes persisted once treatment was ceased. There were consistent increases in HDL-C and in some studies total cholesterol and LDL-C also increased.

The study population was typical of patients with T2DM. The outcome measures used in the studies were standard for studies in T2DM. The statistical analyses were appropriate. The non-inferiority margin used in the non-inferiority studies was clinically significant.

8. Clinical safety

8.1. Studies providing evaluable safety data

Evaluable safety data were provided from all the clinical pharmacology, dose finding and efficacy studies. In addition there was one study [Information redacted] that provided evaluable safety data.

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected: AEs, laboratory tests, hypoglycaemic events, ECGs, vital signs, physical examinations and SMBG.

8.2. Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as a primary outcome.

8.3. Patient exposure

A total of 329 healthy subjects received canagliflozin in 14 completed single-dose Phase 1 trials and 397 healthy subjects received canagliflozin in 16 completed multiple-dose Phase 1 trials. In the four pooled Phase 1 trials in subjects with T2DM, 154 subjects received canagliflozin (104 subjects received <300 mg/day, 10 subjects received 300 mg/day, and 40 subjects received >300 mg/day). (Trials DIA1007, DIA1023, DIA1025, NAP1002) In one additional completed Phase 1 trial in subjects with T2DM (DIA1045), 37 subjects were dosed with canagliflozin.

Exposure in Phase 2 Studies:

- In Study DIA2001, there were 64 subjects exposed to canagliflozin 50 mg once daily, 64 to 100 mg once daily, 65 to 200 mg once daily, 64 to 300 mg once daily and 64 to 300 mg twice daily for up to 12 weeks.
- In Study TA7284-04, there were 82 subjects exposed to 50 mg daily, 74 to 100 mg, 77 to 200 mg and 75 to 300 mg for up to 12 weeks

In Phase 3 studies, the safety of canagliflozin was evaluated in 10,285 subjects with T2DM, including 3,092 subjects treated with canagliflozin 100 mg and 3,462 subjects treated with canagliflozin 300 mg, randomised and dosed in nine double-blind, placebo- or active-controlled Phase 3 clinical trials. In all Phase 3 studies, there were 6645 subjects exposed to canagliflozin with 5936 exposed for 6 months, 4723 for 12 months, 1200 for 18 months and 144 for 24 months (Table 26).

Table 26. Overall Exposure in Canagliflozin Phase 3 Program

	Exposure in Filing			
	Cana 100 mg	Cana 300 mg	Cana Total	Non-Cana
Total Number of Subject in Phase 3 Program	3,139	3,506	6,645	3,640
6-month Exposure	2,844	3,092	5,936	3,162
12-month Exposure	2,260	2,463	4,723	2,392
18-month Exposure	604	596	1,200	569
24-month Exposure	73	71	144	64

Note: The cutoff of Study DIA3015 is end of the study and the cutoff of the rest of the Phase 3 studies is 31 January. 2012. A subject is counted in the 6-month, 12-month, 18-month and 24-month exposure if his/her duration of treatment is greater or equal to 24 weeks, 50 weeks, 76 weeks, and 102 weeks.

A total of 703 subjects with moderate renal failure were exposed to canagliflozin: 338 to 100 mg daily and 365 to 300 mg daily (Table 27).

Table 27. Duration of Exposure to Study Medication - Regardless of Use of Rescue Medication (ISS Phase 3 Moderate Renal Impairment Dataset: Safety Analysis Set)

	Placebo (N=382)	Cana 100 mg (N=338)	Cana 300 mg (N=365)	All Cana (N=703)
Total duration of exposure (weeks)				
N	382	338	365	703
Category, n (%)				
<2 weeks	4 (1.0)	5 (1.5)	1 (0.3)	6 (0.9)
2-<6 weeks	13 (3.4)	4 (1.2)	12 (3.3)	16 (2.3)
6-<12 weeks	9 (2.4)	11 (3.3)	14 (3.8)	25 (3.6)
12-<16 weeks	12 (3.1)	5 (1.5)	7 (1.9)	12 (1.7)
16-<24 weeks	14 (3.7)	14 (4.1)	13 (3.6)	27 (3.8)
24-<28 weeks	116 (30.4)	112 (33.1)	109 (29.9)	221 (31.4)
28-<50 weeks	139 (36.4)	109 (32.2)	122 (33.4)	231 (32.9)
≥50 weeks	75 (19.6)	78 (23.1)	87 (23.8)	165 (23.5)
≥76 weeks	12 (3.1)	13 (3.8)	8 (2.2)	21 (3.0)
Mean (SD)	35.57 (17.612)	37.41 (18.443)	37.31 (18.339)	37.36 (18.376)
Median	30.57	30.79	32.14	31.43
Range	(0.1;89.4)	(0.1;90.4)	(1.3;91.4)	(0.1;91.4)
Total Exposure (subject years)	260.4	242.3	261.0	503.3

Note: Total duration = Treatment duration = last dose date - first dose date + 1(in days).

Overall, there were 270 subjects aged 65 to <75 years exposed to canagliflozin; 138 to 100 mg daily and 132 to 300 mg daily. There were 38 subjects aged ≥75 years exposed to canagliflozin: 21 to 100 mg daily and 17 to 300 mg daily.

Exposure in individual Phase 3 Studies:

- In Study DIA3002, summarised in Table 2, in subjects treated with MET and SU there were 157 subjects exposed to canagliflozin 100 mg, 128 (82%) for ≥24 weeks, and 156 to canagliflozin 300 mg, 128 (82%) for ≥24 weeks.
- In Study DIA3004, summarised in Table 8, there were 90 subjects with moderate renal failure exposed to canagliflozin 100 mg, with 78 (86.7%) exposed for ≥24 weeks, and 89 to 300 mg, with 82 (92.1%) exposed for ≥24 weeks.
- In Study DIA3005, summarised in Table 11, there were 195 subjects exposed to canagliflozin 100 mg in monotherapy, with 168 (86.2%) exposed for ≥24 weeks, and 197 exposed to 300 mg, with 171 (86.8%) exposed for ≥24 weeks.
- In Study DIA3006, summarised in Table 14, there were 368 subjects exposed to canagliflozin 100 mg and MET, with 317 (86.1%) exposed for ≥24 weeks, and 367 exposed to 300 mg and MET, with 328 (89.4%) exposed for ≥24 weeks.

- In Study DIA3008, there were 1445 subjects exposed to canagliflozin 100 mg in comedication with other AHAs, with 542 exposed for ≥50 weeks, and 1441 exposed to 300 mg, with 515 exposed for ≥50 weeks.
- In Study DIA3009, summarised in Table 17, there were 483 subjects exposed to canagliflozin 100 mg in combination with MET, with 367 treated for ≥50 weeks, and 485 exposed to 300 mg, with 361 (74.4%) exposed for ≥50 weeks.
- In Study DIA3010, summarised in Table 20, there were 241 subjects aged ≥55 years treated with canagliflozin 100 mg in comedication with other AHAs, with 219 (90.9%) treated for ≥24 weeks, and 236 treated with 300 mg, with 206 (87.3%) treated for ≥24 weeks.
- In Study DIA3012, summarised in Table 23, there were 113 subjects treated with canagliflozin 100mg in combination with MET and pioglitazone, 103 (91.2%) of whom were treated for ≥24 weeks, and 114 treated with 300 mg, 99 (86.8%) of whom were treated for ≥24 weeks.
- In Study DIA3015, summarised in Table 4, there were 377 subjects treated with canagliflozin 300 mg in combination with MET and SU, with 252 (66.8%) treated for ≥50 weeks.

Additional studies:

- Study OBE2001 was a Phase 2b, randomised, double-blind, placebo-controlled, parallel-group, multicentre, dose-ranging design with four treatment groups that evaluated the safety and efficacy of canagliflozin (50, 100, and 300 mg once daily) versus placebo administered over 12 weeks in non-diabetic overweight and obese subjects. There were 98 subjects exposed to 50 mg, 93 to 100 mg and 96 to 300 mg for up to 12 weeks.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal studies

In Study DIA3002 (Table 2), TEAEs were reported in 90 (57.3%) subjects in the canagliflozin 100 mg group, 97 (62.2%) in the 300 mg and 100 (64.1%) in the placebo. There was a higher incidence of diarrhoea in the canagliflozin 300 mg group than the other two groups (6% vs 3%); and a higher incidence of vaginal mycotic infections in the canagliflozin groups compared with placebo (5% vs 1%).

In Study DIA3004 (Table 8) TEAEs were reported in 70 (77.8%) subjects in the canagliflozin 100 mg group, 66 (74.2%) in the 300 mg group and 66 (73.3%) in the placebo. Hypoglycaemia was more common in the canagliflozin groups: 13.4% vs 4.4%.

In Study DIA3005 (Table 11) TEAEs were reported in 118 (60.5%) subjects in the canagliflozin 100 mg group, 118 (59.9%) in the 300 mg and 94 (49.0%) in the placebo. The pattern of TEAEs was similar for the three groups. In the high glycaemic substudy TEAEs were reported in 29 (61.7%) subjects in the canagliflozin 100 mg group and 22 (50.0%) in the 300 mg.

In Study DIA3006 (Table 14) TEAEs were reported in 225 (61.1%) subjects in the canagliflozin 100 mg group, 204 (55.6%) in the 300 mg, 199 (54.4%) in the sitagliptin and 104 (56.8%) in the placebo. The pattern of TEAEs was similar for the four treatment groups.

In Study DIA3009 (Table 17) TEAEs were reported in 310 (64.2%) subjects in the canagliflozin 100 mg group, 332 (68.5%) in the 300 mg and 326 (67.6%) in the glimepiride. Vulvovaginal pruritus was more common in the canagliflozin groups than glimepiride.

In Study DIA3010 (Table 20), to Week 26, TEAEs were reported in 174 (72.2%) older subjects in the canagliflozin 100 mg group, 184 (78.0%) in the 300 mg and 174 (73.4%) in the placebo.

The rate of UTI increased with increasing dose of canagliflozin: nine (3.8%) subjects in the placebo group, 14 (5.8%) in the canagliflozin 100 mg, and 17 (7.2%) in the 300 mg.

In Study DIA3012 (Table 23) TEAEs were reported in 67 (59.3%) subjects in the canagliflozin 100 mg group, 75 (65.8%) in the 300 mg and 74 (64.3%) in the placebo. Renal AEs were more common in the canagliflozin groups.

In Study DIA3015 (Table 5) TEAEs were reported in 289 (76.7%) subjects in the canagliflozin group and 293 (77.5%) in the sitagliptin. Vulvovaginal pruritus was more common in the canagliflozin group: 15 (4.0%) subjects compared with one (0.3%) in the sitagliptin.

Overall in the placebo controlled studies, in the canagliflozin groups, vaginal mycotic infections (2.9% subjects) and pollakiuria (3.7%) occurred at a greater rate than in the placebo groups (Table 28).

Table 28. Adverse Events in At Least 2% of Subjects in Any Treatment Group by Body System and Preferred Term - Prior to Use of Rescue Medication (ISS Phase 3 Placebo- Controlled Studies Dataset: Safety Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	Placebo (N=646) n (%)	Cana 100 mg (N=833) n (%)	Cana 300 mg (N=834) n (%)	All Cana (N=1667) n (%)
Total no. subjects with the AEs	371 (57.4)	500 (60.0)	494 (59.2)	994 (59.6)
Gastrointestinal Disorders	88 (13.6)	124 (14.9)	128 (15.3)	252 (15.1)
Constipation	6 (0.9)	15 (1.8)	19 (2.3)	34 (2.0)
Diarrhoea	28 (4.3)	26 (3.1)	37 (4.4)	63 (3.8)
Nausea	9 (1.4)	18 (2.2)	18 (2.2)	36 (2.2)
Infections and Infestations	180 (27.9)	247 (29.7)	241 (28.9)	488 (29.3)
Influenza	20 (3.1)	19 (2.3)	16 (1.9)	35 (2.1)
Nasopharyngitis	30 (4.6)	37 (4.4)	44 (5.3)	81 (4.9)
Sinusitis	11 (1.7)	17 (2.0)	8 (1.0)	25 (1.5)
Upper Respiratory Tract Infection	31 (4.8)	38 (4.6)	38 (4.6)	76 (4.6)
Urinary Tract Infection	23 (3.6)	45 (5.4)	33 (4.0)	78 (4.7)
Vulvovaginal Mycotic Infection	4 (0.6)	25 (3.0)	23 (2.8)	48 (2.9)
Metabolism and Nutrition Disorders	41 (6.3)	51 (6.1)	41 (4.9)	92 (5.5)
Hyperglycaemia	16 (2.5)	6 (0.7)	1 (0.1)	7 (0.4)
Hypoglycaemia	13 (2.0)	21 (2.5)	19 (2.3)	40 (2.4)
Musculoskeletal and Connective Tissue Disorders	83 (12.8)	93 (11.2)	104 (12.5)	197 (11.8)
Arthralgia	23 (3.6)	23 (2.8)	19 (2.3)	42 (2.5)
Back Pain	16 (2.5)	23 (2.8)	34 (4.1)	57 (3.4)
Nervous System Disorders	47 (7.3)	74 (8.9)	65 (7.8)	139 (8.3)
Headache	27 (4.2)	34 (4.1)	29 (3.5)	63 (3.8)
Renal and Urinary Disorders	13 (2.0)	61 (7.3)	52 (6.2)	113 (6.8)
Pollakiuria	4 (0.6)	35 (4.2)	26 (3.1)	61 (3.7)
Respiratory, Thoracic and Mediastinal Disorders	41 (6.3)	42 (5.0)	42 (5.0)	84 (5.0)
Cough	15 (2.3)	12 (1.4)	13 (1.6)	25 (1.5)

8.4.1.2. Other studies

In Study DIA2001, TEAEs were reported in 26 (40%) subjects in the placebo group, 32 (50%) in the 50 mg, 30 (47%) in the 100 mg, 26 (40%) in the 200 mg, 26 (41%) in the 300 mg, 36 (56%) in the 300 mg twice daily, and 23 (35%) in the sitagliptin. Nausea, abdominal pain and vomiting appeared to be dose-related side effects in the canagliflozin groups.

In Study TA7284-04, there were 43 TEAEs were reported in 26 (34.7%) subjects in the placebo group, 52 in 37 (45.1%) the 50-mg group, 60 in 34 (45.9%) in the 100-mg group, 61 in 38 (49.4%) in the 200-mg group, and 50 in 34 (45.3%) in the 300-mg group. TEAEs did not appear to increase with dose.

In Study DIA3008 TEAEs were reported in 1026 (71.0%) subjects in the canagliflozin 100 mg group, 1057 (73.4%) in the 300 mg group and 1003 (69.6%) in the placebo group. Overall the pattern of TEAEs was similar for the three treatment groups.

In Study OBE2001 TEAEs were reported in 73 (74%) subjects in the 50 mg group, 54 (58%) in the 100 mg, 60 (63%) in the 300 mg and 54 (61%) in the placebo.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal studies

In Study DIA3002 (Table 2), treatment related TEAEs were reported in 35 (22.3%) subjects in the canagliflozin 100 mg group, 47 (30.1%) in the 300 mg and 22 (14.1%) in the placebo. The TEAEs most commonly attributed to canagliflozin were vulvovaginal infections and UTIs.

In Study DIA3004 (Table 8) treatment related TEAEs were reported in 23 (25.6%) subjects in the canagliflozin 100 mg group, 29 (32.6%) in the 300 mg group and 20 (22.2%) in the placebo. Events occurring in more than two subjects treated with canagliflozin were: UTI (five [2.8%] canagliflozin subjects, four [4.4%] placebo), polyalkiuria (six [3.4%], one [1.1%] respectively), renal impairment (three [1.7%], two [2.2%] respectively), increased urine output (three [1.7%], one [1.1%] respectively), and arthralgia (three [1.7%], none respectively).

In Study DIA3005 (Table 11) treatment related TEAEs were reported in 33 (16.9%) subjects in the canagliflozin 100 mg group, 50 (25.4%) in the 300 mg and 18 (9.4%) in the placebo. Vulvovaginal and genital pruritus were more common in the canagliflozin groups (eight subjects vs none in the placebo).

In Study DIA3006 (Table 14) treatment related TEAEs were reported in 81 (22.0%) subjects in the canagliflozin 100 mg group, 64 (17.4%) in the 300 mg, 47 (12.8%) in the sitagliptin and 18 (9.8%) in the placebo. Polyalkiuria, UTI and vulvovaginitis were more common with canagliflozin than either placebo or sitagliptin.

In Study DIA3009 (Table 17) treatment related TEAEs were reported in 118 (24.4%) subjects in the canagliflozin 100 mg group, 145 (29.9%) in the 300 mg and 109 (22.6%) in the glimepiride. Male and female superficial genital infections, and thirst were more common with canagliflozin than glimepiride. Thirst was reported in 2% of canagliflozin subjects.

In Study DIA3010 (Table 20), to Week 26, treatment related TEAEs were reported in 64 (26.6%) subjects in the canagliflozin 100 mg group, 79 (33.5%) in the 300 mg and 66 (27.8%) in the placebo. Polyuria and vulvovaginitis were more common in the canagliflozin groups.

In Study DIA3012 (Table 23) treatment related TEAEs were reported in 21 (18.6%) subjects in the canagliflozin 100 mg group, 30 (26.3%) in the 300 mg and 27 (23.5%) in the placebo. Pollakiuria was more common in the canagliflozin groups.

In Study DIA3015 (Table 5) treatment related TEAEs were reported in 128 (34.0%) subjects in the canagliflozin group and 105 (27.8%) in the sitagliptin. Vulvovaginal AEs were more common with canagliflozin.

8.4.2.2. Other studies

In Study DIA3008 treatment related TEAEs were reported in 389 (26.9%) subjects in the canagliflozin 100 mg group, 468 (32.5%) in the 300 mg group and 252 (17.5%) in the placebo group. Balinitis and vulvovaginitis were more common with canagliflozin.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal studies

In Study DIA3002 (Table 2) there were no reported deaths. SAEs were reported in five (3.2%) subjects in the canagliflozin 100 mg group, six (3.8%) in the 300 mg and nine (5.8%) in the placebo. There was no apparent pattern to the SAEs.

In Study DIA3004 (Table 8) there were two deaths: one in the canagliflozin 100 mg group (acute pulmonary oedema) and one in the placebo (septic shock). There was an additional off-treatment death in a subject in the 100 mg group, 133 days after ceasing treatment (myocardial infarction). SAEs were reported in ten (11.2%) subjects in the canagliflozin 100 mg group, nine (10.0%) in the 300 mg group and twelve (13.3%) in the placebo. Acute renal failure was reported as an SAE in two canagliflozin treated subjects.

In Study DIA3005 (Table 11) there were two deaths: one in the canagliflozin 100 mg group (pneumonia/ septic shock/ acute renal failure/ ischemic hepatitis) and one in the placebo (brain haemorrhage). SAEs were reported in eight (4.1%) subjects in the canagliflozin 100 mg group, two (1.0%) in the 300 mg and four (2.1%) in the placebo. There was no apparent pattern to the SAEs.

In Study DIA3006 (Table 14) there was one death in the canagliflozin 300 mg group (cerebellar and brainstem stroke) and one in the placebo (stomach cancer). SAEs were reported in twelve (3.3%) subjects in the canagliflozin 100 mg group, ten (2.7%) in the 300 mg, eight (2.2%) in the sitagliptin and four (2.2%) in the placebo. There was no apparent pattern to the SAEs.

In Study DIA3009 (Table 17) there were four deaths: two (0.4%) in the canagliflozin 300 mg group (fall and myocardial infarction/ anaemia/ severe kidney disease) and two (0.4%) in the glimepiride (cervical cancer, myocardial infarction). SAEs were reported in 24 (5.0%) subjects in the canagliflozin 100 mg group, 25 (5.2%) in the 300 mg and 38 (7.9%) in the glimepiride. There was no apparent pattern to the SAEs.

In Study DIA3010 (Table 20), to Week 26, there were no deaths reported. SAEs were reported in ten (4.1%) subjects in the canagliflozin 100 mg group, eight (3.4%) in the 300 mg and twelve (5.1%) in the placebo. The pattern of SAEs was similar for the three treatment groups.

In Study DIA3012 (Table 23) there were no deaths reported during the first 26 weeks of the study. SAEs were reported in three (2.7%) subjects in the canagliflozin 100 mg group, four (3.5%) in the 300 mg and five (4.3%) in the placebo. There was no apparent pattern to the SAEs.

In Study DIA3015 (Table 5) there were two deaths in the canagliflozin group: respiratory/cardiac arrest and cardiac arrest. SAEs were reported in 24 (6.4%) subjects in the canagliflozin group and 21 (5.6%) in the sitagliptin. There was no apparent pattern to the SAEs.

8.4.3.2. Other studies

In Study DIA2001 there were no deaths. There were six SAEs, with one in each treatment group except for sitagliptin where there were none.

In Study TA7284-04 no deaths were reported. There was one SAE in the 50 mg group: lung adenocarcinoma.

In Study DIA3008 death was reported in ten (0.7%) subjects in the canagliflozin 100 mg group (seven cardiovascular, one hepatic cancer, one neurogenic shock, one bronchopneumonia), ten (0.7%) in the 300 mg group (eight cardiovascular, one lung cancer, one amyotrophic lateral sclerosis) and 13 (0.9%) in the placebo group (11 cardiovascular, one pancreatic carcinoma, one pulmonary embolism). SAEs were reported in 166 (11.5%) subjects in the canagliflozin 100 mg group, 183 (12.7%) in the 300 mg group and 174 (12.1%) in the placebo group. There was a higher rate of renal failure and renal impairment in the canagliflozin groups compared to placebo (0.2% vs 0.1% respectively).

In Study OBE2001 there were no deaths. One SAE was reported in the canagliflozin group 25 days after the last dose (arthralgia).

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

In Study DIA3002 (Table 2), DAEs were reported in nine (5.7%) subjects in the canagliflozin 100 mg group, nine (5.8%) in the 300 mg and five (3.2%) in the placebo. Urogenital infections were more common reasons for discontinuation in the canagliflozin groups.

In Study DIA3004 (Table 8) DAEs were reported in three (3.3%) subjects in the canagliflozin 100 mg group, two (2.2%) in the 300 mg group and five (5.6%) in the placebo. There was no apparent pattern to the DAEs.

In Study DIA3005 (Table 11) DAEs were reported in six (3.1%) subjects in the canagliflozin 100 mg group, four (2.0%) in the 300 mg and two (1.0%) in the placebo. There was no apparent pattern to the DAEs.

In Study DIA3006 (Table 14) DAEs were reported in 18 (4.9%) subjects in the canagliflozin 100 mg group, twelve (3.3%) in the 300 mg, seven (1.9%) in the sitagliptin and seven (3.8%) in the placebo. Renal AEs were more common reasons for discontinuing in the canagliflozin groups.

In Study DIA3009 (Table 17) DAEs were reported in 25 (5.2%) subjects in the canagliflozin 100 mg group, 32 (6.6%) in the 300 mg and 18 (5.8%) in the glimepiride. There was a higher incidence of genital pruritus in the canagliflozin groups.

In Study DIA3010 (Table 20), to Week 26, DAEs were reported in five (2.1%) subjects in the canagliflozin 100 mg group, 17 (7.2%) in the 300 mg and ten (4.2%) in the placebo. There was no apparent pattern to the DAEs.

In Study DIA3012 (Table 23) DAEs were reported in three (2.7%) subjects in the canagliflozin 100 mg group, five (4.4%) in the 300 mg and six (5.2%) in the placebo. Two subjects in the canagliflozin 100 mg group discontinued because of decreased GFR.

In Study DIA3015 (Table 5) DAEs were reported in 20 (5.3%) subjects in the canagliflozin group and eleven (2.9%) in the sitagliptin. Seven (1.9%) subjects in the canagliflozin group discontinued because of skin disorders, compared with none in the sitagliptin.

8.4.4.2. Other studies

In Study DIA2001, DAE was reported for two (3%) subjects in the placebo group, one (2%) in the 50 mg, three (5%) in the 100 mg, one (2%) in the 200 mg, two (3%) in the 300 mg, two (3%) in the 300 mg twice daily and none in the sitagliptin.

In Study TA7284-04, there were four DAEs: one in the 50 mg group, two in the 100 mg and one in the 300 mg.

In Study DIA3008 DAEs were reported in 59 (4.1%) subjects in the canagliflozin 100 mg group, 92 (6.4%) in the 300 mg group and 51 (3.5%) in the placebo group. There was no apparent pattern to the DAEs.

In Study OBE2001 DAE was reported for four (4%) subjects in the canagliflozin 50 mg group, three (3%) in the 100 mg, four (4%) in the 300 mg and none in the placebo. There was no apparent pattern to the DAEs.

8.5. Laboratory tests

8.5.1. Liver function

8.5.1.1. Pivotal studies

In Study DIA3002 (Table 2) one subject in the canagliflozin 100 mg group and two in the placebo had elevations in ALT.

In Study DIA3004 (Table 8) one subject in the canagliflozin 100 mg group had elevated ALT >8xULN and one had elevated AST >8xULN.

In Study DIA3005 (Table 11) there was one subject in the canagliflozin 100 mg group and one in the placebo with an elevation in ALT >3xULN. In the high glycaemic substudy one subject in the canagliflozin 300 mg group had ALT >8xULN and AST >5xULN, persisting despite withdrawal of study drug.

In Study DIA3006 (Table 14) ALT >3xULN was reported in three (0.8%) subjects in the canagliflozin 100 mg group, two (0.6%) in the 300 mg, three (0.8%) in the sitagliptin and one (0.6%) in the placebo.

In Study DIA3009 (Table 17) ALT >3xULN was reported in five (1.1%) subjects in the canagliflozin 100 mg group, four (0.9%) in the 300 mg, and two (0.4%) in the glimepiride.

In Study DIA3010 (Table 20) ALT >3xULN was reported in one (0.4%) subjects in the canagliflozin 100 mg group and one (0.4%) in the placebo.

In Study DIA3012 (Table 23) ALT >3xULN was reported in one (0.9%) subject in the canagliflozin 100 mg group.

In Study DIA3015 (Table 5) ALT >3xULN was reported in two (0.5%) subjects in the canagliflozin group and six (1.7%) in the sitagliptin.

8.5.1.2. Other studies

In Study DIA2001, one subject in the 100 mg group had elevated ALT, AST and GGT that resolved during treatment.

In Study TA7284-04 one subject was reported with elevated ALT.

In Study DIA3008 ALT >3xULN was reported in nine (0.6%) subjects in the canagliflozin 100 mg group, seven (0.5%) in the 300 mg, and three (0.2%) in the placebo. AST >3xULN was reported in seven (0.5%) subjects in the canagliflozin 100 mg group, four (0.3%) in the 300 mg, and two (0.1%) in the placebo.

Altogether in the development program there was five (0.15%) subjects in the canagliflozin 100 mg groups, three (0.08%) in the 300 mg and eight (0.11%) in the comparator with ALT or AST ≥3xULN and bilirubin ≥2xULN. None of the episodes in the canagliflozin groups were considered to be definite or probable causality.

In Study OBE2001 one subject in the canagliflozin 50 mg group had elevation in ALT and AST <2xULN and GGT >3x and ≤5xULN without increases in total bilirubin or ALP.

8.5.2. Kidney function

8.5.2.1. Pivotal studies

In Study DIA3002 (Table 2) three subjects in the canagliflozin group had a decrease in GFR >30% from baseline.

In Study DIA3004 (Table 8) three subjects in the canagliflozin groups had elevated serum creatinine, but overall the rate or renal failure was similar to placebo. The mean (SD) change in GFR was -3.44 (6.693) mL/min/1.73m^2 in the canagliflozin 100 mg group, -3.56 (7.458) mL/min/1.73m^2 in the 300 mg and -1.14 (4.875) mL/min/1.73m^2 in the placebo. There were also some changes in serum calcium, magnesium and phosphate in the canagliflozin group.

In Study DIA3005 (Table 11) there were four (2.2%) subjects in the canagliflozin 100 mg group, seven (3.7%) in the 300 mg and four (2.2%) in the placebo with eGFR <80 mL/min/1.73m^2 and decrease >30% from baseline.

In Study DIA3006 (Table 14) there were eight (2.2%) subjects in the canagliflozin 100 mg group, 17 (4.8%) in the 300 mg, 15 (4.2%) in the sitagliptin and three (1.7%) in the placebo with eGFR <80 mL/min/1.73m^2 and decrease >30% from baseline.

In Study DIA3009 (Table 17) there were 19 (4.0%) subjects in the canagliflozin 100 mg group, 24 (5.1%) in the 300 mg and 25 (5.3%) in the glimepiride with eGFR <80 mL/min/1.73m^2 and decrease >30% from baseline.

In Study DIA3010 (Table 20) there were eight (3.4%) subjects in the canagliflozin 100 mg group, twelve (5.3%) in the 300 mg and five (2.2%) in the placebo with eGFR <80 mL/min/1.73m^2 and decrease >30% from baseline.

In Study DIA3012 (Table 23) there were three (2.7%) subjects in the canagliflozin 100 mg group, three (2.8%) in the 300 mg and four (3.6%) in the placebo with eGFR <80 mL/min/1.73m^2 and decrease >30% from baseline.

In Study DIA3015 (Table 5) there were 32 (8.7%) subjects in the canagliflozin 300 mg group and 23 (6.3%) in the sitagliptin with eGFR <80 mL/min/1.73m^2 and decrease >30% from baseline.

Overall in the placebo controlled studies there were 16 (2%) subjects in the canagliflozin 100 mg group, 33 (4.1%) in the 300 mg and 13 (2.1%) in the placebo with eGFR <80 mL/min/1.73m^2 and decrease >30% from baseline. Acute renal failure was reported in two (0.2%) subjects in the canagliflozin 100 mg group, one (0.1%) in the 300 mg and none in the placebo.

8.5.2.2. Other studies

In Study TA7284-04 there were no clinically significant abnormalities in renal function.

In Study DIA3008 renal impairment/failure was twice as likely with canagliflozin than with placebo. Renal AEs were reported in 38 (2.6%) subjects in the canagliflozin 100 mg group, 53 (3.7%) in the 300 mg group and 19 (1.3%) in the placebo group. There were 67 (4.8%) subjects in the canagliflozin 100 mg group, 99 (7.2%) in the 300 mg, and 60 (4.3%) in the placebo with eGFR <80 mL/min/1.73m^2 and decrease >30% from baseline.

8.5.3. Other clinical chemistry

In Study DIA3006 there was a mean decrease in serum urate of 9.9% in the canagliflozin 100 mg group and 9.6% in the 300 mg. In Study DIA3015 there was a mean decrease in serum urate of -25.88 µmol/L in the canagliflozin group.

8.5.4. Haemoglobin

In Study DIA3002 (Table 2) 15 subjects in the canagliflozin group had haemoglobin elevate >20 g/L compared with none in the placebo. In Study DIA3005 (Table 11) there were 14 (7.7%) subjects in the canagliflozin 100 mg group, twelve (6.5%) in the 300 mg and three (1.8%) with ≥20 g/L increase in haemoglobin from baseline. In Study DIA3006 (Table 14) there were 17 (4.9%) subjects in the canagliflozin 100 mg group, 17 (4.9%) in the 300 mg, one (0.3%) in the sitagliptin and two (1.2%) in the placebo with ≥20 g/L increase in haemoglobin from baseline. In Study DIA3008 there were 84 (6.2%) subjects in the canagliflozin 100 mg group, 89 (6.8%) in the 300 mg, and 15 (1.2%) in the placebo with ≥20 g/L increase in haemoglobin from baseline. In Study DIA3009 (Table 17) there were 36 (8.0%) subjects in the canagliflozin 100 mg group, 37 (8.5%) in the 300 mg, and six (1.4%) in the glimepiride with ≥20 g/L increase in haemoglobin from baseline. In Study DIA3010 (Table 20) there were eleven (4.7%) subjects in the canagliflozin 100 mg group, 13 (5.8%) in the 300 mg, and three (1.4%) in the glimepiride with ≥20 g/L increase in haemoglobin from baseline. In Study DIA3012 (Table 23) there were eight (7.3%) subjects in the canagliflozin 100 mg group, six (5.7%) in the 300 mg, and one (0.9%) in the placebo with ≥20 g/L increase in haemoglobin from baseline. In Study DIA3015

(Table 5) there were 26 (7.4%) subjects in the canagliflozin group and seven (3.9%) in the sitagliptin with ≥20 g/L increase in haemoglobin from baseline.

8.5.5. Other haematology

There were no other trends in haematology values across the studies.

8.5.6. Hypoglycaemia

8.5.6.1. Pivotal studies

In Study DIA3002 (Table 2) hypoglycaemia was reported in 43 (27.4%) subjects in the canagliflozin 100 mg group, 47 (30.1%) in the 300 mg and 24 (15.4%) in the placebo. Severe hypoglycaemia was reported in one subject in the 100 mg group and one in the placebo.

In Study DIA3004 (Table 8) hypoglycaemia was reported in 45 (52.9%) subjects in the canagliflozin 100 mg group, 44 (51.2%) in the 300 mg and 32 (36.4%) in the placebo. Severe hypoglycaemia was reported in four (4.7%) subjects in the canagliflozin 100 mg group, one (1.2%) in the 300 mg and one (1.1%) in the placebo.

In Study DIA3005 (Table 11) hypoglycaemia was reported in seven (3.6%) subjects in the canagliflozin 100 mg group, six (3.0%) in the 300 mg and five (2.6%) in the placebo. Severe hypoglycaemia was not reported for any subject in the study.

In Study DIA3006 (Table 14) hypoglycaemia was reported in 16 (4.3%) subjects in the canagliflozin 100 mg group, 17 (4.6%) in the 300 mg, five (1.4%) in the sitagliptin and three (1.6%) in the placebo. Severe hypoglycaemia was reported in one (0.3%) subject in the canagliflozin 100 mg group and one (0.3%) in the 300 mg.

In Study DIA3009 (Table 17) hypoglycaemia was reported in 27 (5.6%) subjects in the canagliflozin 100 mg group, 24 (4.9%) in the 300 mg, and 165 (34.2%) in the glimepiride. Severe hypoglycaemia was reported in two (0.4%) subjects in the canagliflozin 100 mg group, three (0.6%) in the 300 mg and 15 (3.1%) in the glimepiride.

In Study DIA3010 (Table 20) in subjects not on AHA at baseline hypoglycaemia was reported in four (6.7%) subjects in the canagliflozin 100 mg group, three (4.8%) in the 300 mg, and two (3.2%) in the placebo; and severe hypoglycaemia was reported in one (1.7%) in the canagliflozin 100 mg group. In subjects on AHA associated with hypoglycaemia at baseline, hypoglycaemia was reported in 78 (43.1%) subjects in the canagliflozin 100 mg group, 82 (47.4%) in the 300 mg, and 66 (37.7%) in the placebo; and severe hypoglycaemia was reported two (1.1%) subjects in the canagliflozin 100 mg group, one (0.6%) in the 300 mg, and seven (4.0%) in the placebo.

In Study DIA3012 (Table 23) hypoglycaemia was reported in three (2.7%) subjects in the canagliflozin 100 mg group, six (5.3%) in the 300 mg, and three (2.6%) in the placebo. There were no subjects reported with severe hypoglycaemia.

In Study DIA3015 (Table 5) hypoglycaemia was reported in 163 (43.2%) subjects in the canagliflozin 100 and 154 (40.7%) in the sitagliptin. Severe hypoglycaemia was reported in 15 (4.0%) subjects in the canagliflozin 100 and 13 (3.4%) in the sitagliptin.

8.5.6.2. Other studies

In Study DIA2001 hypoglycaemia was reported in one (2%) subject in the placebo group, none in the 50 mg, one (2%) in the 100 mg, four (6%) in the 200 mg, none in the 300 mg, two (3%) in the 300 mg twice daily and three (5%) in the sitagliptin.

In Study TA7284-04, hypoglycaemia was reported in no subject in the placebo group, three (3.7%) in the 50 mg, two (2.7%) in the 100 mg, two (2.6%) in the 200 mg and one (1.3%) in the 300 mg.

In Study DIA3008 hypoglycaemia was reported in 388 (31.4%) subjects in the canagliflozin 100 mg group, 429 (34.6%) in the 300 mg, and 307 (25.5%) in the placebo. Severe hypoglycaemia was reported in 12 (1.0%) subjects in the canagliflozin 100 mg group, 21 (1.7%) in the 300 mg and 18 (1.5%) in the placebo. In subjects not taking either insulin or SU hypoglycaemia was reported in nine (4.3%) subjects in the canagliflozin 100 mg group, six (3.0%) in the 300 mg and four (1.7%) in the placebo; and only one subject in the 300 mg group was reported with severe hypoglycaemia.

8.5.7. Electrocardiograph

8.5.7.1. Pivotal studies

In Study DIA3002 (Table 2) three (2.4%) subjects in the canagliflozin 100 mg group, two (1.7%) in the 300 mg and none in the placebo had an increase in QTc interval >30 ms and <60 ms.

In Study DIA3004 (Table 8) five (7.6%) subjects in the canagliflozin 100 mg group, one (1.4%) in the 300 mg and five (8.5%) in the placebo had an increase in QTc interval >30 ms and <60 ms.

In Study DIA3005 (Table 11) seven (4.4%) subjects in the canagliflozin 100 mg group, six (3.6%) in the 300 mg and four (3.3%) in the placebo had an increase in QTc interval >30 ms and <60 ms.

In Study DIA3006 (Table 14) nine (2.9%) subjects in the canagliflozin 100 mg group, nine (2.8%) in the 300 mg, seven (2.4%) in the sitagliptin and none in the placebo had an increase in QTc interval >30 ms and <60 ms.

In Study DIA3009 (Table 17) four (1.1%) subjects in the canagliflozin 100 mg group, four (1.2%) in the 300 mg, and eight (2.4%) in the glimepiride had an increase in QTc interval >30 ms and <60 ms.

In Study DIA3010 (Table 20) six (2.8%) subjects in the canagliflozin 100 mg group, six (3.1%) in the 300 mg, and three (1.8%) in the placebo had an increase in QTc interval >30 ms and <60 ms.

In Study DIA3012 (Table 23) two (2.0%) subjects in the canagliflozin 100 mg group, two (2.2%) in the 300 mg, and five (6.8%) in the placebo had an increase in QTc interval >30 ms.

In Study DIA3015 (Table 5) twelve (4.9%) subjects in the canagliflozin group and six (2.9%) in the sitagliptin had an increase in QTc interval >30 ms and <60 ms.

8.5.7.2. Other studies

A thorough QT study conducted at the 300 mg (therapeutic) and 1200 mg (supratherapeutic) dose levels, administered as single oral doses, did not demonstrate any significant increase in QTc at either dose level, at any time point compared with placebo (Study DIA1010). At all time points the upper 97.5% CI for the difference in QTc (canagliflozin-placebo) was <10 ms. The positive control (moxifloxacin) did demonstrate prolongation of the QTc.

In Study DIA3008 15 (3.0%) subjects in the canagliflozin 100 mg group, nine (1.9%) in the 300 mg, and four (0.8%) in the placebo had an increase in QTc interval >30 ms and <60 ms.

8.5.8. Vital signs

8.5.8.1. Pivotal studies

Overall in the placebo controlled studies osmotic diuresis related events occurred in 6.2% subjects in the canagliflozin group and 0.8% in the placebo. Volume depletion related AEs were reported in 1.3% subjects in the canagliflozin group and 1.1% in the placebo.

8.5.8.2. Other studies

In Study TA7284-04, at Week 12 the mean (SE) change in SBP was -0.4 (1.5), -5.1 (1.5), -7.8 (1.6), -9.3 (1.1) and -9.6 (1.3) mmHg in the placebo, 50 mg, 100 mg, 200 mg and 300 mg groups,

respectively. The changes in DBP were -1.4 (1.1), -1.9 (1.0), -4.5 (1.1), -4.9 (0.8) and -4.5 (0.8) mmHg in the placebo, 50 mg, 100 mg, 200 mg and 300 mg groups, respectively.

In Study DIA3008 volume depletion related AEs were reported in 41 (2.8%) subjects in the canagliflozin 100 mg group, 66 (4.6%) in the 300 mg group and 27 (1.9%) in the placebo group.

8.5.9. Photosensitivity

In Study DIA1011 a delayed photosensitivity response was demonstrated in 25% subjects with canagliflozin 300 mg daily and also with 300 mg twice daily; compared to 67% subjects treated with ciprofloxacin (positive control) and none with placebo (negative control). An immediate photosensitive response was elicited in 25% subject with canagliflozin 300 mg daily and 58% subjects with canagliflozin 300 mg twice daily compared to none with ciprofloxacin or placebo. The six subjects that developed immediate response with canagliflozin were further studies in Study 1020. All six subjects had photosensitivity reactions at standard irradiance, two at ½ standard irradiance and none at 1/10 standard irradiance. The study report argues that: "Since subjects who had immediate photosensitivity with testing at standard irradiance (30-fold maximum natural light) following administration of canagliflozin, no longer have immediate photosensitivity when irradiance is reduced, but still exceeds maximum natural sunlight (by 3-fold or more), the immediate photosensitivity that was observed at standard irradiance is unlikely to be clinically relevant."

In Study DIA1019 a delayed photosensitivity response was demonstrated in 8% subjects at the canagliflozin 100 mg once daily dose, 17% subjects with canagliflozin 300 mg daily; compared to 67% subjects treated with ciprofloxacin (positive control) and 17% with placebo (negative control). An immediate photosensitive response was elicited in 25% subject with canagliflozin 300 mg daily and 8% ciprofloxacin or placebo; but none with canagliflozin 100 mg daily.

In Study NAP1005 there was no significant difference in phototoxicity index between canagliflozin and placebo, although the mean scores were between those of placebo and ciprofloxacin at the 335 +/- 30 nm wavelength: mean (SD) phototoxicity index 1.0 (0.37) for placebo, 1.57 (0.49) for ciprofloxacin, 1.2 (0.32) for canagliflozin 200 mg and 1.3 (0.35) for canagliflozin 400 mg as single doses.

8.5.10. Vulvovaginal AEs

8.5.10.1. Pivotal studies

In Study DIA3002 (Table 2) female mycotic vulvovaginitis was reported in twelve (14.8%) subjects in the canagliflozin 100 mg group, twelve (17.4%) in the 300 mg and four (5.0%) in the placebo.

In Study DIA3004 (Table 8) vulvovaginal mycotic infection was reported in one subject in the canagliflozin 100 mg group, and one in the 300 mg group.

In Study DIA3005 (Table 11) vulvovaginitis was reported in ten (8.8%) subjects in the canagliflozin 100 mg group, eight (7.4%) in the 300 mg and four (3.8%) in the placebo.

In Study DIA3006 (Table 14) vulvovaginitis was reported in 17 (8.8%) subjects in the canagliflozin 100 mg group, 19 (9.4%) in the 300 mg, two (1.0%) in the sitagliptin and none in the placebo.

In Study DIA3009 (Table 17) vulvovaginal AEs were reported in 26 (11.3%) subjects in the canagliflozin 100 mg group, 34 (13.9%) in the 300 mg and five (2.3%) in the glimepiride.

In Study DIA3010 (Table 20) vulvovaginal AEs were reported in 22 (18.8%) subjects in the canagliflozin 100 mg group, 19 (17.8%) in the 300 mg and four (4.3%) in the placebo. Vulvovaginal mycotic infection was reported in nine (7.7%) subjects in the canagliflozin 100 mg group, six (5.6%) in the 300 mg and one (1.1%) in the placebo.

In Study DIA3012 (Table 23) vulvovaginitis AEs were reported in five (13.9%) subjects in the canagliflozin 100 mg group, ten (19.6%) in the 300 mg and two (5.1%) in the placebo. Vulvovaginal mycotic infection was reported in three (8.3%) subjects in the canagliflozin 100 mg group, six (11.8%) in the 300 mg and none in the placebo.

In Study DIA3015 (Table 5) vulvovaginitis AEs were reported in 42 (24.7%) subjects in the canagliflozin group and nine (5.5%) in the sitagliptin. Vulvovaginal mycotic infection was reported in twelve (7.1%) subjects in the canagliflozin group and five (3.1%) in the sitagliptin.

8.5.10.2. Other studies

In Study DIA2001, treatment emergent vulvovaginal AEs were reported in one (3%) subject in the placebo group, six (20%) in the 50 mg, seven (25%) in the 100 mg, four (13%) in the 200 mg, four (14%) in the 300 mg, seven (19%) in the 300 mg twice daily and two (7%) in the sitagliptin.

In Study TA7284-04, vulvovaginal infections were reported in no subjects in the placebo or 50 mg groups, one (4.5%) in the 100 mg, one (3.7%) in the 200 mg and one (5.0%) in the 300 mg.

In Study DIA3008 vulvovaginitis was reported in 72 (14.9%) subjects in the canagliflozin 100 mg group, 65 (13.1%) in the 300 mg group and 11 (2.3%) in the placebo group.

8.5.11. Urinary tract infection

8.5.11.1. Pivotal studies

In Study DIA3002 (Table 2) UTI was reported in ten (6.4%) subjects in the canagliflozin 100 mg group, nine (5.8%) in the 300 mg and eight (5.1%) in the placebo. Male superficial genital infection was reported in five (6.6%) subjects in the canagliflozin 100 mg group, three (3.4%) in the 300 mg and one (1.3%) in the placebo.

In Study DIA3004 (Table 8) UTIs were reported in five (5.6%) subjects in the canagliflozin 100 mg group, seven (7.9%) in the 300 mg group and five (5.6%) in the placebo.

In Study DIA3005 (Table 11) UTIs were reported in 14 (7.2%) subjects in the canagliflozin 100 mg group, ten (5.1%) in the 300 mg group and eight (4.2%) in the placebo. Male superficial genital infection was reported in two (2.5%) subjects in the canagliflozin 100 mg group, five (5.6%) in the 300 mg and none in the placebo.

In Study DIA3006 (Table 14) UTIs were reported in 20 (5.4%) subjects in the canagliflozin 100 mg group, 13 (3.5%) in the 300 mg, 13 (3.6%) in the sitagliptin and four (2.2%) in the placebo. Male superficial genital infection was reported in seven (4.0%) subjects in the canagliflozin 100 mg group, two (2.4%) in the 300 mg, two (1.2%) in the sitagliptin and one (1.1%) in the placebo.

In Study DIA3009 (Table 17) UTIs were reported in 31 (6.4%) subjects in the canagliflozin 100 mg group, 31 (6.4%) in the 300 mg group and 22 (4.6%) in the glimepiride. Male superficial genital infection was reported in 17 (6.7%) subjects in the canagliflozin 100 mg group, 20 (8.3%) in the 300 mg and three (1.1%) in the glimepiride.

In Study DIA3010 (Table 20) UTIs were reported in 14 (5.8%) subjects in the canagliflozin 100 mg group, 19 (8.1%) in the 300 mg, and 12 (5.1%) in the placebo. Male superficial genital infection was reported in four (3.2%) subjects in the canagliflozin 100 mg group, eight (6.2%) in the 300 mg, and none in the placebo.

In Study DIA3012 (Table 23) UTIs were reported in five (4.4%) subjects in the canagliflozin 100 mg group, four (3.5%) in the 300 mg, and six (5.2%) in the placebo. Male superficial genital infection was reported in three (3.9%) subjects in the canagliflozin 100 mg group, three (4.8%) in the 300 mg, and none in the placebo.

In Study DIA3015 (Table 5) UTIs were reported in 15 (4.0%) subjects in the canagliflozin group and 21 (5.6%) in the sitagliptin. Male superficial genital infections were reported in 19 (2.2%) subjects in the canagliflozin group and one (0.5%) in the sitagliptin.

8.5.11.2. Other studies

In Study DIA2001 urinary tract infection was reported in four (6%) subjects in the placebo group, three (5%) in the 50 mg, two (3%) in the 100 mg, six (9%) in the 200 mg, two (3%) in the 300 mg, three (5%) in the 300 mg twice daily and one (2%) in the sitagliptin.

In Study DIA3008 UTIs were reported in 72 (5.0%) subjects in the canagliflozin 100 mg group, 82 (5.7%) in the 300 mg group and 63 (4.4%) in the placebo group. Male superficial genital infection was reported in 65 (6.8%) subjects in the canagliflozin 100 mg group, 96 (10.2%) in the 300 mg and 13 (1.4%) in the placebo.

8.5.12. Bone mineralisation

In Study DIA3010 (Table 20) there was a decrease in bone mineralization at the hip, relative to placebo, in the canagliflozin 300 mg group. There was no significant difference at other sites. The mean (SD) change from baseline in BMD at the hip was -0.5 (2.1) g/cm^2 for canagliflozin 100 mg, -0.6 (2.1) g/cm^2 for 300 mg and -0.1 (1.9) g/cm^2 for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.4 (-0.8 to -0.0) g/cm^2 for 100 mg and -0.5 (-0.9 to -0.1) g/cm^2 for 300 mg.

Serum CTx (collagen type 1 carboxy-telopeptide) a marker of bone resorption was increased relative to placebo in the canagliflozin groups: mean (SD) % change from baseline in CTx was 25.8 (44.7) % for canagliflozin 100 mg, 34.0 (57.5) % for 300 mg and 8.6 (49.7) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was 17.1 (7.3 to 26.9) % for 100 mg and 24.9 (15.0 to 34.8) % for 300 mg.

Although not statistically significant, serum P1NP (propeptide amino-term type 1 procollagen), a marker of bone formation, was decreased in the canagliflozin groups relative to placebo: mean (SD) % change from baseline in CTx was 2.0 (26.0) % for canagliflozin 100 mg, 0.4 (23.8) % for 300 mg and 6.8 (58.1) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -5.7 (-13.1 to 1.7) % for 100 mg and -6.9 (-14.3 to 0.6) % for 300 mg.

8.5.13. Cardiovascular events

Overall, MACE-plus events were reported in 66 (2.1%) subjects with canagliflozin 100 mg, 64 (2.0%) with 300 mg and 71 (2.1%) with comparator.

8.6. Post-marketing experience

8.6.1. Post-marketing data

No post marketing data were included in the submission.

8.7. Evaluator's overall conclusions on clinical safety

Overall the frequency and pattern of TEAEs was similar for canagliflozin and for placebo and comparator. The frequency of TEAEs did not appear to be dose related. However, the rates of vulvovaginal mycotic infection in females and superficial genital infection in males were increased with canagliflozin. Polyuria was also more common with canagliflozin.

There were few deaths and none appeared to be related to treatment with canagliflozin.

The rate and pattern of SAEs was similar to placebo and comparator. Renal SAEs were more common with canagliflozin.

The rates and pattern of DAE was similar to placebo and comparator. DAE due to a renal AE was more common in the canagliflozin groups.

Although in individual studies there appeared to be more subjects in the canagliflozin groups with ALT ≥3xULN, overall in the development program the rates of ALT or AST ≥3xULN and bilirubin ≥2xULN were similar for canagliflozin and comparator. None of the episodes in the canagliflozin groups were considered to be definite or probable causality.

Decreased renal function and renal failure were more common with canagliflozin than placebo or comparator. Overall in the placebo controlled studies there were 16 (2%) subjects in the canagliflozin 100 mg group, 33 (4.1%) in the 300 mg and 13 (2.1%) in the placebo with eGFR <80 mL/min/1.73m^2 and decrease >30% from baseline. Acute renal failure was reported in two (0.2%) subjects in the canagliflozin 100 mg group, one (0.1%) in the 300 mg and none in the placebo.

Hypoglycaemia was more common with canagliflozin than placebo, but less common than with glimepiride. The rate of hypoglycaemia with canagliflozin was increased with SU comedication. Severe hypoglycaemia was uncommon with canagliflozin.

An increase in an increase in QTc interval >30 ms and <60 ms was more common with canagliflozin than with comparator, but a thorough QT study did not indicate QTc increase of regulatory concern.

Phototoxicity was demonstrated with canagliflozin but would not be expected to occur at normal sun exposures.

Vulvovaginal AEs were reported in up to 25% of female subjects treated with canagliflozin. Male superficial genital infections were reported in up to 8.3% of male subjects treated with canagliflozin.

In elderly subjects there was a decrease in bone mineralisation at the hip with canagliflozin relative to placebo. In Study DIA3010 there was a decrease in bone mineralization at the hip, relative to placebo, in the canagliflozin 300 mg group. The mean (SD) change from baseline in BMD at the hip was -0.5 (2.1) g/cm^2 for canagliflozin 100 mg, -0.6 (2.1) g/cm^2 for 300 mg and -0.1 (1.9) g/cm^2 for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.4 (-0.8 to -0.0) g/cm^2 for 100 mg and -0.5 (-0.9 to -0.1) g/cm^2 for 300 mg.

The adverse event profile is reflected in the RMP.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The efficacy of canagliflozin has been demonstrated in:

- Monotherapy
- In combination with MET
- In combination with MET and SU
- In combination with MET and Pioglitazone
- As add-on therapy in moderate renal failure
- In older subjects

The effect size was clinically significant.

Efficacy in combination with insulin was not demonstrated in a pivotal study.

9.2. First round assessment of risks

Canagliflozin was well tolerated with a similar rate of TEAEs to placebo or comparator. There were few deaths or SAEs.

There is an increased rate of vulvovaginal AEs in females and superficial genital infections in males.

There is an increased risk of renal impairment, but it is not clear whether there is an increased risk of irreversible renal impairment.

There appears to be an effect on bone mineralisation.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of canagliflozin, given the proposed usage, is favourable.

10. First round recommendation regarding authorisation

The application for authorisation of canagliflozin for the following indication should be rejected:

> *INVOCANA is indicated in adults with type 2 diabetes mellitus to improve glycaemic control as:*
>
> *Monotherapy*
>
> *When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.*
>
> *Add-on therapy*
>
> *Add-on therapy with other anti-hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see PRECAUTIONS; INTERACTIONS WITH OTHER MEDICINES and PHARMACOLOGY for available data on different add-on therapies).*

The reasons for rejection are:

- Insufficient data demonstrating efficacy in combination with insulin. The data presented for this indication come from a substudy of Study DIA3008, were conducted in a selected population, over an 18 week duration of treatment and with no formal hypothesis testing intended in the study protocol.
- In its current wording the proposed indication does not refer to specific agents in combination which may increase the likelihood of use with agents where there is no experience.

The TGA could consider approving the following alternative indication:

> *INVOCANA is indicated in adults with type 2 diabetes mellitus to improve glycaemic control as:*
>
> *Monotherapy*
>
> *When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.*
>
> *Add-on therapy*

Add-on therapy with metformin alone or in combination with sulfonylureas or pioglitazone, when these, together with diet and exercise, do not provide adequate glycaemic control (see PRECAUTIONS; INTERACTIONS WITH OTHER MEDICINES and PHARMACOLOGY for available data on different add-on therapies).

Efficacy has not been demonstrated in combination with insulin.

11. Clinical questions

The Evaluator does not have any questions.

12. Second round evaluation of clinical data submitted in response to questions

Not applicable.

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