19 September 2013
EMA/374133/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Canagliflozin

International non-proprietary name: Canagliflozin

Procedure No. EMEA/H/C/002649/0000

Note

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

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Product information

Name of the medicinal product:	Invokana
Applicant:	Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse BELGIUM
Active substance:	canagliflozin
International Nonproprietary Name/Common Name:	canagliflozin
Pharmaco-therapeutic group (ATC Code):	Drugs used in diabetes, other blood glucose lowering drugs, excluding insulins (A10BX11)
Therapeutic indication(s):	Invokana is indicated in adults aged 18 years and older 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 glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5, and 5.1 for available data on different add-on therapies).
Pharmaceutical form:	Film-coated tablet
Strengths:	100 mg and 300 mg

Route of administration:	Oral use
Packaging:	blister (PVC/Alu)
Package sizes:	10 tablets, 30 tablets, 90 tablets and 100 tablets

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List of abbreviations

%CV	percent coefficient of variation
3-OMG	3-O-methyl glucose
ACE	angiotensin converting enzyme
ADR	adverse drug reaction
Ae	Cumulative amount excreted into the urine
Ae,%dose	Total amount excreted into the urine, expressed as a percentage of the administered dose
Aet1-t2	Amount excreted into urine during a collection interval from t1 to t2
AHA	antihyperglycaemic agent
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMG	a-methylglucoside
ANOVA	Analysis of variance
APD60	action potential duration at 60% repolarization
API	Active Pharmaceutical Ingredient
Apo B	apolipoprotein B
AR	Assessment Report
ARB	angiotensin II receptor blocker
ASM	Active Substance Manufacturer
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC24	area under the plasma concentration-time curve from time 0 to 24 hours
AUC∞	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
AUCinf	area under the plasma concentration-time curve from time 0 to infinite time
AUClast	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
AUMC	Area under the first moment of the concentration versus time curve from the time of dosing up to a specific time, t, to infinite time, or to the time of the last measurable concentration
BA	bioavailability
BG	blood glucose
BID	twice daily
BLQ	below the limit of quantitation
BMD	bone mineral density
BrdU	bromo-deoxyuridine
BSA	body surface area
Ca	calcium
CANA	Canagliflocin
CANVAS	Study DIA3008
CFU	Colony Forming Units
CHD	coronary heart disease
CHMP	Committee for Medicinal Products for Human Use

CHOK1	Chinese hamster ovary cell line K1
CI	confidence interval
Cl	chloride
CL	total systemic clearance
CLCR	creatinine clearance
Cmax	maximum plasma concentration
CoA	Certificate of Analysis
CV	cardiovascular
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interactions
DIO	diet induced obese
DNJ	1-deoxynorjirimycin
DPP-4	dipeptidyl-peptidase-4
DSC	differential scanning calorimetry
DXA	dual-energy x-ray absorptiometry
EAC	endpoint adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOP2	end of Phase 2
ESRD	End-Stage Renal Disease
ESRD	end-stage renal disease
FBG	fluid-bed granulation
FDA	Food and Drug Administration
Fe	Total amount excreted into the feces
Fe,% dose	Total radioactivity excreted into the feces, expressed as a percentage of the administered dose,
FPG	fasting plasma glucose
FPG	fasting plasma glucose
FS-MMTT	frequently-sampled mixed-meal tolerance test
FT-IR	Fourier transform infrared spectroscopy
FT-Raman	Fourier transform Raman spectroscopy
GC	Gas Chromatography
GCP	Good clinical practise
GFR	glomerular filtration rate
GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practice
GLP-1	glucagon-like peptide-1
GLUT1	glucose transporter 1
GLUT2	glucose transporter 2
GLUT4	glucose transporter 4
GMP	Good Manufacturing Practice
GMR	Geometric mean ratio

HbA1c	haemoglobin A1c (glycated haemoglobin)
HCl	Hydrochloric acid
HCT	haematocrit
HDL-C	high-density lipoprotein-cholesterol
HEK	human embryonic kidney
HGB	haemoglobin
High Glycaemic Substudy	DIA3005 substudy in subjects with more severe hyperglycemia (HbA_{1c} >10.0% to £12.0%)
HOMA2-%B	homeostatic model assessment of beta-cell function using HOMA2 calculations
HPbCD	hydroxypropyl-b-cyclodextrin
HPLC	high-performance liquid chromatography
HR	hazard ratio
HSG	high-shear granulation
HSG	high-shear granulation
hSGLT1	human SGLT1
hSGLT2	human SGLT2
hSGLT4	human sodium glucose co-transporter-4
hSGLT6	human sodium glucose co-transporter-6
hSMIT1	human sodium/myo-inositol co-transporter-1
IAS	Integrated Analysis of Safety
IC50	inhibiting concentration at 50%
ICH	International Conference on Harmonisation
IPC	In-process control
IR	Infrared
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
J&JPRD	Johnson & Johnson Pharmaceutical Research & Development, LLC
JNJ-28431754	Canagliflozin
JRD	Janssen Research & Development, LLC (the company)
K	potassium
Kd	equilibrium dissociation constant
KF	Karl Fischer
KIM-1	kidney injury molecule-1 (also known as TIM-1)
LCT	Leydig cell tumor
LDL-C	low-density lipoprotein-cholesterol
LH	luteinizing hormone
LOA	Letter of Access
LOCF	last observation carried forward
LOD	(1) Loss on Drying, (2) Limit of Detection
LoQ	List of Questions
LOQ	Limit of Quantification
LS	least-squares
MAA	Marketing Authorisation Application
MACE	major adverse cardiovascular events

MACE plus	MACE and hospitalized unstable angina (UA).
MDCKII	Madin-Darby canine kidney II
MDR1	multi-drug resistance 1
MDRD	Modification of Diet in Renal Disease
MMTT	mixed-meal tolerance test
MPG	Mean plasma glucose
MPG_{24}	mean plasma glucose concentrations from 0 to 24 hours
MRP2	multidrug resistance-associated protein 2
MRT	the time corresponding to the average time the number of molecules absorbed reside in the body
MS	Mass Spectrometry
MTPC	Mitsubishi Tanabe Pharma Corporation (the development partner)
N/A	not applicable
Na	sodium
NADP	nicotinamide adenine dinucleotid phosphate
NAG	N-acetyl β-D-glucosaminidase
ND	Not detected
NDA	New Drug Application
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOAEL	no-observed-adverse-effect level
NPE	non-particle-engineered
NT	Not tested
OECD	Organisation for Economic Co-Operation and Development
OGTT	oral glucose tolerance test
OOS	Out of Specifications
OSOM	outer stripe of the outer medulla
P	phosphorus
PD	Pharmacodynamic
PDE	Permitted Daily Exposure
PDLC	predefined limit of change
PE	particle-engineered
PE	Polyethylene
P-gp	P-glycoprotein
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	pharmacokinetic
PP	per protocol
PPARγ	peroxisome proliferator-activated receptor-gamma
PPG	post-prandial glucose
Ppm	parts per million
PTH	parathyroid hormone
PTT	prothrombin time
PWG	Pathology Working Group

QD	once daily
RBC	red blood cell count
RH	Relative Humidity
RLG	radioluminography
ROW	rest of world
RRT	Relative retention time
RSD	Relative standard deviation
RTG/RT_G	renal threshold for glucose
RTT(s)	renal tubular tumor(s)
S9	exogenous mammalian metabolic activation system
SAP	statistical analysis plan
SBP	systolic blood pressure
SCE	Summary of Clinical Efficacy
SD	standard deviation
SE	standard error
Sec	section
SEM	standard error of the mean
SGLT1	sodium-glucose co-transporter-1
SGLT2	sodium-glucose co-transporter -2
SMIT1	sodium/myo-inositol co-transporter-1
SOC	system organ class
SU	sulphonylurea
t½	elimination half-life
T2DM	type 2 diabetes mellitus
TAMC	Total Aerobic Microbial Count
TG	Triglyceride
TGA	thermal gravimetric analysis
TLC	Thin Layer Chromatography
t_{max}	time to reach maximum concentration
TMDS	1,1,3,3-tetramethyldisiloxane
TR	total radioactivity
TS	tosylate salt
TSE	Transmissible Spongiform Encephalopathies
TTC	Threshold of Toxicological Concern
TYMC	Total Yeasts and Moulds Count
UDPGA	uridine 5'-diphospho-glucuronic acid
UGE	urinary glucose excretion
UGE_{24}	24-hour urinary glucose excretion
UGT	uridine diphosphate glucuronyl transferase
ULN	upper limit of normal
UreaN	urea nitrogen
US	United States
USP	United States Pharmacopoeia
UV	ultraviolet
UV-A	ultraviolet A

UV-B	ultraviolet B
Vd/F	apparent volume of distribution based on the terminal elimination phase
Vdss	The apparent steady-state volume of distribution
VO_2	oxygen consumption
VSS	apparent volume of distribution at steady state
VTE	Venous thromboembolism
WBA	whole-body autoradiography
XRD	X-Ray Diffraction
ZDF	Zucker Diabetic *fa/fa* (Fatty)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 22 June 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Invokana, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 November 2011.

The applicant applied for the following indication:

Invokana 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 sections 4.4, 4.5, and 5.1 for available data on different add-on therapies).

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/164/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/164/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance canagliflozin contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 23 March 2009, 28 October 2009 and 21 October 2010. The Scientific Advice pertained to the non-clinical and clinical aspects of the dossier.

Licensing status

Canagliflozin has been given a Marketing Authorisation in the Unites States on 29 March 2013 and in Australia on 6 September 2013.

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Janssen-Cilag S.p.A.
Via C. Janssen
IT-04010 Borgo San Michele
Latina
Italy

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Martina Weise Co-Rapporteur: Kristina Dunder

- The application was received by the EMA on 22 June 2012.
- The procedure started on 18 July 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 October 2012 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 5 October 2012.
- During the meeting on 15 November 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 15 November 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 February 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 March 2013.
- During the CHMP meeting on 25 April 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 25 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 7 June 2013.
- During the CHMP meeting 27 June 2013, the CHMP agreed on a follow-on List of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated follow-on List of

outstanding issues on16 August 2013.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the follow-on List of outstanding issues to all CHMP members on 27 August 2013.
- On 17 September 2013, outstanding issues were addressed by the applicant during an oral explanation.
- During the meeting on 19 September 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Invokana.

2. Scientific discussion

2.1. Introduction

The prevalence of diabetes worldwide is rising rapidly and is estimated to reach 4.4% of the world's population or approximately 366 million people by 2030. The long-term manifestations of diabetes contribute to its status as a leading cause of premature illness and mortality worldwide.

There are currently agents from a number of different classes that are available for the treatment of type 2 diabetes mellitus (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.

Many of the current T2DM treatments are associated with safety or tolerability issues, including hypoglycemia, edema, or gastrointestinal adverse experiences which can limit dose and hence therapeutic benefit. Further, some of the current anti-hyperglycaemic agents (AHAs) are associated with weight gain, which is particularly problematic as over 85% of patients with T2DM are overweight and obese. Additional weight gain can increase insulin resistance, an underlying pathophysiologic mechanism of T2DM. Only few AHAs (eg, metformin and glucagon-like peptide-1 [GLP-1] analogues) lead to weight loss.

There is a need for novel treatment options for T2DM, due to the increasing global prevalence of the disease, its progressive nature which eventually requires combination therapy in most patients as well as the undesirable effects of currently available therapies.

2.2. Quality aspects

2.2.1. Introduction

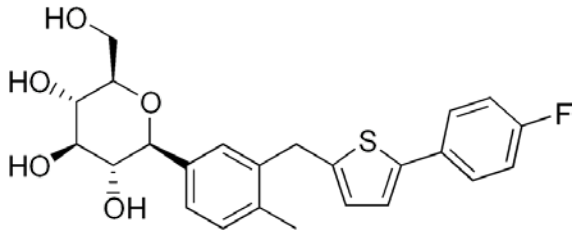
The finished product is presented as film-coated tablets containing 100 mg and 300 mg of canagliflozin (hemihydrate) as active substance.

Other ingredients are: lactose anhydrous, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate for the tablet core and polyvinyl alcohol, titanium dioxide, macrogol (polyethylene glycol), talc, iron oxide yellow (100 mg tablet only) for the film-coating.

The product is available in PVC/Alu blisters.

2.2.2. Active Substance

The chemical name of canagliflozin hemihydrate is (1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]-methyl]-4-methylphenyl]-D-glucitol hemihydrate and has the following structure:



Canagliflozin hemihydrate is a white to off-white powder, practically insoluble in water and freely soluble in ethanol and non-hygroscopic. The particle size distribution is controlled to ensure a consistent finished product manufacturing process; studies showed that the particle size has no impact to the performance *in vivo*.

Canagliflozin exhibits stereoisomerism due to the presence of five chiral centres. The diastereomeric purity of the drug substance is controlled by an achiral assay/purity HPLC method.

Polymorphism has been observed for canagliflozin: the manufactured form I is a hemihydrate, and an unstable amorphous Form II. Form I is consistently produced by the proposed commercial synthesis process. As the manufacturing process consists of several recrystallization steps and polymorphic form II is amorphous it is accepted not to implement XRD test to the specification of the active substance.

Manufacture

Canagliflozin is manufactured by one source and is synthesized in four main synthetic steps plus two purification steps using well defined starting materials with acceptable specifications.

The five isolations by crystallization in combination with the design of the manufacturing process result in a process with a high purifying capability. As a result, the early steps of the synthesis outside GMP control are not anticipated to impact on the quality of the active substance.

Process validation on three consecutive batches has been completed successfully. The validation batches were tested with the validated analytical methods used for batch release. The analytical results demonstrate that all validation batches meet the proposed specification limits.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The manufacturing process yields one diastereoisomer of the active substance. It is not necessary to perform a test for chiral purity on canagliflozin as the impurity is controlled by the general analytical method for impurities.

Specification

The active substance specification includes tests for: appearance, identity (IR, UV), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), heavy metals (Ph.Eur.), residue on ignition (Ph. Eur.), and particle size distribution.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data on nine commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on six commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package in a container closure system representative of that intended for the market were provided for the following time/ICH conditions: 9 months under long term conditions at 25 ºC / 60 % RH, 9 months under intermediate conditions at 30 ºC / 75 % RH and up to 6 months under accelerated conditions at 40 ºC / 75 % RH.

Photostability testing following the ICH guideline Q1B was performed. Results on stress conditions (including high temperature, acid, alkaline, oxidising) were also provided. The active substance is stable at high temperature and humidity and degrades moderately under basic and peroxide conditions. Canagliflozin is unstable under photolytic and radical oxidation conditions.

The following parameters were tested*:* appearance, assay, chromatographic purity, water content and particle size. The analytical methods used were the same as for release and were stability indicating. No trends were observed.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical development

The finished product is 100 mg or 300 mg film-coated tablets manufactured by fluid-bed granulation. Both strengths are manufactured from a common granulation blend. The film-coated tablets are capsule-shaped, film-coated with different colours for each strength and debossed for identification. The product is packed in PVC/Al blisters. The compositions of the Opadry mixes were presented.

A satisfactory formulation development is provided. The development began with an oral suspension and progressed to wet fluid bed granulation. Results from high shear granulation as well as fluid bed are included. The aim was to use a dose proportional formulation that could be compressed as multiple strengths. A high active substance load was necessary to avoid large tablets. Design of experiments was used to evaluate the influence of particle size, filler ratio, disintegrant level and binder level, as well as lubricant level and blend time. No design space was claimed.

There are no major differences between the manufacturing process used for the clinical trials batches and that proposed for marketing. To note that the manufacturing process and formulation of batches used for Phase 3 Trials and Stability testing are the same as those proposed for marketing. A dissolution bridging study was conducted to bridge results from the manufacturer of clinical batches (Spring House, Pennsylvania) and commercial manufacturer (Gurabo, Puerto Rico).

Dissolution was tested by the regulatory dissolution method. The discriminatory power of the dissolution method was sufficiently demonstrated.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The primary packaging is PVC blisters backed with push-through aluminium foil. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

Lactose anhydrous is the single excipient of animal origin use in canagliflozin tablets and is certified by the supplier not to contain calf rennet. Magnesium stearate is of vegetable origin. An acceptable BSE/TSE Statement is provided.

Manufacture of the product

The manufacturing process consists of eight main steps: preparation of dry ingredients, preparation of the binder solution, preparation of the granulation, sieving and final blending, compression, preparation of the film-coating suspension, film-coating of the tablets and packaging. The process is considered to be a standard manufacturing process.

A satisfactory process validation scheme to be completed prior to commercial launch was submitted.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: identification (IR, UV), appearance, assay (UPLC/HPLC), impurities (UPLC/HPLC and LC-MS/MS), dissolution, uniformity of dosage units (Ph. Eur.), microbiological purity (Ph. Eur.).

Batch analysis results are provided for eight 100 mg batches and eighteen 300 mg batches from the proposed manufacturing site (commercial scale) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three commercial scale batches of each strength of finished product stored under long term conditions for 18 months at 25 ºC / 60 % RH, intermediate conditions for 18 months at 30 ºC / 75 % RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, dissolution, assay, impurities, water content and microbiological purity. The analytical procedures used are stability indicating.

In addition, photostability studies performed as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products demonstrate that the medicinal product is not photosensitive.

Based on available stability data, the shelf-life with no special storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

Canagliflozin is an orally active inhibitor of sodium-glucose co-transporter-2 (SGLT2). The low-affinity/high capacity SGLT2 transporter in the proximal renal tubule reabsorbs the majority of glucose filtered by the renal glomerulus. Pharmacological inhibition of SGLT2 is expected to decrease renal glucose re-absorption, and thereby increase urinary glucose excretion (UGE) and lower plasma glucose in patients with type 2 diabetes.

Canagliflozin has been characterised in a battery of in vitro and in vivo pharmacodynamic, pharmacokinetic, and toxicologic studies.

A non-clinical testing strategy was followed consistent with the proposed clinical indication, route of administration, and dosing regimen (100 and 300 mg QD). The non-clinical development program adhered to regulatory guidance for non-clinical development of drugs.

2.3.2. Pharmacology

Non-clinical pharmacology studies of canagliflozin have been conducted both in cell-based assays and in animal experiments using normal and diabetic animal models. In addition, pivotal studies on cardiovascular and pulmonary safety in conscious dogs and neurobehavioral safety in rats were conducted, according to GLP, to address the safety pharmacological profile of canagliflozin.

Primary pharmacodynamic studies

The Applicant has demonstrated the pharmacological activity of canagliflozin *in vitro* and in animal models, normal animals, diabetic (db/db mice and Zucker Diabetic fa/fa (ZDF) rats) and obese animals. *In vitro* studies performed in rat and human demonstrated that canagliflozin has a high affinity for human SGLT2 vs SGLT1 (IC50 4.2 nM vs 663 nM). It is agreed that there is a high degree of sequence homology between human and rodents and that these used animals are relevant models to study canagliflozin. Furthermore, canagliflozin has similar affinity to ratSGLT2 compared to dapagliflozin, other SGLT2 inhibitor (IC50 3.7 nM and 3.0 nM for canagliflozin and dapagliflozin, respectively). However, dapagliflozin has a higher affinity to humanSGLT2 than canagliflozin (IC50 1.1 nM compared to 4.2 nM). Regarding SLGT1, canagliflozin and dapagliflozin have similar affinity to ratSLGT1 (IC50 555 nM and 620 nM for canagliflozin and dapagliflozin, respectively) and around 2x higher affinity for human SGLT1 compared to dapagliflozin (IC50 663 nM and 1391 nM for canagliflozin and dapagliflozin, respectively).

The primary pharmacological studies in all animal models, including diabetics (db/db mice and ZDF rats) and obese mice, showed a dose-dependent (up to 30 mg/kg single dose) increase of UGE and reduction of blood glucose levels after a canagliflozin treatment.

Secondary pharmacodynamic studies

Secondary pharmacodynamic studies in mice and rats (mildly hyperglycaemic) demonstrated a reduction in body weight (or a decrease in weight gain) following repeated administration of canagliflozin (2-4 weeks). In one study with older hyperglycaemic, diabetic rats weight gain was increased. In general, food intake was not altered during canagliflozin treatment. These findings were coupled with improved glucose handling during an OGTT and increases in plasma insulin levels and lowering in HbA1c values (hyperglycaemic *fa/fa* rats).

Safety pharmacology programme

Safety pharmacology studies were performed to assess the potential effect of canagliflozin treatment on the cardiovascular system, CNS and the respiratory system.

In *in vitro* safety pharmacology studies canagliflozin showed no effect on the cardiovascular system (inhibition of hERG currents, isolated Langendorff perfused rabbit heart) in concentrations up to 1 µM. Calculated C_{max} exposure safety margins for the *in vivo* cardiovascular and pulmonary assays in conscious dogs were 61-times using the 100 mg once daily human dose, and 14-times for the 300 mg once daily human dose. Canagliflozin did not cause any neurobehavioral changes in rats at oral doses up to 1000 mg/kg, and AUC exposure safety margins at the high dose were 214-times and 57-times for the 100 and 300 mg once daily clinical doses, respectively (human data taken from studies DIA1007 and DIA1023).

2.3.3. Pharmacokinetics

Absorption

Oral administration of canagliflozin resulted in good absorption in mice, dogs, and monkeys. However, absorption was markedly reduced in rat. C_{max} was reached rapidly in all species following oral administration, with T_{max} values ranging between 1 hour (mouse) and 3.5 hours (monkeys). Due to the prolonged oral absorption in rats, T_{max} values ranged from 4 to 7 hours following single and repeated dosing. The absolute bioavailability was highest in mouse (>100%), probably caused by enterohepatic circulation, followed by dog (up to 68%), monkey (49%), and rat (35%). For humans absolute bioavailability was 65%. Elimination half-life of canagliflozin was most rapid in mice (4 to 5 hours) and slow in rats, dogs, and monkeys (6 to 8 hours). The volume of distribution (Vd) of canagliflozin was approximately similar (1.6 to 2.4 l/kg) in the mouse, rat, and monkey, and smaller (0.6 to 0.8 l/kg) in the dog (higher than total body water).

Distribution

Canagliflozin showed a high protein binding (> 98%) at concentrations below (0.45 µM) and above (45 µM) human exposure at the anticipated 100 mg (C_{max} of 0.98 µg/ml, 2.2 µM) and 300 mg (C_{max} of 4.1 µg/ml, 9.3 µM) daily doses throughout species. HSA is likely responsible for the majority of canagliflozin protein binding.

Blood to plasma ratios were highest for rat (0.78 to 1.0), intermediate for human (0.66 to 0.71), and lowest for dog (0.51 to 0.61) indicating no distribution of canagliflozin into blood cells.

In distribution studies with ^{14}C-canagliflozin, canagliflozin was found in blood, plasma, and most tissues (including eye and skin). Highest concentrations were observed in kidney, liver and glandular tissues especially in the renal cortex and the harderian gland. Canagliflozin and its metabolites were hardly distributed into brain, bone and white fat. Maximum total radioactivity concentrations for blood, plasma, eye, and pigmented skin were 1.30, 1.53, 1.25, and 1.56 µg/g or ml at the low dose or 17.8, 22.6, 12.6, and 24.7 µg/g or ml at the high dose, respectively. No accumulation in tissues were observed in relevant plasma concentrations, radioactivity levels in skin and eye were comparable to those in plasma. This is in particular of interest as a photosensitizing potential was claimed for canagliflozin in *in vitro* and *in vivo* assays.

Metabolism

Twenty metabolites (M1-20) of canagliflozin were detected in *in vitro* and *in vivo* metabolism studies. All human metabolites were also present in at least one animal species. *In vitro* studies showed that unchanged drug was the major component in human liver microsomes, and in mouse, rat, dog, rabbit, and human hepatocytes. M7 *O*-glucuronide was the major metabolite in mice (27-46%) and humans (28%) and was also present in the other species. M6 carboxy metabolite was formed in hepatocytes of all species and was the main metabolite in male rats (42%) and dogs (13%). It was also present in human hepatocytes (2%) but was not formed in human liver microsomes. In *in vivo* studies, unchanged drug was the major component in plasma of all species after 24 hours. In human plasma the remaining drug-related products were *O*-glucoronides M5 and M7 and hydroxylated drug metabolite M9 up to 12 hours but not after 24 hours. In dog and rat no metabolites were detected in plasma, in mice M7 and M9 were present at lower amounts as compared to humans. However, in the toxicity studies with high doses in mice, rats and dogs M5 and M7 were detected in plasma, liver and kidney. At low doses metabolites M5 and M7 were not found in rat plasma faeces and urine but are found as major metabolites in humans in plasma and urine (>10% of parent). M7 was the major metabolite found in rat bile, M5 was also present but to a lesser extent. Furthermore M7 was formed in rat hepatocytes. M5 and M7 undergo hydrolisation in faeces and are therefore not detectable.

Excretion

About 90% to 94% of the administered dose was excreted excreted in animal (mouse, rat, and dog) faeces. About 2% to 7% of the administered dose was recovered in animal urine. Biliary excretion was furthermore tested in mice and rats.

Taken together, in humans the primary metabolic clearance pathway of canagliflozin is through its direct glucuronidation in liver whereas in animal species oxidation is the major metabolic pathway, yielding various metabolites not present in humans in vivo (e.g. M1, M2, M4, M6, M8). Human plasma levels of *O*-glucuronides M5 and M7 approached a peak of ~30% of the sample radioactivity

Canagliflozin or its metabolites M5 and M7 did not induce nor inhibit CYPs at clinically relevant concentrations (IC_{50} canagliflozin for the inhibition of CYP2B6 and CYP2C8 = 16 and 75 µM, respectively; IC_{50} M5 = 55 and 64 µM, respectively; IC_{50} canagliflozin for the inhibition of CYP2C9 = 80 µM and CYP3A4/testosterone = 27 µM). Canagliflozin was not found to be a substrate or inhibitor of SLCs or URAT1 but was found to be a substrate for transporters MDR1 and MRP2.

Canagliflozin crossed the placental barrier. Foetal systemic exposure was approximately the same as maternal blood exposure.

Canagliflozin and its metabolites passed into milk with milk to plasma ratios of 1.05 to 1.55.

2.3.4. Toxicology

Single dose toxicity

Canagliflozin was well tolerated after a single dose in mice (oral gavage and i.p.) and rats (oral gavage). The maximum non-lethal oral dose of canagliflozin was 2000 mg/kg (high dose) in mice (both sexes) and male rats, and 1000 mg/kg in female rats. The maximum non-lethal i.p. dose of canagliflozin was 500 mg/kg in mice and female rats, and 125 mg/kg in male rats.

Repeat dose toxicity

Repeat-dose toxicity was evaluated in mice, rats, rabbits, and dogs dosed for up to 3 months, 6 months, 5 days, and 1 year, respectively. Generally, various finding were noted in the repeat-dose toxicity studies within or across species. Most of the observed effects in mice, rats and dogs studies were considered to be secondary to the pharmacological action of the substance. The Applicant submitted further mechanistic studies to discuss the findings related to hyperostosis, renal safety, and stomach erosions in fasted rats.

In mouse, canagliflozin was well tolerated at doses up to 100 mg/kg/day after 3-month oral administration. Effects related to the pharmacological properties of the substance as distention cecum and increase glycogen accumulation were observed at doses 25x higher than the human exposure.

In rat, the kidney was a potential target organ for toxicity. Urinalysis changes observed in the 3- and 6-month studies were relate to mineralization. An increase in trabecular bone volume (hyperostosis) was seen after repeated dose administration to young animals (6 o 8 weeks old at the initiation of dosing). When hyperostosis was investigated in mature rats and compared to young, hyperostosis was more pronounced in young rats indicating that these findings occurred in young actively growing rats. These effects, not observed in any other species, were reversible in the 3-month rat study after an 8-week recovery period. Analysis performed in the 3- and 6-month rat study did not show change in bone mineral density at any dose or abnormal bone architecture (DXA, Dual-energy x-ray absorptiometry, scanning). Investigation on hyperostosis in rats with low calcium diet showed an increase on canagliflozin AUC value from 357 µg.h/ml to 538 µg.h/ml compared to rats fed with normal calcium diet and an inhibition of canagliflozin treatment-related hyperostosis. A reduction in 1,25-dihydroxyvitamin D, parathyroid hormone (PTH) and calciotin were observed in serum as a possible consequence of increases in intestinal calcium absorption. The overall conclusion from the mechanistic studies suggested that canagliflozin-mediated hyperostosis in rats was related to carbohydrate malabsorption and its sequelae and should not be considered of relevance to human safety.

In dog, the treatment with canagliflozin was well tolerated and a NOAEL of 30 mg/kg/day (more than 16x of clinical exposure) was determined based on mortality, clinical observations, renal changes associated with urinalysis changes.

Genotoxicity

A standard battery of genotoxicity tests was performed with canagliflozin. Canagliflozin was tested in vitro in AMES and mouse lymphoma assay and *in vivo* in rat bone marrow micronucleus and liver Comet assays with no biologically relevant adverse observations.

Carcinogenicity

Two GLP-conform carcinogenicity studies were performed in CD-1 mice and SD rats.

In the mouse study, no treatment related neoplasms nor palpable masses were observed. Furthermore, no canagliflozin-mediated effects on mortality, body weight, or body weight gain were observed. There was an increase in urinary tract obstruction which was considered to be a mouse urologic syndrome which is a relatively common genito-urinary disease of male mice of various strains, and is reported to be of multifactorial pathogenesis that frequently causes death in male mice on long-term toxicology studies. Therefore, the NOAEL for this study was set at 100 mg/kg/day. Safety margins at the NOEL of 100 mg/kg/day of 28x and 7.4x for males and 51x and 14x for females were calculated towards AUC exposure levels at the clinical dose of 100 mg and 300 mg, respectively.

In the rat study, in males and females a significantly increased incidence of benign pheochromocytomas in both sexes at 100 mg/kg/day was observed. In males there was also a treatment related effect for the incidence of malignant pheochromocytomas at the high dose. Survival-adjusted analysis of pheochromocytoma (benign and malignant) tumour rates were 10%, 8%, 13%, and 57% in males at 0, 10, 30, and 100 mg/kg/day, respectively, showing the absence of a treatment-related effect at 30 mg/kg/day. Furthermore, survival was significantly increased in the 30 mg/kg/day dose groups. Therefore, the NOEL for pheochromocytomas was set at 30 mg/kg/day.

Furthermore, in high dose animals of both sexes an increased incidence of renal tubular tumours (RTT) was observed. One of these tumours was of the amphophilic-vacuolar phenotype, all others were basophilic. In the mid dose two tumours of the amphophilic-vacuolar phenotype were found in male rats. These three amphiphilic–vacuolar tumours are considered to be spontaneous and not treatment-related. Furthermore, there was no dose-dependency. This was also confirmed by a pathology working group which conducted a blinded review of the renal histological findings. The NOEL for renal tubular tumours was set at 30 mg/kg/day. Safety margins for pheochromocytomas and RTT of 17x and 4.5x for males and 27x and 7.2x for females were calculated towards AUC exposure levels at the clinical dose of 100 mg and 300 mg, respectively.

Benign Leydig cell tumours (LCTs) were detected at an increased incidence relative to controls across all dose groups in male rats. A NOEL could not be set based upon the observed incidence of tumours. Occurrence of LCTs might be due to decreases in testosterone levels and subsequent increases in LH levels upon canagliflozin treatment. The outcome of the conducted toxicity studies where LH and testosterone levels were measured are controversial and do not give a final mechanistic explanation of incidences of LCTs in the rat.

All tumour findings in the rat carcinogenicity study are summarized in the following table.

Table 1. Tumour findings in the 2-year rat carcinogenicity study.

Tumour findings	Gender	Control	Low dose	Mid dose	High dose
Pheochromocytoma, benign	Male	4/65	4/64	7/64	**26/65**
	Female	2/65	1/63	3/62	**7/64**
Pheochromocytoma, malignant	Male	0/65	0/64	1/64	2/65
	Female	0/65	0/63	0/62	0/64
Testes adenoma, benign	Male	1/65	**8/65**	**20/64**	**24/65**
Renal tubule adenoma, benign	Male	0/65	0/65	1/64	**8/65**
	Female	0/65	0/64	0/65	7/65
Renal tubule carcinoma, malignant	Male	0/65	0/65	1/64	5/65
	Female	0/65	0/64	0/65	2/65

Statistically significant tumour findings are shown in bold (Fisher's Exact Test).

To further understand the occurrence of pheochromocytomas and RTT in the high dose, an extensive programme of mechanistic studies was conducted (complemented by mechanistic studies on hyperostosis). It was assumed that rat-specific carbohydrate malabsorption (due to SGLT1 inhibition in the gut) and its consequences such as decreased luminal pH, increased intestinal calcium absorption and consecutively increased urinary calcium excretion caused these tumour findings.

In a first set of experiments it was shown that carbohydrate malabsorption was present in male rats at canagliflozin treatment. Canagliflozin caused a profound reduction (>90%) in 3-O-methyl glucose (3-OMG) plasma levels indicating inhibition of glucose/galactose absorption relative to vehicle control. In a further study a significant increase in cecal glucose content was observed with 100 mg/kg/day canagliflozin treatment relative to vehicle control. Additionally, canagliflozin lead to a decrease in the jejunal/ileal pH a sign for increased carbohydrate fermentation.

Feeding the rats with a glucose- and galactose-free diet (both sugars are a substrate of SGLT1) for 6 months prevented decrease in luminal pH, increased calcium excretion and hyperostosis. Hence, the interconnection between intestinal SGLT1 inhibition and increased calcium excretion/hyperostosis could be established (note that the organism has two possibilities to handle calcium that is absorbed in surplus, excreting it via kidney or storing it in bones; both options obviously were used). In this mechanistic study renal changes (hyperplasia, calcification and inflammation) were also markedly reduced. Adrenal changes (in particular hyperplasia) were also strongly reduced in the rats on glucose- and galactose-free diet. Hence, it can be expected that the pheochromocytomas observed in this species were also dependent on SGLT1 inhibition, although the pathophysiological link is less clear in this case.

Reproduction Toxicity

A fertility study in rats, embryo-foetal development studies in rats and rabbits and a pre-postnatal development study in rats were conducted with oral application of canagliflozin. An additional study on embryo-foetal development was performed using the combination of canagliflozin and metformin. Canagliflozin showed no effects on fertility and early embryonic development up to the highest dose of 100 mg/kg/day (safety margin of 73x or 19x to human therapeutic exposure at a dose of 100 mg or 300 mg).

In the embryo-foetal development study in rats with canagliflozin alone, skeletal anomalies associated with the state of ossification were observed in foetuses of the high dose canagliflozin group. The applicant contributed these findings towards maternal toxicity. However, maternal toxicity did not result in a decrease in foetal body weights, which would have been expected as a prerequisite for developmental delays in foetuses. Therefore, other effects of canagliflozin like changes in calcium homeostasis might be responsible for skeletal ossification delays in foetuses. Ossifications delays were also observed in the embryo-foetal development study with canagliflozin plus metformin. Reductions in ossifications were more pronounced for canagliflozin plus metformin than for metformin alone.

No effects of canagliflozin were observed on embryo-foetal development in the rabbit. The NOAEL was thus established at the highest dose of 100 mg/kg/day (safety margin of 70x or 19x to human therapeutic exposure at a dose of 100 mg or 300 mg).

In the study on pre-/postnatal development, the NOAEL was established at 100 mg/kg/day (safety margin of 73x or 19x to human therapeutic exposure at a dose of 100 mg or 300 mg; see table above). Effects on offspring functional development and litter parameters in F1-dams were

noticed at this dose, however, a correlation could be shown towards low absolute body weights in offspring and F1-dams.

A study on juvenile toxicity in rats which was still on-going at submission was provided with the answers to the D120 list of questions. Findings in the juvenile toxicity study in rats were in general consistent with effects seen in repeat-dose toxicity studies in adult rats. Changes in urine parameters, increases in kidney weights and hyperostosis were observed. These findings were reversible. Because of partial reversibility of pelvic dilatation in juvenile male rats, the NOAEL was established at 4 mg/kg/day corresponding to AUC values up to 2.4x and 0.6x the AUC for the 100 and 300 mg doses in humans, respectively.

Local Tolerance

The Applicant has provided two studies assessing the eye irritation and skin sensitization potential of canagliflozin to support the development of safe handling procedures during the manufacturing process.

In an eye irritation bovine corneal opacity-permeability assay, canagliflozin was classified as a borderline non to mild eye irritant. Results from a skin sensitization murine local lymph node assay indicated that canagliflozin was not a contact sensitizer.

Other toxicity studies

Phototoxicity

In vitro and *in vivo* phototoxicity studies were performed because canagliflozin shows UV absorption with an absorption peak at 291 nm. In a photo-Ames test canagliflozin was not considered to be photomutagenic.

In an *in vitro* neutral red uptake assay canagliflozin was considered to be photosensitizing *in vitro*. The photosensitizing potential of canagliflozin was further tested in pigmented rats following oral administration. Canagliflozin did not cause ocular photosensitization at any dose level in the same study. The NOAEL for photosensitization in pigmented rats was set at 5 mg/kg/day. Canagliflozin induced skin photosensitization (mild to moderate erythema and edema) at ≥ 50 mg/kg/day after UV-A and UV-B light exposure. At 500 mg/kg/day skin reactions were consistent with phototoxicity (1/5 M and 3/5 F).

Studies on Impurities

Canagliflozin hydroperoxide is formed during storage. Based on the analyses of batches so far the Applicant proposed a specification limit of 220 ppm equivalent to a maximum daily intake (DI) of 66µg/d based on the proposed maximum therapeutic daily dose. The DI was considered justified by occupational data (endogenous peroxide production and PDE calculation derived from repeated dose toxicology studies with hydrogen peroxide). Considering that the limit for hydrogen peroxide in drinking water is 100µg/l and hydrogen peroxide is also naturally occurring in fruits and vegetables up to mg-amounts/kg the additional peroxide exposure from canagliflozin hydroperoxide is minimal and considered acceptable.

2.3.5. Ecotoxicity / environmental risk assessment

Phase I:

The applicant submitted an OECD 117 study on the n-octanol/water partition coefficient. The log Kow is 1.95.

The predicted environmental concentration (PEC) of canagliflozin in surface water ($PEC_{surfacewater}$) was calculated to be 1.5 µg/L and revised to 0.163 µg/L.

The predicted environmental concentration of canagliflozin in groundwater ($PEC_{groundwater}$) was calculated to be 0.041 µg/L.

The predicted environmental concentration of canagliflozin in sediment (PECsed) was calculated to be 0.000309 mg/kg.

Canagliflozin PEC surface water, groundwater and microorganism values are below the action limits and canagliflozin is not a PBT substance as log Kow does not exceed 4.5.

Phase II:

The applicant submitted OECD 121, OECD 301, and OECD 308. As more than 10 % (65.2/58.1 % at day 14) of the active ingredient shift to sediment, risk assessment for the sediment compartment was performed by the applicant. No terrestrial assessment is required.

The applicant submitted OECD 209 (activated sludge respiration inhibition test), OECD 201 (algal growth inhibition test), OECD 211 (daphnia reproduction test), OECD 210 (fish early life stage test), and OECD 218 (sediment dweller toxicity test). In addition, short term tests on daphnia and fish were submitted (OECD 202 and 203). All tests are valid and plausible.

Table 2. Summary of main study results

Substance (INN / Invented Name): canagliflozin			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		No plausible data	not potentially PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	No plausible data	
	BCF	no plausible data	
Persistence	DT50 or ready biodegradability		not P
Toxicity	NOEC or CMR	NOEC = 0.56 mg/L (Daphnia, 21 d)	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$,	1.5 µg/l	µg/L	> 0.01 threshold Y
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 121	K_{oc} =5.9	.
Ready Biodegradability Test	OECD 301	Not readily biodegradable	
Aerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50\ water}$: 2.2 / 6.4 d $DT_{50\ whole\ system}$: 30 / 39 d $DT_{50\ sediment}$: 25.1 / 38.5 d	

		Mineralisation: 11.4 / 4.0 % (101 d) Bound residues: 34.2 / 29.4 % (101 d) Sediment shifting: 65.2 / 58.1 % (14 d)			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOErC	≥ 8	mg/L	mean measured
Daphnia sp. Reproduction Test/ *Daphnia magna*	OECD 211	NOEC	0.56	mg/L	mean measured
Fish, Early Life Stage Toxicity Test/*Species* / *Pimephales promelas*	OECD 210	NOEC	4.8	mg/L	mean measured
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	100	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC	≥ 100	mg/kg dry weight	nominal

Considering the above data, canagliflozin is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

2.3.6.1 Pharmacology

Sufficient pharmacodynamic activity of canagliflozin on SGLT2 could be demonstrated in rat and human *in vitro* models and in several *in vivo* models of mice, rats, and dogs.

No functional or binding assays were performed showing an inhibitory effect of canagliflozin on SGLT2 and SGLT1 of other species (mouse, rabbit, and dog) which were also used in the toxicology programme. However, primary and/or pharmacodynamic activity of canagliflozin has been sufficiently shown in all species included. Therefore, it is not deemed necessary to investigate canagliflozin's action on SGLT2 from these species *in vitro*.

In *in vitro* and *in vivo* safety pharmacology studies canagliflozin showed no effects on the cardiovascular and respiratory system and did not induce neurobehavioral changes. Safety margins are sufficient.

2.3.6.2. Pharmacokinetics

In humans the primary metabolic clearance pathway of canagliflozin is through its direct glucuronidation in liver whereas in animal species oxidation is the major metabolic pathway, yielding various metabolites not present in humans *in vivo* (e.g. M1, M2, M4, M6, M8). Human plasma levels of *O*-glucuronides M5 and M7 approached a peak of ~30% of the sample radioactivity. These two metabolites, M5 and M7, were not found in rat plasma at low doses. M7 was the major metabolite found in rat bile, while M5 was also present but to a lesser extent, independent of the dose. Furthermore M7 was formed in rat hepatocytes. In conclusion, rats are forming M5 and M7 and are expected to be exposed to these metabolites to a low extent although they cannot be detected in plasma by the methods used. As these metabolites are *O*-glucuronides

and showed no pharmacological activity and showed no activity against CYPs and other transporters, they are not considered as a toxicological concern.

2.3.6.3. Toxicology

In general, canagliflozin was well tolerated after repeated dosing in mice, rats, rabbits, and dogs. Mostly, toxicity findings could be attributed to an exaggerated pharmacological effect of canagliflozin (increased urinary glucose and electrolyte excretion and urine volume reduced serum glucose, reduced body weight and body weight gain). Increases in kidney weights and tubular dilatation were primarily observed in rats already at low doses and in the high doses in mice and dogs in the 3-month study (200 mg/kg/day, which was later reduced to 100 mg/kg/day). No increase in kidney weights was observed in the one year dog study (high dose 100 mg/kg/day). In the rat the limiting toxicity was hyperostosis.

The applicant hypothesised that rat-specific carbohydrate malabsorption caused by intestinal SGLT1 inhibitory activity of canagliflozin and subsequent increases in calcium absorption in the gut are causes for the observed hyperostosis. In the rat canagliflozin is absorbed slowly (C_{max} at 4-7 hours) with a low bioavailabilty (35%), which might lead to high canagliflozin concentrations in the gut lumen and a consecutive inhibition of SGLT1. As a consequence, glucose and galactose are malabsorbed which can result in increased intestinal calcium absorption due to pH lowering in the intestine caused by carbohydrate fermentation. Since increased intestinal calcium absorption was also regarded as the reason for the neoplastic findings in rat, various mechanistic studies have been performed by the applicant to verify these hypotheses. These mechanistic studies provide sufficient evidence and sound explanations of the causes of hyperostosis and increased urinary calcium excretion. As hyperostosis was not observed in other animal species and changes in bone markers and calcium excretion were not observed in clinical trials, hyperostosis is not expected to occur in humans.

In the rabbit, the primary PD effect of canagliflozin, increased urinary glucose excretion was not demonstrated. Simultaneously, *in vitro* studies on the rabbit SGLT2 are lacking. Thus, the suitability of this species (in respect to responsiveness to the study drug) for studying toxicology was not directly shown. On the other hand, there were clear signs of toxicity observed in the study which are in line with SGLT2 inhibition, in particular weight loss, increases in serum creatinine and decrease in serum sodium. Thus, it is likely that canagliflozin is effective in rabbits.

From combination studies in rats it can be concluded that that the combination of canagliflozin and metformin are well tolerated and no toxicities can be expected due to drug-drug interactions.

The observed incidences of renal tubular tumours (RTT) and pheochromocytomas were addressed by the Applicant in various mechanistic studies e.g. monitoring carbohydrate malabsorption or feeding glucose- and-galactose free diets. These studies demonstrated that renal changes (hyperplasia, calcification and inflammation) were most likely (as already expected from physiological considerations) a consequence of the need for the kidney to excrete unusual high amounts of calcium. This strongly supports the assumption that renal tumours that developed on the basis of the mentioned renal alterations were rat-specific and dependent on carbohydrate malabsorption that was not observed in humans. Furthermore, related side effects of glucose malabsorption such as flatulence or diarrhoea were not present in phase III studies, further demonstrating that this is a rat specific phenomenon.

Concerning pheochromocytomas it can be assumed that carbohydrate malabsorption, which among others may lead to shortage of glucose in the organism, along with the probably energy-dependent need of excreting high amounts of calcium induces a high adrenergic tone in the animal. This could lead to the observed adrenal hyperplasia. But even if this speculative

mechanism is not true, it is reassuring that the link between adrenal hyperplasia and rat-specific carbohydrate malabsorption could be confirmed.

Nevertheless, the provided hypothesis relies on the fact that canagliflozin is poorly absorbed in the rat, with a bioavailability of 35%, leading to increased local concentrations in the gut capable of inhibiting SGLT1. The Applicant provided a theoretical estimate of the local concentrations of canagliflozin in the gut, arriving at a 12-fold higher concentration in rats at 100 mg/kg (dose which resulted in pheochromocytoma and RTT), as compared to humans treated with 300 mg (the highest clinical dose). Considering the differences in pharmacokinetics between rats and humans, the actual ratio is likely to be higher.

The exact concentration needed to inhibit intestinal SGLT1 is difficult to estimate, given that canagliflozin is a competitive SGLT inhibitor and that local glucose as well as drug concentrations are likely to vary depending on meal intakes. Referring to data from one clinical and one rat study, the Applicant argued that the results clearly demonstrate the difference between rats and humans, showing glucose malabsorption in rats at 100 mg/kg but not in humans at 300 mg. It was possible to demonstrate inhibition of a SGLT1 substrate in rats, further strengthening the hypothesis of low oral bioavailability in the rat, leading to a longer intestinal dwelling time with consequently higher local concentration of canagliflozin.

In conclusion, the Applicant's line of argument in support for a rat-specific inhibitory effect on intestinal SGLT1 is convincing and acceptable as a plausible mechanism behind the disturbed calcium homeostasis and associated tumourigenic effect in the rat carcinogenicity study.

Occurrence of LCTs might be due to decreases in testosterone levels and subsequent increases in LH levels upon canagliflozin treatment. The outcome of the conducted toxicity studies were LH and testosterone levels were measured are controversial and do not give a final mechanistic explanation of incidences of LCTs in the rat. Nevertheless, the rat has been shown to be susceptible to develop LCTs in other carcinogenicity studies by various non-genotoxic agents. Furthermore, LCTs found in rats after canagliflozin treatment were mostly benign. It can be concluded, that occurrence of LCTs is most likely species specific.

In the study on fertility and early embryonic development in SD rats, canagliflozin showed no effects on male and female fertility and reproductive performance

Skeletal anomalies associated with the state of ossification (reduced ossification of metatarsal bones) were observed in foetuses of the high dose canagliflozin alone group in the embryo-foetal development study in rats. The applicant considered the skeletal findings to be related to the reduced maternal body weight gain and thus to maternal toxicity. However, maternal toxicity did not result in a decrease in foetal body weights, which would first have been expected as a sign of developmental delay and would then result in skeletal anomalies. It was also not possible to correlate those dams showing clear effects on body weights with foetuses showing skeletal anomalies. Ossifications delays were also observed in the embryo-foetal development study with canagliflozin plus metformin. Reductions in ossifications were more pronounced for canagliflozin plus metformin than for metformin alone. Skeletal findings might be attributed to disturbances in calcium homeostasis.

The NOAEL for offspring functional development and reproductive performance was at the high dose of 100 mg/kg/day, as effects observed on development in high dose pups (air righting response, sexual maturation) and on pregnancy parameters of high dose F1-dams correlated with low absolute body weights of offspring and dams.

Canagliflozin was considered to be photosensitizing *in vitro* and showed skin photosensitization in pigmented rats. However, clinical data (see clinical section for detailed discussion) indicated that phototoxicity would play only a role at light intensities beyond bright daylight.

2.3.6.4. Ecotoxicity / environmental risk assessment

Canagliflozin PEC surface water, groundwater and microorganism values are below the action limits and canagliflozin is not a PBT substance as log Kow does not exceed 4.5.

Considering the available data, canagliflozin is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The CHMP was of the view that the PD activity of canagliflozin has sufficiently been demonstrated in *in vitro* and *in vivo* models.

In non-clinical animal species canagliflozin has been demonstrated to be well tolerated and toxicity findings are generally related to an exaggerated pharmacological effect of canagliflozin. Hyperostosis, renal and tumour findings are considered to be a rat specific phenomenon. Rat skeletal findings might be attributed to disturbances in calcium homeostasis. These findings are considered to have no consequence to humans.

Observed phototoxicity *in vitro* and in rats is not considered to be clinically relevant.

With regards to the ERA, the data submitted so far do not indicate a risk for the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

The table below summarizes the phase 3 clinical trials that have been submitted in support of this application:

Table 3: Phase III Clinical Studies of CANA

Study ID/Type (No. Centers)	Study Design, Duration (Duration to primary endpoint/ Duration of extension phase)	HbA_{1c} Inclusion Criterion	Study Treatment Daily Dosing (QD)	No. Subjects per Treatment Arm (mITT)	Primary Efficacy Endpoint
MONOTHERAPY					
DIA3005 Main Study[a] Monotherapy (90 centers)	R, DB, PC, PG 52 weeks double-blind (26 wks / 26 wks)	≥7.0% to ≤10.0%	Placebo CANA 100 mg CANA 300 mg	192 195 197	Δ BL to Wk 26 in HbA_{1c}
High Glycaemic substudy Monotherapy (40 centers)	R, DB, PG 26 weeks double-blind (26 wks / no extension)	>10.0% to ≤12.0%	CANA 100 mg CANA 300 mg	47 44	Δ BL to Wk 26 in HbA_{1c}
ADD-ON TO AHA MONOTHERAPY					
DIA3006[a] Add-on to metformin monotherapy (169 centers)	R, DB, PC, AC, PG 52 weeks double-blind (26 wks / 26 wks)	≥7.0% to ≤10.5%	Placebo CANA 100 mg CANA 300 mg Sitagliptin 100 mg	183 368 367 366	Δ BL to Wk 26 in HbA_{1c}
DIA3009 Add-on to metformin monotherapy (157 centers)	R, DB, AC, PG 104 weeks double-blind (52 wks / 52 wks)	≥7.0% to ≤9.5%	CANA 100 mg CANA 300 mg Glimepiride (titrated from 1 to 6 or 8 mg)	483 485 482	Δ BL to Wk 52 in HbA_{1c}
ADD-ON TO DUAL COMBINATION AHA THERAPY					
DIA3002 Add-on to metformin + sulphonylurea (85 centers)	R, DB, PC, PG 52 weeks double-blind (26 wks / 26 wks)	≥7.0% to ≤10.5%	Placebo CANA 100 mg CANA 300 mg	156 157 156	Δ BL to Wk 26 in HbA_{1c}
DIA3012[a] Add-on to metformin + pioglitazone (74 centers)	R, DB, PC, PG 52 weeks double-blind (26 wks / 26 wks)	≥7.0% to ≤10.5%	Placebo CANA 100 mg CANA 300 mg	115 113 114	Δ BL to Wk 26 in HbA_{1c}
DIA3015 Add-on to metformin + sulphonylurea (140 centers)	R, DB, AC, PG 52 weeks double-blind (52 wks / no extension)	≥7.0% to ≤10.5%	CANA 300 mg Sitagliptin 100 mg	377 378	Δ BL to Wk 52 in HbA_{1c}
SPECIAL POPULATION STUDIES					
DIA3010 Older adults (≥55 to ≤80 years of age) (90 centers)	R, DB, PC, PG 104 weeks double-blind (26 wks / 78 wks)	≥7.0% to ≤10.0%	Placebo CANA 100 mg CANA 300 mg	237 241 236	Δ BL to Wk 26 in HbA_{1c}
.					
SPECIAL POPULATION STUDIES					
DIA3004 Moderate renal	R, DB, PC, PG 52 weeks	≥7.0% to ≤10.5%	Placebo CANA 100	90 90	Δ BL to Wk 26 in HbA_{1c}

Study ID/Type (No. Centers)	Study Design, Duration (Duration to primary endpoint/ Duration of extension phase)	HbA_{1c} Inclusion Criterion	Study Treatment Daily Dosing (QD)	No. Subjects per Treatment Arm (mITT)	Primary Efficacy Endpoint
impairment (eGFR ≥30 to <50 mL/min/1.73m^2) (89 centers)	double-blind (26 wks / 26 wks)		mg CANA 300 mg	89	
CARDIOVASCULAR ASSESSMENT STUDY WITH EFFICACY SUBSTUDIES					
DIA3008 Cardiovascular study (369 centers)	R, DB, PC, PG Duration is event driven based on number of MACE events	≥7.0% to ≤10.5% (with history or high risk of CV disease)	Placebo CANA 100 mg CANA 300 mg	1441[b] 1445[b] 1441[b]	Assessment of hazard ratio for MACE events
Glycaemic Efficacy Substudies					
Insulin substudy (316 centers)	R, DB, PC, PG 18 weeks double-blind (18 wks / no extension)	≥7.0% to ≤10.5% while receiving insulin as monotherapy or in combination with other AHAs[c]	Placebo CANA 100 mg CANA 300 mg	565 566 587	Δ BL to Wk 18 in HbA_{1c}
Sulphonylurea substudy (80 centers)	R, DB, PC, PG 18 weeks double-blind (18 wks / no extension)	≥7.0% to ≤10.5% while SU monotherapy[d]	Placebo CANA 100 mg CANA 300 mg	45 42 40	Δ BL to Wk 18 in HbA_{1c}

[a] Subjects assigned to placebo were switched to sitagliptin during the double-blind extension period.

[b] Randomized and treated subjects (ie, safety analysis set).

[c] The primary analysis population discussed in this ISE for the DIA3008 Insulin substudy was defined as subjects randomized to any of the 3 insulin strata who were receiving insulin ≥30 IU/day at study entry (Population 2).

[d] The primary analysis population discussed in this ISE for the DIA3008 SU Substudy was defined as subjects on protocol-specified doses of SU monotherapy regardless of the stratification used for randomization (Population 1).

Key: Δ = change from, AC = active-controlled, AHA = anti-hyperglycaemic agent, BL = baseline, CV = cardiovascular, DB = double-blind, eGFR = estimated glomerular filtration rate, MACE = major adverse cardiovascular events, mITT = modified intent-to-treat population, No = number, PC = placebo-controlled, PG = parallel group, QD = once daily, R = randomized, SU = sulphonylurea; wks = weeks.

2.4.2. Pharmacokinetics

Pharmacokinetics (PK) and pharmacodynamics (PD) of canagliflozin were investigated in 35 Phase 1 clinical pharmacology studies and in 5 biopharmaceutic studies.

An overview is presented in the table below.

Table 4 : Number of Studies and Number of Subjects Administered Canagliflozin in Studies Included in the Summary of Clinical Pharmacology Studies

Type of Study	Number of Studies	Population	Number of Subjects
Phase 1			
Mass-Balance	1 (NAP1006)	Healthy subjects	6
Single-Dose	3 (NAP1001, DIA1001, DIA1015)	Healthy subjects	89 (48+17+24)
Multiple-Dose	3 (NAP1008, DIA1030, DIA1032)	Healthy subjects (healthy obese subjects in NAP1008)	121 (60+27+34)
	3 (NAP1002, DIA1007, DIA1023)	Subjects with T2DM	140 (93+20+27)
PD	1 (DIA1022)	Healthy subjects	24
	2 (DIA1025, DIA1045)	Subjects with T2DM	51 (14+37)
Hepatic Impairment	1 (DIA1013)	Otherwise healthy subjects with mild or moderate hepatic impairment or normal hepatic function	16
Renal Impairment	1 (DIA1003)	Otherwise healthy subjects with mild, moderate, or severe renal impairment, with end-stage renal disease, or with normal renal function	40
Non-Caucasian Subjects	3 (TA-7284-01, TA7284-02, DIA1008)	Japanese subjects (healthy and T2DM) or healthy Indian subjects	96 (30+51 +15)
Drug-Drug Interaction	12 (NAP1004, DIA1002, DIA1004, DIA1006, DIA1009, DIA1014, DIA1016, DIA1028, DIA1029, DIA1031, DIA1034, DIA1048)	Healthy subjects	248 (16+28+ 29+28+22+ 18+13+18+ 14+18+30+ 14)
QT/QTc	1 (DIA1010)	Healthy subjects	58
Photosensitivity	4 (NAP1005, DIA1011, DIA1019, DIA1020)	Healthy subjects	67 (12+25+24+ 6)
Phase 2	1 (DIA2001)	Subjects with T2DM	287
	1 (OBE2001)	Nondiabetic obese subjects	250
Phase 3	3 (DIA3004, DIA3005, DIA3009)	Subjects with T2DM	839 (160+220+45 9)
Total	40		2,332

Number of subjects refers to those subjects who received at least 1 dose of canagliflozin, and only subjects from the Phase 2 and Phase 3 studies that were included in the population PK analysis.

Absolute oral bioavailability was investigated in study DIA 1021. In vivo metabolism of 14C-canagliflozin was studied in feces, urine, and plasma collected from healthy male subjects after a single oral dose of 192 mg 14C-canagliflozin in a mass-balance study (study NAP1006).

Single dose PK was investigated in healthy subjects in study NAP1001, DIA 1001 and DIA 1015, multiple dose PK in Study NAP1008, DIA1030, and DIA 1032. In subjects with T2DM single and multiple dose PK was investigated in study NAP1002, DIA 1007, and DIA 1023, and in addition (supportive) in study TA-7284-02. In addition to the Phase 1 clinical pharmacology studies, PK and/or PD assessments of canagliflozin from 2 Phase 2 studies and 3 Phase 3 studies were included in population PK analyses.

Analytical methods were validated and appropriately described for the determination of canagliflozin by LC-MS/MS, for the metabolites M5 and M7 (LC-MS/MS methods), the α-anamer

and the drugs determined in the interactions studies. Specific issues are discussed in the context of the respective studies. PK data and statistical analyses were appropriate.

Major findings related to GCP were reported by the applicant for some studies and the PK data for canagliflozin from these studies (NAP1001, NAP1002, NAP1004, NAP1005, NAP1006, and NAP1008) were not considered reliable and therefore were not presented. Only PK data from metabolites and PD data were reported from these studies.

The bridging strategy between different formulations used in the clinical development included preclinical considerations, cross study PK comparisons, PD comparisons, gastro plus simulations, the investigation of physicochemical characteristics and two relative bioequivalence studies (DIA1017 and (supportive) TA-7284-03). All data obtained with the different formulations used during the clinical program (oral suspension, tablets with high-shear granulation (HSG), fluid-bed granulation (FBG), non-particle-engineered and particle-engineered (NPE, PE), without and with film-coating) are considered transferable to the to-be-marketed formulation.

An overview over the PK parameters across studies is provided below as a summary of pooled analyses in Table 5 (single dose PK across studies) and in Table 6 (multiple dose PK across studies).

Table 5: Pharmacokinetic Parameters of Canagliflozin Following Single-Dose Administration of 100 and 300 mg Canagliflozin in Healthy Subjects (Pooled Analysis)

	100 mg			300 mg		
Parameter	N	Mean (SD)	%CV	N	Mean (SD)	%CV
t_{max}, h [a]	33	1.50 (1.00 - 5.00)	-	178	1.98 (0.98 - 6.00)	-
C_{max}, ng/mL	33	1,059 (274)	25.9	178	2,792 (760)	27.2
AUC_{∞}, ng.h/mL	28	6,818 (1,542)	22.6	176	22,953 (5,633)	24.5
$t_{1/2}$, h	28	10.6 (2.13)	20.1	176	13.1 (3.28)	25.0

CV = coefficient of variation, N = number of subjects.
Studies included in the pooled analysis for the 100-mg dose: DIA1015 and DIA1030.
Studies included in the pooled analysis for the 300-mg dose: DIA1008, DIA1013, DIA1015, DIA1017, DIA1021, DIA1029, DIA1030, and DIA1043.
[a] Median (range).

Table 6: Pharmacokinetic Parameters of Canagliflozin Following Multiple-Dose Administration of 100 and 300 mg Canagliflozin in Healthy Subjects (Pooled Analysis)

	100 mg			300 mg		
Parameter	N	Mean (SD)	%CV	N	Mean (SD)	%CV
t_{max}, h [a]	38	1.00 (1.00 - 4.00)	-	114	1.42 (1.00 - 6.00)	-
C_{max}, ng/mL	38	1,029 (221)	21.5	114	3,148 (866)	27.5
AUC_{24h}, ng.h/mL	38	6,247 (1,196)	19.1	114	22,612 (5,051)	22.3

CV = coefficient of variation, N = number of subjects.
Studies included in the pooled analysis for the 100-mg dose: DIA1019, DIA1030, and DIA1032.
Studies included in the pooled analysis for the 300-mg dose: DIA1019, DIA1028, DIA1030, DIA1031, DIA1032, DIA1034, and DIA1048.
[a] Median (range).

Absorption

Canagliflozin was rapidly absorbed. T_{max} was approximately 1 to 2 hours and was independent of the dose. In-vitro investigations in colon carcinoma-derived (Caco)-2 cells suggested an intermediate permeability and the involvement of the efflux pump P-gp in the human intestine. The oral bioavailability was about 65%.

There was no effect of food on PK as demonstrated in a single dose study (DIA 1043) with 300 mg tablets. Similarly there was no food effect on PD parameters (Study NAP1001, part 2)).

Canagliflozin may therefore be taken with or without food. Considering that doses at about 300 mg may delay glucose absorption (see below) it is advised to take canagliflozin before breakfast.

Distribution

The mean apparent volume of distribution at steady state (Vss) of canagliflozin following a single i.v. infusion in healthy subjects was 119 L. This suggests an extensive tissue distribution. There was no relevant redistribution to blood cells. In vitro plasma protein binding of canagliflozin was 98.3% to 98.5%, predominantly to human serum albumin (97.3%)

Elimination

In plasma, mainly unchanged canaglifglozin was measured (about 57% of the plasma exposure). Among the metabolites the inactive o-glucuronides M5 and M7 were most important, accounting for 1.9 – 30% and 16 – 29% of the plasma exposure, respectively, depending on the time point. In vitro, other metabolic pathways in human hepatocytes were carboxylation (M6, 2%) and monooxygenation (M9, 1%). Metabolite M9 was also found in human liver microsomes. It accounts for 2.4% to 3.7% of the total drug-related components in human plasma. Metabolites M7 (17% of a radioactively labelled dose) and M5 (13%) were found in urine, M9 (7.0%) and M7 (3.2%), but not M5 were detected in faeces. Anomerisation of the β-anomer to the α-anomer did not occur to a clinically relevant amount.

The clearance of canagliflozin was about 12.2 L/h indicating a low clearance drug. Mean $t_{1/2}$ was dose independent and was between 10.6 and 13.1 hours over the clinical studies for doses between 100 and 300 mg qd. Oral doses were excreted by approximately 60% via faeces and by about 33% by the kidneys. Across studies, renal excretion of unchanged canaglifozin was below 1%, and of M5 and M7 13.3 and 17.2%, respectively. To the contrary, in the feces unchanged canagliflozin accounted for 40% and the metabolites M9 and M7 were detected only in low concentrations (7.0 and 3.2%, respectively). De-glucuronidation in the faeces may be a possible explanation for the absence of M5 in faeces. Although no human data on biliary excretion of unchanged drug are available, most likely glucuronidation is the major elimination pathway, and biliary excretion of unchanged canagliflozin is not a major route of elimination. The potential for a clinically relevant interaction based on hepatic transporter inhibition is considered low. No enterohepatic pathway of clinical relevance was observed.

No inhibition or inhibition only at high concentrations was observed for several UGTs studied in an in vitro study (UGT1A4, UGT1A9, UGT1A1, UGT1A6 and UGT2B7). Based on the expected in vivo concentrations no interaction is foreseen at therapeutic systemic levels.

Whereas the role of genetic polymorphisms for UGT2B4 remains to be determined, there was a robust finding of increased exposure in the range of about 26 - 54% of canagliflozin carrying UGT1A9*3 alleles, trough concentrations were 81% higher for carriers of the UGT1A9*3 allele. Since the individual values were within the overall observed range dose adaption in patients with known UGT1A9 and UGT2B4 alleles is not considered necessary.

Dose proportionality and time dependencies

C_{max} and AUC values increased dose proportional (50 – 300mg qd) after single dose and multiple dose administration. There was no time dependent accumulation when canagliflozin was administered at multiple doses. The exposure was about 36% higher at steady state which was reached after about 4 days of qd dosing with 50 to 300 mg canagliflozin. The exposure (AUC) was not different between qd and bid administration.

Special populations

There were no relevant differences in the PK of canagliflozin between healthy subjects and patients with T2DM.

Patients with severe hepatic failure with a Child-Pugh-Score >9 were not investigated. In patients with mild to moderate hepatic failure, only mild changes were observed, i.e. C_{max} and AUC values increased by less than 11%. Oral clearance was unchanged and the differences in volume of distribution (approx. 14% greater and approx. 20% lower in subjects with mild and moderate hepatic impairment as compared to subjects with normal hepatic function) and $t_{1/2}$ (14.8h, 17.6h, and 13.1h in subjects with normal hepatic function and mild and moderate hepatic impairment, respectively) are not considered of clinical relevance. In conclusion, dose adaption is not considered necessary in patients with mild to moderate hepatic impairment for PK reasons.

In subjects with renal failure there was an increase in exposure that could not be explained by changes in renal clearance per se since renal clearance of unchanged canagliflozin is <1%. AUC was higher in subjects with a CLCR 50 to <80 mL/min by about 17%, with CLCR 30 to <50 mL/min by about 63%, and with a CLCR <30 mL/min by about 50%. No change was observed in patients with end-stage renal disease requiring haemodialysis. It is unclear to which extent baseline differences not related to renal function or indirect effects have contributed to the result.

Dose normalized AUC values were 22% higher in females. This is not considered of clinical relevance in the absence of other factors increasing exposure.

There was no relevant difference in PK, dose proportionality and exposure between Western, Japanese and Indian subjects. The moderately higher exposure of 33% observed in subjects weighing <78.2 kg as compared to subjects weighing >95.2 kg is not considered of clinical relevance.

However, in the elderly the observed increase in AUC values by about 29% could be relevant. Since in elderly subjects BP lowering effects may be more relevant for safety reasons, the recommended dose titration starting at 100 mg is appropriate.

Pharmacokinetic interaction studies

In-vitro investigations indicated potential interactions at the level of P-gp, MDR1 and MRP2 transporters. Canagliflozin does not appear to be a transported by NTCP, OAT1, OAT3, OATP1B1 or OCT1. Neither does it seem to inhibit OATP1B1 OAT1, OAT3, NTCP, OCT1 and OCT2. P-gp appears to be inhibited at an intestinal level (IC50 19 uM in MDCK cells using digoxin as substrate) and possibly also to some extent systemically (in the kidney).

Canagliflozin (10 µM [4,440 ng/mL]) did not induce CYP1A2, 2C9, 2C19, or 3A4 activity in human hepatocytes. In human liver microsomes canagliflozin and M7 were weak inhibitors of CYP2B6 and 2C8. Probe specifically CYP2C9 and CYP3A4 was also weakly inhibited by canagliflozin, with testosterone (IC50 = 27 µM) as a substrate, but not with midazolam. In-vitro investigations indicated potential interactions at the level of P-gp, MDR1 and MRP2 transporters, CYP3A4 and CYP2C9 to be addressed in clinical DDIs. Canagliflozin is primarily metabolized by glucuronidation. The isoenzyme CYP3A4 is involved in the formation of metabolite M9. Interactions studies are not considered necessary for CYP 3A4. Clinically relevant interactions were observed only for Rifampin and Digoxin.

A clinically relevant interaction occurred at the level of UGTs involved in the formation of M5 and M7. Rifampin mediated enzyme induction decreased plasma Cmax of canagliflozin by 30% and AUC by 52%, respectively. The nonspecific inhibitor of UGTs probenecid, on the other hand, increased plasma $C_{max,ss}$ and $AUC_{T,ss}$ values for canagliflozin by about 13% and 21%, respectively. In addition, cyclosporine, a potent inhibitor of P-gp increased AUC values by 23%.

HCTZ increased canagliflozin AUC by about 8 – 12%. More importantly, there was a numerical increase in orthostatic hypotension, when both drugs were coadministered. There was a moderate

increase in AEs related to volume depletion in patients pre-treated with HCTZ. This is covered in the SPC in section 4.4 and 4.5.

Canagliflozin increased Cmax of ethinyl estradiol and levonorgestrel by 22%, but did not change the overall exposure. Cmax and AUCinf of simvastatin and of simvastatin acid were slightly increased by canagliflozin by numerically 9 – 12% (simvastatin) and 18 – 26% (simvastatin acid), respectively. No relevant PK interactions were observed at the level of CYP2C9 for Gliburide and Warfarin INF values were also not affected. Canagliflozin did not change the PK of Metformin by a clinically relevant amount. Co-administration of canagliflozin increased the Cmax of digoxin by about 36% and AUC levels by about 20%. Since Digoxin has a narrow therapeutic range this interaction should be mentioned in the SmPC. The assumed mechansim, an inhibition at the level of P-gp is also relevant for other digitalis glycosides.

A DDI with dabigatran has not been performed. Based on the data provided, the likelihood of co-administration in the relevant patient population seems to be low and a clinical DDI is not considered necessary. The theoretical potential for a PK interaction is included in the SmPC.

2.4.3. Pharmacodynamics

Mechanism of action

Canagliflozin is an orally active, reversible inhibitor of SGLT2 (50% inhibitory concentration [IC50] of 4.2 nM [1.86 ng/mL]) that is being developed as an oral anti-hyperglycaemic agent. In addition, canagliflozin also possesses intrinsic, albeit substantially less potent, SGLT1 inhibitory activity. The low-affinity/high-capacity SGLT2 transporter in the early proximal convoluted renal tubule reabsorbs most of the filtered glucose. A relatively small amount of glucose is reabsorbed by SGLT1, a high-affinity/low-capacity glucose transporter. By inhibiting SGLT2, the transporter responsible for the majority of renal glucose reabsorption, canagliflozin lowers the renal threshold for glucose excretion (RT_G), thereby leading to increased UGE and decreased plasma glucose concentrations in hyperglycaemic subjects. The increased UGE with SGLT2 inhibition also translates to a loss of calories and weight loss.

Primary and Secondary pharmacology

Primary pharmacology

Canagliflozin inhibits SGLT2 and with considerably lower affinity SGLT1.

In **healthy subjects**, canagliflozin increased mean 24-hour urinary glucose excretion (UGE24h) by up to 60 – 70 g. The maximal effect was achieved at doses ≥200 mg qd. The 24-hour mean renal threshold of glucose excretion (RTG) decreased dose-dependently with single- and multiple-dose administration of canagliflozin. A maximal decrease to about 50 – 60 mg/dL could be achieved. No relevant differences were observed after single dose or multiple dose administration and between qd and bid dosing of 100 mg and of 300 mg at steady state.

In **patients with T2DM,** the effect of canagliflozin on UGE was more pronounced (≥ 100 g/day at doses > 100 g/day). This can be explained by the fact that UGE is influenced by both glucose plasma concentrations and GFR. The maximal effect on UGE24h was seen at doses ≥ 200 mg qd or even at lower doses. As expected, (pretreatment) RTG baseline values were generally higher in the patients with T2DM than the commonly reported values of 180 to 200 mg/dL for healthy subjects. RTG was related to 24h mean plasma glucose (MPG). Canagliflozin decreased 24-hour mean RTG in a dose-dependent manner. A maximal decrease to about 70 to 90 mg/dL was achieved with doses ≥ 200 mg qd.

Fasting plasma glucose (FPG) concentrations, post prandial glucose concentrations and 24-hour mean plasma glucose (MPG24h) decreased in a dose-dependent manner in subjects with T2DM. A mean decrease of FPG by ≥40 mg/dL and of MPG24h by ≥30 mg/dL was achieved with doses of 100 mg qd and higher.

Over the whole period of 4 weeks in the clinical pharmacology program the effect on UGE, RTG and reductions in FPG and MPG24h was sustained.

Based on the PD results, a maximum daily dose of 300 mg of canagliflozin appears justified.

A delay in post prandial glucose absorption with decreased post prandial glucose excursions was observed with 300 mg canagliflozin in healthy subjects and patients with T2DM that was independent from the effect on UGE. This effect was not explained by delayed gastric emptying and may possibly be due to inhibition of intestinal SGLT1 by high intestinal concentrations of canagliflozin after oral intake.

Placebo-adjusted decreases in body weight by approximately 1.3 – 2.2 kg in healthy volunteers and by 1 - 1.5 kg in subjects with T2DM, respectively, were observed during 2 to 4 weeks of canagliflozin administration. This was not due to changes in appetite and satiety, as assessed by VAS in different studies. Both nutrient loss due to renal glucose excretion and osmotic diuresis may contribute to this effect.

The data for insulin sensitivity in the therapeutic dose range were not conclusive. At supratherapeutic doses (400 mg qd and 300 mg bid) improvements in insulin sensitivity were observed after 2 weeks. For lower doses no significant effects were seen over 2 weeks in the pharmacology program. In the clinical program there were trends toward an improvement but no statistically significant effects.

As an indicator of beta cell function, insulin secretion rate increased by more than 50 % with canagliflozin 100 mg qd.

Secondary pharmacology

The Applicant conducted a thorough QT/QTc study in 60 healthy subjects as a randomized, double-blind, placebo- and positive-controlled (moxifloxacine 400 mg), double-dummy, 4-way crossover, single-center trial of oral CANA at therapeutic (300 mg) and supratherapeutic (1,200 mg) doses, administered as single doses. QT intervals were extracted from continuous 12-lead ECG Holter recordings and corrected according to Fridericia (QTcF), Bazett (QTcB) and study-specific power (QTcP) correction methods.

Moxifloxacin, the positive control, yielded the expected results (QTc prolongation by 5 to 10 ms). Neither visual inspection of the results nor formal statistical analysis gave any hint that CANA could prolong the QT interval in a relevant way.

Pharmacodynamic interactions

No PD interactions were observed between canagliflozin and simvastatin, or warfarin. Co-administration with HCTZ was associated with a small increase in RTG and mean plasma glucose leves and slightly lower UGE. Co-administration of canagliflozin 300 mg qd with metformin 2000 mg qd was associated with a slight decreased in UGE24h, a slight increase in RTG and no effect on plasma glucose levels as compared to canagliflozin alone. Co-administration with gliburide was not associated with synergistic or additive effects. Cmax of plasma glucose were similar, when canagliflozin was administered alone or in combination with gliburide, AUC 0-4 and AUC0-10 was slightly lower in the combination group AUC0-24 was even slightly above the value for canagliflozin alone.

2.4.4. Discussion on clinical pharmacology

Overall, absorption, distribution, metabolism and elimination of canagliflozin have been adequately characterised. Time dose and time dependency were investigated in healthy subjects and in patients with T2DM patients. In subjects with T2DM PK was comparable to healthy subjects and there were no relevant differences attributable to race.

Transferability of the data of the clinical program to the marketing formulation has been demonstrated. The final formulation has been used sufficiently in phase III studies.

Albeit canagliflozin is sensitive to light, the applicant has demonstrated that this was not relevant in the clinical program.

The effect of food on C_{max} and T_{max} in one study (TA-7284- part 2) can possibly be attributed to the formulation (oral suspension). It still remains to be determined to which extent unabsorbed drug, biliary excreted drug or, potentially, excreted hydrolysed (unstable during analysis procedures) glucuronide contribute to unchanged canagliflozin in faeces. The UGT2B4 contribution has not been confirmed in vivo, but a clinically meaningful drug-drug interaction at this level is unlikely.

Mild to moderate differences in exposure relating to gender, body weight and mild to moderate hepatic failure are not considered of clinical relevance per se but exposure may possibly be more pronounced in case these conditions coincide. Since patients with severe hepatic failure were excluded from the pharmacological and clinical development program, use of canagliflozin is not recommended in these patients.

The increase in exposure in elderly subjects by 29% could be of relevance with respect to dehydration-related AEs such as a decrease in BP. Therefore, initial dose titration as recommended (starting with 100 mg qd) is considered appropriate.

In patients with renal failure there was an increase in exposure related to the degree of renal failure by up to 63% in patients not on haemodialysis. In patients with end stage renal failure on haemodialysis, exposure was unchanged. Canagliflozin cannot be eliminated by haemodialysis. Due to efficacy and safety considerations, a reduced dose of 100 mg/d of canagliflozin is recommended in patients with eGFR below 60 ml/min/1.73m^2 and canagliflozin should not be used in patients with an eGFR <45 ml/min/1.73m^2

PK simulations indicated that factors like body weight, BMI, renal function, age, gender, and UGT1A9 carrier status, when combined, may lead to an increased exposure by 52 – 78% for Cmax and 63 – 125% for AUC in worst case scenarios. The decision for a dose escalation in these patients should mainly be based on tolerability considerations. This is adequately described in the product information.

In the pharmacogenomic-exposure analysis using data from phase I, phase II, and phase III studies mean plasma canagliflozin trough concentrations were 81% higher for carriers of the UGT1A9*3 allele (21 carriers and 711 non-carriers). As pooled analysis may dilute the PGx effect, the applicant discussed whether the size of the effect was as expected based on the in vitro and in vivo data and the scientific literature. The effects are reflected in the SmPC.

The interaction profile has been well characterized addressing the metabolic pathways and clinically relevant co-administered drugs. Substrate activity of M5 and M7 for human OAT3 and MRP2 was not assessed, which is not considered of clinical relevance. It was questioned whether the interaction with digoxin is sufficiently representative for a possible interaction with dabigatran but the applicant has provided data that substantiated that the likelihood of coadministration is low and therefore no clinical DDI study is required.

A new in vitro study was provided to address the inhibitory potential of canagliflozin on BCRP and OATP1B3 and whether it is a substrate. Canagliflozin was found to be a substrate for BCRP but not for OATP1B3. Since BCRP inhibition by canagliflozin in the GI tract may not be excluded, this is adequately addressed in the labelling. Canagliflozin showed some inhibition of OATP1B3 but, based on comparisons with estimated hepatic inlet concentrations, in vivo inhibition of OATP1B3 can be excluded.

The applicant has performed two in vitro induction studies. Neither of them included high enough concentrations for intestinal 3A4 induction to be investigated. However, this may not be possible due to cell toxicity. Shorter incubation times than usual were applied. This was appropriate for mRNA measurements. A single dose of cyclosporine, a potent inhibitor of P-gp, increased AUC values by 23%. The applicant has performed a "simulation" of the effect of cyclosporine at steady state in comparison with a single dose. In the present SmPC cyclosporine is listed among drugs not affecting canagliflozin exposure. This is considered appropriate as the small additional effect is not considered to be a problem from a safety perspective.

There is no interaction study with cholestyramine. HCTZ increased canagliflozin AUC by about 8 – 12%. Canagliflozin increased C_{max} of ethinyl estradiol and levonorgestrel by 22%, but did not change the overall exposure. C_{max} and AUCinf of simvastatin and of simvastatin acid were slightly increased by canagliflozin by numerically 9 – 12% (simvastatin) and 18 – 26% (simvastatin acid), respectively. No relevant PK interactions were observed at the level of CYP2C9 for Gliburide and Warfarin INF values were also not affected. Canagliflozin did not change the PK of Metformin by a clinically relevant amount. Co-administration of canagliflozin increased the C_{max} of digoxin by about 36% and AUC levels by about 20%. Since Digoxin has a narrow therapeutic range this interaction is included in the SmPC. The assumed mechanism, an inhibition at the level of P-gp, is also relevant for other digitalis glycosides.

Taken together the PK characteristics of canagliflozin are well characterized for healthy subjects and subjects with T2DM. The differences in exposure in the a.m. subgroups and the relevant interactions have been sufficiently addressed in the SmPC.

The PD effect on UGE was more pronounced in patients with T2DM than in healthy subjects. There was a ceiling effect on RTG with daily doses ≥200 mg indicating a low potential of hypoglycaemia induced by canagliflozin even in case of overdosage. The exposure response relationship indicated that the EC50 values based on free (unbound) canagliflozin concentrations were 0.21 to 0.32 ng/mL (0.5 to 0.7 nM). Considering the excretion of canagliflozin (<1%) , the concentrations of canagliflozin in the lumen of the proximal tubule was estimated to be similar to the unbound concentrations in plasma, which is about 6 to 8 times lower as compared to the estimated in vitro IC50 value of 4.2 nM. The applicant has pointed out that the low dissociation rate of canagliflozin from SGLT2 may provide an explanation for the difference between in vitro IC 50 values and estimated concentrations.

In subjects with renal failure the effect on UGE was inversely related to renal function. In addition to the higher exposure in these patients the results in non-diabetic subjects suggested that, below a CLCR of 40 – 50 ml/min, a relevant clinical efficacy may not be expected. This is further discussed in the context of efficacy and safety in the clinical studies in patients with T2DM.

Data on urinary output in response to canagliflozin has been presented in response by the Applicant. Urinary volume was moderately increased with a trend to a dose-response relationship, consistent with an osmotic diuresis. Serum creatinine and BUN increased moderately, transient mild increases in serum Mg and phosphate were observed, as well as transient increases in urinary excretion of sodium.

2.4.5. Conclusions on clinical pharmacology

The applicant performed several clinical pharmacology studies to investigate the relevant pharmacological aspects of canagliflozin. Overall, pharmacokinetics and pharmacodynamics were sufficiently investigated.

2.5. Clinical efficacy

Three Phase 2 studies and 9 Phase 3 studies have been submitted in support of the current application. The 9 Phase 3 studies, apart from providing support for the sought indication, also include one study in elderly and one study in patients with moderate renal impairment.

The Phase 2 studies DIA2001 and TA-7284-04 were dose-finding studies. Study OBE2001 investigated the effect of canagliflozin on body weight in non-diabetic subjects. This study is not considered relevant for the current application and will not be further discussed.

Across the Phase 3 clinical studies, a total of 7,803 subjects were randomized and received at least 1 dose of study drug. This included 4,994 subjects treated with canagliflozin (100 mg or 300 mg), 1,583 treated with placebo, and 1,226 treated with an active comparator (744 sitagliptin, 482 glimepiride).

2.5.1. Dose response studies

Study DIA2001 was a placebo-controlled dose-finding study for canagliflozin in T2DM subjects whose glycaemia was not optimally controlled with maximally (or near maximal) effective doses of metformin. A total of 451 subjects, randomized to 1 of 7 treatment groups (65 placebo, 64 canagliflozin 50 mg qd, 64 canagliflozin 100 mg qd, 65 canagliflozin 200 mg qd, 64 canagliflozin 300 mg qd, 64 canagliflozin 300 mg bid, 65 sitagliptin 100 mg qd), comprised the intent-to-treat (ITT) analysis set.

The baseline demographic and disease characteristics were balanced across the treatment groups. Across all subjects, the mean baseline HbA1c value was 7.7%, the mean baseline BMI was 31.5 kg/m2, and the median age was 54 years. Almost all subjects (96%) were receiving a daily dose of 1,500 mg metformin. A high proportion of subjects (89%) completed the 12-week treatment period.

The results for the analyses of the primary efficacy endpoint (change from baseline in HbA1c to Week 12) and 2 major secondary endpoints (change from baseline in FPG and percent change from baseline in body weight at Week 12) are summarized for the placebo and canagliflozin dose groups in the table below.

Table 7: Summary of Primary and Major Secondary Efficacy Endpoints at Week 12 LOCF (Study DIA2001: Intent-to-Treat Analysis Set)

Efficacy Endpoint/ Statistic	Placebo	Canagliflozin Treatment Groups				
		50 mg qd	100 mg qd	200 mg qd	300 mg qd	300 mg bid
HbA1c (%)						
N	61	62	62	62	60	62
Baseline, mean (SD)	7.71 (0.832)	8.01 (1.006)	7.81 (0.967)	7.57 (0.793)	7.70 (1.041)	7.71 (0.883)
Change from BL, mean	-0.22	-0.79	-0.76	-0.70	-0.92	-0.95
Diff of LS mean (SE) (minus placebo)		-0.45 (0.116)	-0.51 (0.116)	-0.54 (0.116)	-0.71 (0.117)	-0.735 (0.116)
(95% CI) [a]		(-0.747,-0.148)	(-0.804,-0.207)	(-0.841,-0.244)	(-1.006,-0.405)	(-1.209,-0.432)
P value vs placebo[a]		<0.001	<0.001	<0.001	<0.001	<0.001
Fasting plasma glucose (mmol/L)						
N	62	63	63	62	61	62
Baseline, mean (SD)	9.0 (2.10)	9.5 (2.49)	9.3 (2.30)	8.8 (2.04)	8.8 (2.38)	8.6 (1.77)
Change from BL, mean	0.2	-0.9	-1.4	-1.5	-1.4	-1.3
Diff of LS mean (SE) (minus placebo)		-0.9 (0.27)	-1.4 (0.27)	-1.8 (0.27)	-1.8 (0.27)	-1.7 (0.27)
(95% CI) [a]		(-1.39,-0.34)	(-1.98,-0.92)	(-2.33,-1.27)	(-2.32,-1.26)	(-2.25,-1.19)
P value vs placebo[a]		<0.001	<0.001	<0.001	<0.001	<0.001
Body weight						
N	62	63	64	63	62	62
Baseline, mean (SD) (kg)	85.5 (19.58)	87.5 (16.40)	87.7 (15.49)	87.7 (17.22)	87.8 (15.79)	86.3 (19.90)
Percent change from BL, mean	-1.1	-2.3	-2.6	-2.7	-3.4	-3.4
Diff of LS mean (SE) (minus placebo)		-1.3 (0.5)	-1.5 (0.5)	-1.6 (0.5)	-2.3 (0.5)	-2.3 (0.5)
(95% CI) [a]		(-2.2,-0.3)	(-2.5,-0.6)	(-2.6,-0.7)	(-3.3,-1.4)	(-3.3,-1.4)
P value vs placebo[a]		0.009	0.002	<0.001	<0.001	<0.001

[a] The LS mean difference with associated p value and CIs were based on an ANCOVA model with terms for treatment, baseline value, and MMTT stratum.

Key: BL = baseline, CI = confidence interval, Diff = difference, LOCF = last observation carried forward, LS = least squares, N = number, SE = standard error, Wk = week.

A dose-response with regards to HbA1c was observed for the doses 50 to 300 mg canagliflozin, with no additional effect for the 300 mg bid dose. A less apparent dose-response was observed for FPG. The responder analysis supports the HbA1c data. The proportion of subjects with HbA1c values <7.0% at Week 12 (LOCF analysis) was 42%, 53%, 61%, 72%, and 65% for canagliflozin 50 mg qd, 100 mg qd, 200 mg qd, 300 mg qd, and 300 mg bid treatment groups, respectively, compared to 34% for the placebo group. A dose-response was also observed for body weight with no additional effect at the 300 mg bid dose. Efficacy results for sitagliptin were consistent with published results. The data support the choice of the doses 100 mg and 300 mg once daily.

Study TA-7284-04 was a placebo-controlled, dose-finding study in adults from Japan with T2DM of canagliflozin (50, 100, 200, 300 mg qd) as monotherapy that was conducted by the sponsor's development partner, MTPC.

A total of 382 subjects, randomized to 1 of 5 treatment groups, received at least 1 dose of study drug, and had at least 1 post-baseline efficacy measurement (primary analysis population): 75 placebo, 82 canagliflozin 50 mg, 74 canagliflozin 100 mg, 76 canagliflozin 200 mg, and 75 canagliflozin 300 mg. The baseline demographic and diabetic characteristics were generally balanced across the treatment groups. Across all subjects, the mean baseline HbA1c value was 7.7%, and the mean baseline BMI was 25.7 kg/m2. Slightly more than one-half of subjects (56%) had not received prior treatment with an AHA. Most subjects (94%) completed the 12-week treatment period.

The LS mean differences, compared to the placebo group, in the change from baseline to Week 12 in HbA1c were -0.72%, -0.90%, -0.90%, and -0.99% in the canagliflozin 50 mg, 100 mg, 200 mg, and 300 mg groups, respectively.

In this monotherapy study, the response to canagliflozin was slightly higher than in study DIA2001. A rather weak dose-response with regards to HbA1c was observed with no apparent difference between the 100mg and 200 mg dose.

2.5.2. Main studies

The Phase 3 program consists of 9 studies, all pivotal to the sought indication. The studies can be grouped according to specific uses of canagliflozin in patients with T2DM:

- Canagliflozin as monotherapy was studied in DIA3005.

- Canagliflozin as add-on to AHA monotherapy was studied in DIA3006, DIA3009 and DIA3008 (sulfonylurea substudy).

- Canagliflozin as add-on to dual combination AHA therapy was studied in DIA3002, DIA3012 and DIA3015.

- Canagliflozin as add-on to insulin was studied in DIA3008 (insulin substudy).

Further to this, studies were performed in patients with renal impairment (DIA3004) and in elderly (DIA3010). The cardiovascular safety study (CANVAS) (DIA3008) is still ongoing.

The overall design of the developmental Phase III program was adequate.

There were similarities in the design features for the Phase 3 studies, which are presented together.

Methods

- **Design**

The design of the phase III studies differs dependent on the requirement for specific background diabetic treatment: the CANA phase III studies in which specific background diabetic therapy was required only patients already treated with the protocol-specified background therapy could directly enter a 2-week single-blind placebo run-in period. The other patients entered a dose-adjustment/ dose stable run-in period (8 to 12 weeks) in which they received only the protocol-specified AHA regimen. Those with inadequate glycaemic control at the week -2 visit entered the single-blind placebo run in period and were eligible to be randomised at day 1, if they met the other enrolment criteria.

Several studies (DIA3004, DIA3008, and DIA3010) did not require a particular diabetes regimen; in these studies, subjects with inadequate glycaemic control meeting other study enrolment criteria had CANA added to their ongoing, current, stable diabetes treatment regimen.

The placebo controlled phase III studies DIA3002, DIA3004, DIA3005, DIA3006, DIA3010 and DIA3012 had a core double blind period for evaluation of the primary endpoint at 26 weeks. For the DIA3008 Insulin and SU substudies the primary efficacy evaluation was at 18 weeks. In the two active comparator non-inferiority studies (DIA3009 glimepiride, DIA3015 sitagliptin) the primary efficacy endpoint was at 52 weeks. Each of the phase III studies except DIA3015, the DIA3005 high glycaemic substudy, and the DIA3008 substudies had long-term extension treatment periods of up to 78 additional weeks.

- **Study Participants**

Inclusion and exclusion criteria

Inadequate glycaemic control was defined in most of the studies as an HbA1c level of HbA1c ≥7.0% and ≤10.5%, except for the high glycaemic study (substudy of study 3005), where the HbA1c entry criterion was ≥10 to ≤12% and for study DIA3009 where subjects were to have an HbA1c between ≥7.0% and ≤9.5%. Only subjects with a diagnosis of T2DM were eligible for enrolment. The age range was ≥18 to ≤80 years of age across most phase III studies. In DIA3004, the age range was ≥25 years with no upper age limit, in DIA3008 the age range was ≥30 years (with CV history) or ≥50 years (with presence of cardiovascular risk factors) with no upper age limit, and in DIA3010 the age range was ≥55 to ≤80 years. Both men and woman were eligible for enrolment in all phase III studies. Women were required to be postmenopausal, surgically sterile, or practicing birth control and could not be pregnant or breast feeding.

Exclusion criteria common to the majority of phase III studies were repeated FPG>270 mg/dL during the pre-treatment phase despite optimal diet and exercise, history of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis and pancreatectomy, severe renal impairment, cardiovascular disease (myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident) and uncontrolled hypertension. In addition, elevations of aminotransferase levels and bilirubin indicative for hepatic impairment were defined as exclusion criteria.

- **Treatments**

All studies included both CANA doses (100 and 300 mg), with the exception of study DIA3015 which included only the 300 mg dose.

Criteria for rescue

The pre-specified glycaemic targets (which became more stringent in the course of the trial) for rescue or withdrawal were largely the same in each of the phase III studies. Subjects continued in the study (with no change in protocol-specified procedures) after rescue therapy was initiated. In DIA3015, there was no rescue therapy, and subjects meeting pre-specified glycaemic targets were withdrawn. The specific rescue therapy for each study was selected to be complementary to the type of background AHA therapy and with local prescribing practises.

- **Baseline characteristics**

Key baseline demographic, anthropometric and disease characteristics of subjects comprising the ITT analysis sets are summarized for each phase III study in the following tables:

Table 8: Demographic and Baseline Anthropometric and Diabetes Characteristics – Study-by-Study Comparison (ISE Phase III Studies: Modified Intent-to-Treat Analysis Set [Total])

Characteristic	Monotherapy	Dual Therapy			Triple Therapy			Add-on to Insulin	Special Populations	
	DIA3005	DIA3006 Add-on to Metformin	DIA3009 Add-on to Metformin	DIA3008 SU Substudy[a]	DIA3002 Add-on to Metformin + SU	DIA3015 Add-on to Metformin + SU	DIA3012 Add-on to Metformin + PIO	DIA3008 Substudy[b]	DIA3004 Renal Impairment	DIA3010 Older Adults
Age (years)										
N	584	1284	1450	127	469	755	342	1718	269	714
Mean (SD)	55.4 (10.61)	55.4 (9.42)	56.2 (9.22)	64.8 (7.65)	56.7 (9.30)	56.7 (9.46)	57.4 (10.03)	62.8 (7.65)	68.5 (8.28)	63.6 (6.24)
Median	56.0	56.0	57.0	65.0	58.0	57.0	57.0	63.0	69.0	63.0
Range	(24;79)	(21;79)	(22;80)	(44;82)	(27;79)	(21;91)	(27;78)	(32;85)	(39;96)	(55;80)
Category, n (%)										
<35	21 (3.6)	19 (1.5)	20 (1.4)	0	6 (1.3)	10 (1.3)	2 (0.6)	1 (0.1)	0	0
35 – <65	445 (76.2)	1059 (82.5)	1187 (81.9)	58 (45.7)	379 (80.8)	601 (79.6)	247 (72.2)	1017(59.2)	83 (30.9)	441 (61.8)
≥65	118 (20.2)	206 (16.0)	243 (16.8)	69 (54.3)	84 (17.9)	144 (19.1)	93 (27.2)	700 (40.7)	186 (69.1)	273 (38.2)
Sex, n (%)										
N	584	1284	1450	127	469	755	342	1718	269	714
Male	258 (44.2)	605 (47.1)	756 (52.1)	72 (56.7)	239 (51.0)	422 (55.9)	216 (63.2)	1143 (66.5)	163 (60.6)	396 (55.5)
Female	326 (55.8)	679 (52.9)	694 (47.9)	55 (43.3)	230 (49.0)	333 (44.1)	126 (36.8)	575 (33.5)	106 (39.4)	318 (44.5)
Race, n (%)										
N	584	1284	1450	127	469	755	342	1718	269	714
White	395 (67.6)	901 (70.2)	978 (67.4)	95 (74.8)	387 (82.5)	485 (64.2)	252 (73.7)	1342 (78.1)	215 (79.9)	552 (77.3)
Black, African-American	41 (7.0)	45 (3.5)	61 (4.2)	1 (0.8)	26 (5.5)	88 (11.7)	20 (5.8)	45 (2.6)	5 (1.9)	57 (8.0)
Asian	85 (14.6)	182 (14.2)	284 (19.6)	29 (22.8)	4 (0.9)	132 (17.5)	55 (16.1)	230 (13.4)	27 (10.0)	61 (8.5)
Other	63 (10.8)	156 (12.1)	127 (8.8)	2 (1.6)	52 (11.1)	50 (6.6)	15 (4.4)	101 (5.9)	22 (8.2)	44 (6.2)
Ethnicity, n (%)										
N	584	1284	1450	127	469	755	342	1718	269	714
Hispanic or Latino	180 (30.8)	373 (29.0)	242 (16.7)	11 (8.7)	109 (23.2)	159 (21.1)	54 (15.8)	121 (7.0)	21 (7.8)	104 (14.6)
Not Hispanic or Latino	402 (68.8)	908 (70.7)	1202 (82.9)	116 (91.3)	359 (76.5)	594 (78.7)	283 (82.7)	1591 (92.6)	240 (89.2)	607 (85.0)
Unknown/Not reported	2 (0.3)	3 (0.3)	6 (0.4)	0	1 (0.2)	2 (0.2)	5 (1.5)	6 (0.4)	8 (3.0)	3 (0.4)
Baseline BMI (kg/m^2)										
N	584	1283	1450	127	469	755	342	1715	269	714
Mean (SD)	31.6 (6.24)	31.8 (6.24)	31.0 (5.41)	29.9 (5.79)	33.0 (6.48)	31.6 (6.91)	32.6 (6.76)	33.8 (6.29)	33.0 (6.15)	31.6 (4.57)
Category, n (%)										
<30	266 (45.6)	565 (44.0)	673 (46.4)	72 (56.7)	159 (33.9)	355 (47.0)	133 (38.9)	491 (28.6)	87 (32.3)	270 (37.8)
≥30	318 (54.4)	718 (55.9)	777 (53.6)	55 (43.3)	310 (66.1)	400 (53.0)	209 (61.1)	1224 (71.2)	182 (67.7)	444 (62.2)

Table 9: Demographic and Baseline Anthropometric and Diabetes Characteristics – Study-by-Study Comparison (ISE Phase III Studies: ITTset)

Characteristic	Monotherapy	Dual Therapy			Triple Therapy			Add-on to Insulin	Special Populations	
	DIA3005	DIA3006 Add-on to Metformin	DIA3009 Add-on to Metformin	DIA3008 SU Substudy[a]	DIA3002 Add-on to Metformin + SU	DIA3015 Add-on to Metformin + SU	DIA3012 Add-on to Metformin + PIO	DIA3008 Substudy[b]	DIA3004 Renal Impairment	DIA3010 Older Adults
Baseline HbA_{1c} (%)										
N	584	1283	1450	127	469	755	342	1716	269	714
Mean (SD)	8.0 (0.97)	7.9 (0.90)	7.8 (0.79)	8.4 (1.00)	8.1 (0.92)	8.1 (0.91)	7.9 (0.96)	8.3 (0.90)	8.0 (0.87)	7.7 (0.78)
Category, n (%)										
<7.0%	68 (11.6)	161 (12.5)	195 (13.4)	3 (2.4)	33 (7.0)	64 (8.5)	43 (12.6)	59 (3.4)	29 (10.8)	108 (15.1)
7 - <8%	242 (41.4)	536 (41.7)	683 (47.1)	53 (41.7)	193 (41.2)	295 (39.1)	148 (43.3)	629 (36.6)	110 (40.9)	350 (49.0)
8 - <9%	177 (30.3)	402 (31.3)	441 (30.4)	33 (26.0)	152 (32.4)	247 (32.7)	91 (26.6)	642 (37.4)	94 (34.9)	202 (28.3)
9 - ≤10%	80 (13.7)	161 (12.5)	125 (8.6)	28 (22.0)	78 (16.6)	133 (17.6)	52 (15.2)	318 (18.5)	36 (13.4)[c]	53 (7.4)
>10%	17 (2.9)	23 (1.8)	6 (0.4)	10 (7.9)	13 (2.8)	16 (2.1)	8 (2.3)	68 (4.0)		1 (0.1)
Duration of diabetes (years)										
N	584	1284	1450	127	469	755	342	1718	269	714
Median	3.0	5.7	5.0	9.0	8.6	8.0	9.7	15.0	15.0	10.0
BL eGFR- (mL/min/1.73m^2)										
N	584	1284	1449	125	469	755	342	1716	269	714
Mean (SD)	87.1 (20.28)	88.6 (18.47)	90.2 (18.74)	69.3 (18.55)	89.4 (19.65)	87.5 (19.14)	86.4 (18.59)	74.9 (19.02)	39.4 (6.88)	77.5 (16.57)
Median	85.0	87.0	88.2	69.0	88.0	86.0	84.0	74.0	39.0	76.0
Range	(38,227)	(44,169)	(33,181)	(32,116)	(26,163)	(50.0;164.0)	(48,144)	(27,159)	(24,61)	(37,153)
Category, n (%)										
<60	32 (5.5)	40 (3.1)	38 (2.6)	44 (35.2)	15 (3.2)	41 (5.4)	25 (7.3)	348 (20.3)	268 (99.6)	94 (13.2)
60 - <90	324 (55.5)	665 (51.8)	715 (49.3)	65 (51.2)	235 (50.1)	382 (50.6)	184 (53.8)	1014 (59.0)	1 (0.4)	456 (63.9)
≥90	228 (39.0)	579 (45.1)	696 (48.0)	16 (12.6)	219 (46.7)	332 (44.0)	133 (38.9)	354 (20.6)		164 (23.0)
Microvascular complication										
N	584	1284	1450	127	469	755	342	1718	269	714
n (%)	40 (6.8)	286 (22.3)	269 (18,6)	55 (43.3)	124 (26.4)	251 (33.2)	66 (19.3)		216 (80.3)	212 (29.7)

- **Outcomes/endpoints**

The **primary efficacy endpoint** in each of the phase III studies was the change from baseline in HbA_{1c} at the primary assessment timepoint (Week 18, Week 26, or Week 52, depending on the study). Key **secondary endpoints** (associated with hypothesis testing in most of the phase III studies), were changes from baseline in FPG, the proportion achieving a HbA_{1c} target of <7.0% (and <6.5%), changes from baseline in body weight, SBP, and lipid parameters (for results please refer to safety section). Pharmacodynamic endpoints assessed (in selected phase III studies) included RT_G, and specific beta-cell function/ insulin secretion PD endpoints.

- **Randomisation**

All phase III studies and the phase IIb dose range studies DIA2001 and OBE-2001 used randomized, double-blind designs. Several studies used stratified randomization and Study3008 used stratification to include patients into substudies.

- **Blinding**

Core periods of all phase III studies and the phase IIb dose range studies were double-blind.

- **Statistical methods**

All phase III studies submitted in support of the efficacy of canagliflozin used similar statistical methods and were adequately powered. Seven studies were designed to show the superiority of canagliflozin to placebo on HbA1c in different add-on scenarios, the remaining two studies were designed to show non-inferiority of canagliflozin to an active comparator on HbA1c. The primary analysis was conducted on the modified intent-to-treat (mITT) analysis set (all randomized patients with at least one dose). Missing values were imputed using a last observation carried forward (LOCF) approach. For the individual studies, supportive analyses were also conducted on the per protocol (PP) analysis set (mITT subset at primary assessment timepoint without rescue therapy and no major protocol violations), and the completer's analysis set (mITT subset at primary assessment timepoint without rescue therapy). Sensitivity analyses using Mixed Models for Repeated Measures were additionally conducted.

The primary efficacy endpoint for the phase III studies was the change in HbA1c from baseline to Week 18, Week 26 or Week 52. The analysis of the change from baseline in HbA1c was performed using an ANCOVA model that included the factor treatment and randomization stratification factors as fixed effects and the baseline HbA1c value as a covariate (baseline eGFR as additional covariate for DIA3004). Treatment differences between each canagliflozin group and the comparator (placebo or active comparator) were estimated as least-squares (LS) means with two-sided 95% confidence intervals. P-values for testing superiority were calculated for comparisons of the LS means. A similar analysis approach was used for the analysis of continuous secondary efficacy endpoints. A logistic regression model with treatment and stratification factors as fixed factors and baseline HbA1c as covariate (baseline eGFR as additional covariate for DIA3004) was used to analyze the secondary categorical endpoint of the proportion of subjects with HbA1c <7.0%. In each Phase III study, a pre-specified sequential testing procedure (and incorporation of a Hochberg procedure to split type I error spent) was used for testing the treatment differences of the primary and major secondary efficacy endpoints which controls the family-wise type I error rate at 5%. A non-inferiority margin of 0.3% was used for comparisons of canagliflozin after 52 weeks of treatment in the non-inferiority studies.

In case non-inferiority was demonstrated, a step-down procedure to superiority assessment was foreseen. Assay sensitivity in these studies was established by examining the efficacy of the comparator over the double-blind treatment period.

Summary of results of individual phase III studies

Monotherapy study (DIA3005)

Study DIA3005: this study evaluated the efficacy of canagliflozin 100 mg and 300 mg, administered as monotherapy in adults with T2DM who had inadequate glycaemic control on diet and exercise. The study included a main study in 584 subjects who had mild to moderate baseline hyperglycemia (HbA_{1c} ≥7.0% to ≤10.0%) randomized to placebo or CANA (100mg or 300mg), and a high glycaemic substudy that included 91 subjects with a baseline HbA_{1c} of >10.0% to ≤12.0% randomized to active therapy with either CANA dose (100mg or 300 mg). In both study components, subjects were treated over a core double-blind period of 26 weeks.

A high proportion of subjects (87%) in the DIA3005 main study completed 26 weeks of double blind treatment, with the rate of discontinuation higher in the placebo group (17%) than in either the canagliflozin 100 mg (12%) or 300 mg (11%) groups.

Results for the main study showed clinically relevant, dose-dependent reductions in HbA_{1c} at week 26 of -1.16% for canagliflozin 300 mg relative to placebo ($p<0.001$) and –0.91% for canagliflozin 100 mg relative to placebo ($p<0.001$). Results of the primary analysis were supported by results on secondary glycaemic parameters with dose-dependent reductions in FPG, proportion of subjects achieving HbA1c goals and body weight. The number of patients in need for rescue medication was below 3% in each CANA group (compared to 22.9% in the placebo group). Blood pressure was reduced in a dose-dependent and clinical relevant fashion: reductions in SBP from baseline to week 26 were -3.34mmHg and -5.04mmHg with CANA 100 mg and 300 mg, compared to 0.38 mmHg with placebo. Modest reductions were seen for diastolic blood pressure in both CANA groups compared to placebo (-1.67mmHg and -2.14mmHg with CANA 100 mg and 300 mg, compared to -0.10 with placebo).

Key features and results of this study are summarised in the following table:

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin as Monotherapy in the Treatment of Subjects With Type 2 Diabetes Mellitus Inadequately Controlled With Diet and Exercise		
Study identifier	28431754-DIA3005	
Study design	Randomized, double-blind, 3-arm, parallel-group study (with a 26-week, placebo-controlled, core double-blind period plus a 26-week, active-controlled, extension double-blind period)	
Primary objectives	To assess the effect of CANA relative to placebo on HbA_{1c} after 26 weeks of treatment; the safety and tolerability of CANA	
Hypothesis	Superiority	
Treatments groups	CANA 100, 300 mg Placebo	Number of subjects treated by treatment group: Main Study: CANA 100 mg (N=195), CANA 300 mg (N=197) Placebo (N=192) High Glycaemic Substudy:

		CANA 100 mg (N=47), CANA 300 mg (N=44)
Duration of Run-in Period	2-week single-blind placebo run-in period	
Duration of treatment	26 weeks (core double-blind period)	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline to Week 26
	Key secondary	Change from Baseline to Week 26 in: Fasting plasma glucose (FPG) Proportion of subjects with HbA_{1c} <7.0% Body weight
Database lock date	23 September 2011	
Primary analysis description	Analysis of covariance (ANCOVA) model with treatment and stratification factors as fixed effects and HbA_{1c} baseline value as covariate	
Analysis population	Number of subjects in mITT population (Main Study): Placebo (N=192), CANA 100 mg (N=195), CANA 300 mg (N=197)	
Primary efficacy results (Main Study)	Baseline	Week 26
	Mean (SD): Placebo 7.97 (0.955); CANA 100 mg 8.06 (0.959); CANA 300 mg 8.01 (0.988)	Placebo-subtracted LS mean (SE): CANA 100 mg -0.91 (0.091); CANA 300 mg -1.16 (0.091)
	P value:	CANA 100 mg <0.001; CANA 300 mg <0.001
Key Secondary Results (Main Study)	FPG: Change From Baseline to Week 26 – LOCF: Placebo-subtracted LS Mean (SE): CANA 100 mg -1.97 (0.190); CANA 300 mg -2.41 (0.189)	
	Proportion of Subjects With HbA_{1c} <7.0% at Week 26 – LOCF: Placebo 20.6; CANA 100 mg 44.5; CANA 300 mg 62.4	
	Body Weight: Percent Change From Baseline to Week 26 – LOCF: Placebo-subtracted LS Mean (SE): CANA 100 mg -2.2 (0.3); CANA 300 mg -3.3 (0.3)	

High glycaemic substudy: The 91 subjects comprising the mITT analysis set for the DIA3005 high glycaemic substudy had a mean baseline HbA_{1c} of 10.6% No hypothesis testing was planned for this substudy. Mean changes from baseline to week 26 in HbA_{1c} (LOCF) were -2.13% and -2.56% for canagliflozin 100 mg and 300 mg, respectively. Twelve% to 17% of subjects achieved target control (HbA_{1c} <7.0%). The lower number of responders as compared to other phase III studies can be explained by a high baseline HbA1c above 10% in this study. Results on secondary endpoints supported the findings on HbA1c: descriptive summaries of primary and secondary endpoints are displayed in the following table:

Mean (SD) or Proportion of Efficacy Endpoints at Week 26 LOCF (High Glycemic Substudy)

(Study 28431754DIA3005: Modified Intent-to-Treat Analysis Set)

Endpoint	CANA 100 mg (N=47)	CANA 300 mg (N=44)
Change from baseline in HbA_{1c} (%)	-2.17 (1.504)	-2.61 (1.184)
Proportion achieving HbA_{1c} <7 % (target)	17.4	11.6
Change from baseline in FPG (mmol/L)	-4.28 (2.926)	-4.77 (3.218)
Change from baseline in 2-hour PPG (mmol/L)	-6.16 (3.885)	-7.46 (4.359)
% change from baseline in body weight	-3.0 (3.5)	-3.8 (3.9)
Change from baseline in SBP (mmHg)	-4.04 (10.680)	-5.11 (12.477)
% change from baseline in HDL-C	2.5 (18.3)	11.1 (17.0)
% change from baseline in TGs	3.6 (54.0)	-8.6 (35.1)

Key: HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, FPG=fasting plasma glucose, PPG=post-prandial glucose, SBP=systolic blood pressure, TGs=triglycerides

Generally, this study supports the efficacy of CANA as monotherapy.

Studies add-on to AHA monotherapy (DIA3006, DIA 3009)

Study DIA3006: this study aimed at investigating the add-on use of CANA in subjects with inadequate glycaemic control on (sub)maximal doses of **metformin**. It included 1,284 subjects treated over the 26-week core double-blind period. A sitagliptin 100 mg treatment arm was also included, although no formal statistical testing was planned or performed for the 26-week double-blind period.

A total of 87% of treated subjects completed 26 weeks of treatment, with the proportion of subjects discontinued prior to the Week 26 visit modestly higher in the placebo group (15%) compared to the canagliflozin 100mg (13%), canagliflozin 300mg (12%), and sitagliptin (13%) groups.

The change from baseline in HbA_{1c} at week 26 for CANA 300mg relative to placebo was –0.77% ($p<0.001$) and –0.62% ($p<0.001$) for CANA 100 mg. The placebo-subtracted HbA_{1c} lowering response at week 26 for sitagliptin 100mg was -0.66%. Both doses of CANA also achieved statistical significance with respect to the secondary endpoints of FPG, proportion achieving HbA_{1c} target, and 2-hour PPG (during a MMTT procedure). Body weight decreased modestly with the CANA groups compared to placebo (placebo-adjusted changes from baseline -2.5% and -2.9%). The effect of sitagliptin on body weight was neutral. Blood pressure was clinically relevantly influenced by both dose strengths of CANA (SBP: -3.84mmHg and -5.06mmHg with CANA 100 mg and 300 mg, 1.52mmHg with placebo, -1.83mmHg with sitagliptin; DBP: -2.19 mmHg and 3.09mmHg with CANA 100 mg and 300 mg, 0.28mmHg with placebo, -1.11 mmHg with sitagliptin).

The improvement in fasting insulin secretion (numerically superior over sitagliptin) measured by HOMA2-%B is notable given the lack of any direct effect of CANA to stimulate beta-cell insulin secretion. The improvement in HOMA2-%B may be explained by the reversal of glucotoxicity leading to improved beta-cell function.

Generally, this study supports the efficacy of both doses of CANA when added to a background therapy of metformin. Key results of this study are summarized in the following table:

Key features and results of this study are summarised in the following table:

Title: A Randomized, Double-Blind , Placebo and Active Controlled, 4-arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety and Tolerabilty of JNJ-28431754 (Canagliflozin) Compared With Sitagliptin and Placebo in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycaemic Control on Metformin Therapy		
Study identifier	28431754-DIA3006	
Study design	Randomized, double-blind, parallel-group study (with a 26-week placebo- and active-controlled, core double-blind period and a 26-week active-controlled, extension double-blind period)	
Primary objectives	To assess the effect of CANA relative to placebo on HbA_{1c} after 26 weeks of treatment; the safety and tolerability of CANA	
Hypothesis	Superiority	
Treatments groups	CANA 100, 300 mg Placebo Sitagliptin 100 mg	Number of subjects treated by treatment group: CANA 100 mg (N=368); CANA 300 mg (N=367) Placebo (N=183) Sitagliptin 100 mg (N=366)
Duration of Run-in Period	2-week single-blind placebo run-in period	
Duration of treatment	26 weeks (core double-blind period)	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline to Week 26
	Key secondary	Change from Baseline to Week 26 in: Fasting plasma glucose (FPG) Proportion of subjects with HbA_{1c} <7.0% Body weight
Database lock date	15 November 2011	
Primary analysis description	Analysis of covariance (ANCOVA) model with treatment and stratification factors as fixed effects and HbA_{1c} baseline value as covariate	
Analysis population	Number of subjects in mITT population: Placebo (N=183), CANA 100 mg (N=368), CANA 300 mg (N=367), Sita (N=366)	
Primary efficacy results	Baseline	Week 26
	Mean (SD): Placebo 7.96 (0.896); CANA 100 mg 7.94 (0.879); CANA 300 mg 7.95 (0.931); Sita 100 mg 7.92 (0.875)	Placebo-subtracted LS mean (SE): CANA 100 mg -0.62 (0.071); CANA 300 mg -0.77 (0.071): Sita 100 mg -0.66 (0.071)
	P value:	CANA 100 mg <0.001; CANA 300 mg <0.001
Key Secondary Results	FPG: Change from Baseline to Week 26 (LOCF): Placebo-subtracted LS Mean (SE): CANA 100 mg -1.65 (0.169); CANA 300 mg -2.23 (0.170); Sita 100 mg -1.26 (0.170)	
	Proportion of Subjects with HbA_{1c} <7.0% at Week 26: Placebo 29.8; CANA 100 mg 45.5; CANA 300 mg 57.8; Sita 100 mg 54.5	
	Body Weight: Percent Change from Baseline to Week 26 (LOCF): Placebo-subtracted LS Mean (SE): CANA 100 mg -2.5 (0.3); CANA 300 mg -2.9 (0.3); Sita 100 mg -0.0 (0.3)	

Study DIA3009: this study aimed at evaluating the efficacy and safety of CANA 300 mg and 100 mg compared to the SU, glimepiride, as add-on therapy in subjects with inadequate glycaemic control on (sub)maximal doses of metformin. The study included a 52-week core active-controlled double-blind treatment phase, followed by a 52-week extension active-controlled, double-blind treatment period.

A total of 1,452 subjects were randomised to CANA 100 mg, CANA 300 mg, placebo or glimepiride. The mean maximum dose achieved with glimepiride was 6 mg, and as such, the active comparator was sufficiently up-titrated. A non-inferiority margin of 0.3% was selected.

At baseline, 95% of subjects had a metformin total daily dose at least 2,000 mg/day, and almost all (99%) subjects remained on stable doses of metformin during the double-blind period, as specified by the protocol.

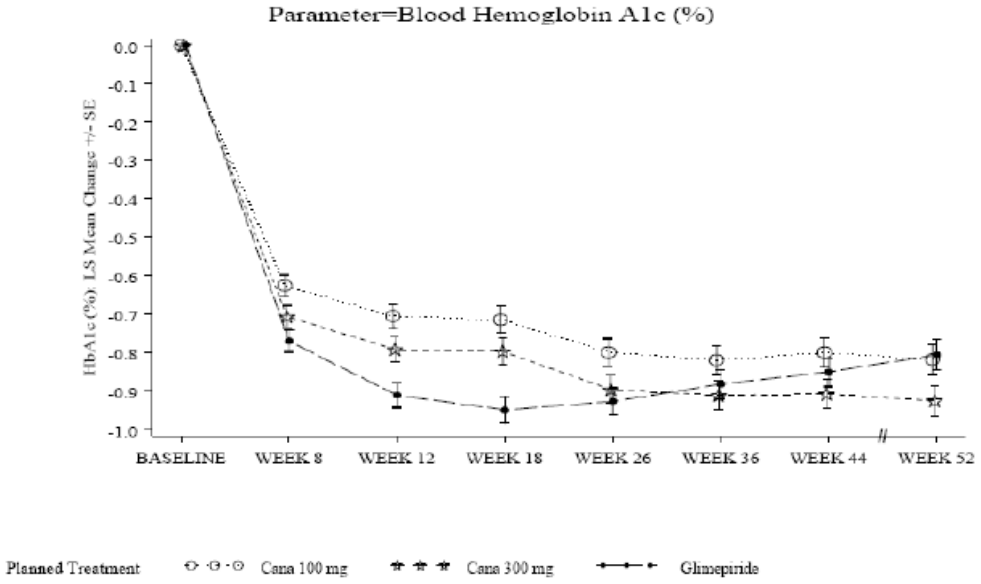
In the CANA 100mg and 300mg groups the mean changes from baseline in HbA1c at week 52 showed a reduction of -0.78% and -0.89%, respectively, compared to a change of- 0.79% in the glimepiride group. The upper limits of both 95% CIs for the difference in HbA1c for each CANA dose comparison to glimepiride were less than the pre-specified non-inferiority margin of 0.3%. A step-down to an assessment of superiority was pre-specified; the upper limit of the 95% CI between CANA 300 mg and glimepiride was <0%, demonstrating superiority for CANA to glimepiride. The HbA1c lowering response to CANA 100 mg was not superior to that of glimepiride in this study. The absolute HbA1c reductions in the three treatment arms were about -0.7% and are considered to be clinically relevant, although the true effect cannot be assessed in the absence of a placebo arm.

The results on the secondary glycaemic endpoints (FPG lowering, proportion of responders) generally supported those on HbA1c. Body weight decreased in the CANA groups compared to a small gain in the glimepiride group. A substudy investigating body composition showed that fat loss contributed significantly to body weight reduction. Glimepiride-substracted change in systolic blood pressure was -3.48mmHg and -4.76mmHg for the 100mg and 300 mg dose, respectively.

Trends in favour of CANA as compared to glimepiride were also shown for measures of beta cell function (HOMA-2%B). Notably, the improvement in HOMA-2%B was numerically superior to glimepiride which acts directly at the beta cell. Reversal of of glucotoxicity leading to improved beta-cell function may play a role.

With glimepiride the durability of HbA1c lowering was worse compared to both CANA doses which showed little change through week 52. The waning of effect is known for insulin secretagogues. Durability of the effect of CANA can be further assessed based on data of the long term extension study.

Figure 4: HbA_{1c}: LS Mean Change From Baseline Over Time – LOCF
(Study 28431754-DIA3009: Modified Intent-to-Treat Analysis Set)



Overall, this study showed non-inferior efficacy and suggests better durability of the effect of both CANA doses compared to SU treatment when added to metformin.

Glimepiride-substracted change in systolic blood pressure was -3.48mmHg and -4.76mmHg for the 100mg and 300 mg dose, respectively.

Key features and results of this study are summarised in the following table:

Title: A Randomized, Double-blind, 3-Arm, Parallel-group, 2-Year (104-Week), Multicenter Study to Evaluate the Efficacy, Safety, and Tolerabilty of JNJ-28431754 100 mg and JNJ - 28431754 300 mg Compared With Glimepiride in the Treatment of Subjects With Type 2 Diabetes Mellitus not Optimally Controlled on Metformin Monotherapy		
Study identifier	28431754-DIA3009	
Study design	Randomized, double-blind, active-controlled, parallel-group study (with a 2-year double-blind treatment phase)	
Primary objectives	To compare the HbA_{1c} -lowering efficacy of CANA with glimepiride after 52 weeks of treatment	
Hypothesis	Non-inferiority	
Treatments groups	CANA 100, 300 mg Glimepiride (starting dose: 1 mg; titrated to 6 mg or 8 mg)	Number of subjects treated by treatment group: CANA 100 mg (N=483), CANA 300 mg (N=485) Glimepiride (N=482)
Duration of Run-in Period	2-week single-blind placebo run-in period	
Duration of treatment	52 weeks (of 104-week study)	
Endpoints and definitions	Primary	Change from baseline to Week 52 of the HbA_{1c}-lowering efficacy of CANA after 52 weeks of treatment
	Key secondary	Change from Baseline to Week 52 in: Fasting plasma glucose (FPG) Proportion of subjects with HbA_{1c} <7.0% Body weight
Database lock date	25 January 2012	
Primary analysis	Analysis of covariance (ANCOVA) model with treatment and stratification	

description	factors as fixed effects and HbA_{1c} baseline value as covariate. The upper bound of the 95% CI of the treatment difference in LS means was used in the non-inferiority testing of the comparison with the non-inferiority margin 0.3%.	
Analysis population	Number of subjects in mITT population: CANA 100 mg (N=483), CANA 300 mg (N=485), Glimepiride (N=482)	
Primary efficacy results	Baseline	Week 52
	Mean (SD): CANA 100 mg 7.78 (0.787); CANA 300 mg 7.79 (0.779); Glimepiride: 7.83 (0.795)	Glimepiride-subtracted LS mean (SE): CANA 100 mg -0.01 (0.050); CANA 300 mg -0.12 (0.050)
	95% CI:	CANA 100 mg (-0.109%; 0.085%) CANA 300 mg (-0.217%; -0.023%)
Key Secondary Results	FPG: Change from Baseline to Week 52 (LOCF): Glimepiride-subtracted LS Mean (SE): CANA 100 mg -0.33 (0.114); CANA 300 mg -0.51 (0.114)	
	Proportion of Subjects with HbA_{1c} <7.0%: CANA 100 mg 53.6; CANA 300 mg 60.1; Glimepiride: 55.8	
	Body Weight: Percent Change from Baseline to Week 52 (LOCF): Glimepiride-subtracted LS Mean (SE): CANA 100 mg -5.2 (0.3); CANA 300 mg -5.7 (0.3)	

Studies add-on to dual combination AHA therapy (DIA3002, DIA3012, DIA3015)

Study DIA3002: the aim of this study was to examine the add-on use of CANA compared to placebo in subjects with inadequate glycaemic control on (sub)maximal doses of metformin and SU. A total of 469 patients were randomised and 381 patients completed the 26 week double blind treatment. The percentage of patients who were discontinued prior to week 26 was modestly higher in the placebo group compared to the pooled canagliflozin group (21% vs. 18%). At baseline, 90% of subjects were on a metformin total daily dose of at least 2,000 mg/day, and 97% subjects received the minimum daily dose for a SU as required by the protocol. Through week 26, 99% and 96% of subjects remained on stable doses of metformin and of SU, respectively, as specified by the protocol.

The mean change in HbA1c was statistically significantly higher in both CANA groups compared to placebo. The reductions at both doses (-0.92% and -0.71% for CANA 300 mg and 100mg, respectively, placebo-adjusted change from baseline at week 26) were clinically relevant. The results of the secondary glycaemic endpoints (FPG lowering, proportion of responders) generally supported those on HbA1c. Only a relatively small decrease in body weight with the CANA groups compared to placebo was observed in this study, likely due to the concomitant treatment with SUs (-2% and -2.6% in the CANA 100mg and 300mg groups, respectively, compared to a change of -0.6% in the placebo group). Trends in favour or CANA were shown for SBP, while the reduction of DBP was borderline clinically relevant (SBP: -4.89mmHg and -4.27mmHg with CANA 100mg and 300mg and -2.65mmHg with placebo; DBP: -2.85mmHg and -2.25mmHg with CANA 100mg and 300 mg and -1.72mmHg with placebo).

Notably, the effect on HbA1c and FPG was achieved by week 12 for both doses of CANA. A small but inconsistent increase from week 12 to week 26 in HbA1c was observed with CANA 100 mg. The profile of FPG change from baseline to week 26 showed a nadir at week 6 in both CANA groups with a modest rise, more evident in the 100 mg group. Data of the ongoing double-blind

extension period of this study may provide further understanding of the course of HbA1c over time. However, comparisons of the durability of HbA1c lowering of CANA with active comparators (studies DIA3009 and 3015) showed superior durability of both CANA doses.

Generally, this study supports the efficacy of both doses of CANA as add-on to a background therapy of metformin and SU.

Key features and results are summarised in the following table:

Title: A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycaemic Control on Metformin and Sulphonylurea Therapy		
Study identifier	28431754-DIA3002	
Study design	Randomized, double-blind, placebo-controlled, 3-arm, parallel-group, muticenter study (with a 26-week, core double-blind period plus a 26-week, extension double-blind period)	
Primary objectives	To assess the effect of CANA relative to placebo on HbA_{1c} after 26 weeks of treatment; to assess the safety and tolerability of CANA	
Hypothesis	Superiority	
Treatments groups	Placebo CANA 100, 300 mg	Number of subjects treated by treatment group: CANA 100 mg (N=157), CANA 300 mg (N=156) Placebo (N=156)
Duration of Run-in Period	2-week single-blind placebo run-in period	
Duration of treatment	26 weeks (core double-blind period)	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline to Week 26
	Key secondary	Change from Baseline to Week 26 in: Fasting plasma glucose (FPG) Proportion of subjects with HbA_{1c} <7.0% Body weight
Database lock date	07 October 2011	
Primary analysis description	Analysis of covariance (ANCOVA) model with treatment and stratification factors as fixed effects and HbA_{1c} baseline value as covariate	
Analysis population	Number of subjects in mITT population: Placebo (N=156), CANA 100 mg (N=157), CANA 300 mg (N=156)	
Primary efficacy results	Baseline	Week 26
	Mean (SD): Placebo 8.12 (0.896); CANA 100 mg 8.13 (0.926); CANA 300 mg 8.13 (0.942)	Placebo-subtracted LS Mean (SE): CANA 100 mg -0.71 (0.097); CANA 300 mg -0.92 (0.097)
	P value:	CANA 100 mg <0.001; CANA 300 mg <0.001
Key Secondary Results	FPG: Change from Baseline to Week 26 (LOCF): Placebo-subtracted LS Mean (SE): CANA 100 mg -1.24 (0.259); CANA 300 mg -1.92 (0.260)	
	Proportion of Subjects with HbA_{1c} <7.0% at Week 26: Placebo 18.0; CANA 100 mg 43.2; CANA 300 mg 56.6	
	Body Weight: Percent Change from Baseline to Week 26 (LOCF): Placebo-subtracted LS Mean (SE): CANA 100 mg -1.4 (0.4); CANA 300 mg -2.0 (0.4)	

Study 3012: the aim of this study was to examine the add-on use of CANA in subjects with inadequate glycaemic control on (sub)maximal doses of metformin and pioglitazone.

Of the 342 randomized and dosed subjects, 87% completed 26 weeks of double-blind treatment, with the proportion of subjects who were discontinued prior to Week 26 higher in the placebo group versus the pooled canagliflozin group (21% vs 10%). At baseline, 91% of subjects had a metformin total daily dose at least 2,000mg/day; 68% of subjects were on pioglitazone 30 mg and 32% were on pioglitazone 45 mg. Through week 26, almost all subjects remained on stable doses of metformin and PIO, as specified by the protocol.

Mean change in HbA1c was statistically significantly higher in both CANA groups compared to placebo. The reductions at both doses (-0.76% and -0.62% for CANA 300 mg and 100mg, respectively, placebo-substracted change from baseline at week 26) were clinically relevant. The results on the secondary glycaemic endpoints (FPG lowering, proportion of responders) generally supported those on HbA1c. Body weight decreased in both CANA groups compared to placebo. Clinical relevant improvements were shown for SBP and DBP: reductions from baseline to week 26 were achieved in the 100mg and 300mg CANA groups compared to placebo (SBP: placebo -1.67 mmHg, CANA 100mg -5.13 mmHg, CANA300 mg -4.62mmHg; DBP: placebo -1.18 mmHg, CANA 100mg -2.83 mmHg, CANA 300 mg -3.52 mmHg).

Generally, this study supports the efficacy of both doses of CANA as add-on to a background therapy of metformin and pioglitazone.

Key efficacy endpoints are summarised in the following table:

Title: A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel Group, 26 Week Multicenter Study with a 26 Week Extension to Evaluate the Efficacy, Safety, and Tolerability of JNJ 28431754 (Canagliflozin) Compared with Placebo in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycaemic Control on Metformin and Pioglitazone Therapy		
Study identifier	28431754-DIA3012	
Study design	Randomized, double-blind, parallel-group, 3-arm study (with a 26-week, placebo-controlled, core double-blind period plus a 26-week, active-controlled, extension double-blind period)	
Primary objectives	To assess the effect of CANA relative to placebo on HbA_{1c} after 26 weeks of treatment; the safety and tolerability of CANA	
Hypothesis	Superiority	
Treatments groups	CANA 100, 300 mg Placebo	Number of subjects treated by treatment group: CANA 100 mg (N=113), CANA 300 mg (N=114) Placebo (N=115)
Duration of Run-in Period	2-week single-blind placebo run-in period	
Duration of treatment	26 weeks (core double-blind period)	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline to Week 26
	Key secondary	Change from Baseline to Week 26 in: Fasting plasma glucose (FPG) Proportion of subjects with HbA_{1c} <7.0% Body weight
Database lock date	19 December 2011	
Primary analysis description	Analysis of covariance (ANCOVA) model with treatment and stratification factors as fixed effects and HbA_{1c} baseline value as covariate	
Analysis population	Number of subjects in mITT population: Placebo (N=115), CANA 100 mg (N=113), CANA 300 mg (N=114)	
Primary efficacy results	Baseline	Week 26

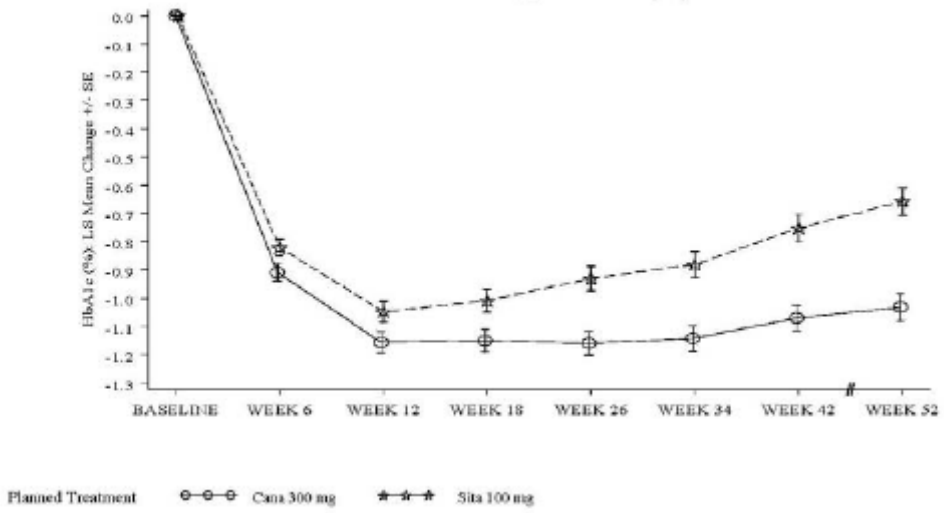
	Mean (SD): Placebo 8.00 (1.010); CANA 100 mg 7.99 (0.940); CANA 300 mg 7.84 (0.911)	Placebo-subtracted LS mean (SE): CANA 100 mg -0.62 (0.095); CANA 300 mg -0.76 (0.096)
	P value:	CANA 100 mg <0.001; CANA 300 mg <0.001
Key Secondary Results	FPG: Change from Baseline to Week 26 (LOCF): Placebo-subtracted LS Mean (SE): CANA 100 mg -1.63 (0.214); CANA 300 mg -1.98 (0.214)	
	Proportion of Subjects with HbA_{1c} <7.0%: Placebo 32.5; CANA 100 mg 46.9; CANA 300 mg 64.3	
	Body Weight: Percent Change from Baseline to Week 26 (LOCF): Placebo-subtracted LS Mean (SE): CANA 100 mg -2.7 (0.4); CANA 300 mg -3.7 (0.4)	

Study DIA 3015: the aim of this study was to investigate the efficacy and safety of CANA 300 mg compared to the DDP-inhibitor sitagliptin, both as add-on therapy to (sub)maximal doses of metformin and SU. It included 755 randomized and dosed subjects treated over the 52-week double-blind period. The proportion of subjects who completed 52 weeks of treatment was higher for the canagliflozin 300 mg group (67%) than for the sitagliptin group (56%), which was primarily due to a higher proportion of subjects in the sitagliptin group who were discontinued from the study due to meeting glycaemic withdrawal criteria (23% vs 11% for canagliflozin). (Note: in DIA3015, subjects meeting prespecified glycaemic targets were to be withdrawn from the study instead of being treated with rescue therapy, which contributed substantially to the lower completion rate in DIA3015 compared to the other phase III studies.) The remaining percentage of subjects who discontinued from this study from each treatment group (21% for sitagliptin and 22% for canagliflozin 300 mg) is consistent with the percentage seen in the other 52-week canagliflozin phase III study (DIA3009).

During the double-blind period, 98% and 90% of subjects remained on stable doses of metformin and of SU, respectively, as specified by the protocol. The lower percentage of subjects remaining on a stable dose of SU than metformin mainly reflects downtitration of the SU to avoid hypoglycemia; there was no difference between the canagliflozin and sitagliptin groups in the percentage of subjects having a decrease in SU dose (8% and 9%, respectively).

The mean change in HbA1c showed clinically relevant improvements in both treatment arms with changes from baseline of -1.03% and -0.66%, respectively. Since the upper limit of the 95% CI for the difference in HbA1c between CANA and sitagliptin was less than 0 (-0.25%) even superiority of CANA could be demonstrated. Over the 52 week treatment period the response was attenuated to a greater extent with sitagliptin suggesting better durability of effect with CANA.

Figure 4: HbA_{1c}: LS Mean Change from Baseline Over Time – LOCF
(Study 28431754DIA3015: Modified Intent-to-Treat Analysis Set)



The results on the number of responders as well on FPG showed consistent results. Body weight was decreased by 2.5% with CANA 300 mg while sitagliptin showed a neutral effect.

In addition, clinically relevant reductions of SBP and DBP were observed in the CANA group with little change of these parameters in the sitagliptin treated patients: Treatment with CANA led to a decrease in systolic blood pressure of -5.7 mmHg, compared to an increase of 0.7mmHg in the sitagliptin 100 mg dose. Diastolic blood pressure decreased with CANA 300 mg by -3.28 mmHg and by -0.32 mmHg with sitagliptin 100 mg.

CANA 300 mg seems to improve beta-cell function (improvement of HOMA2%-B and by FS-MMTT derived measures of beta-cell function) compared to sitagliptin.

This non-inferiority study did not investigate the CANA 100 mg dose applied for. However, there are data from other studies (DIA2001, DIA3006) investigating sitagliptin and CANA 100 mg, which show clinically relevant antihyperglycaemic efficacy in the same order of magnitude for both active treatments. Although no formal non-inferiority comparison was performed in these studies these data are considered to support an add-on claim of CANA 100 mg in patients pre-treated with metformin and SU.

Overall, this study demonstrates non-inferior and even superior efficacy of CANA compared to sitagliptin.

Key features and results are summarised in the following table:

Title: A Randomized, Double-blind, Active-controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerabilty of Canagliflozin Versus Sitagliptin in the Treatment of Subjects with Type 2 Diabetes Mellitus with Inadequate Glycaemic Control on Metformin and Sulphonylurea Therapy	
Study identifier	28431754-DIA3015
Study design	Randomized, double-blind, active-controlled study
Primary objectives	To assess the effect of the addition of treatment with CANA compared with the addition of treatment with sitagliptin on HbA_{1c} after 52 weeks; the safety and tolerability of CANA
Hypothesis	Non-inferiority

Treatments groups	CANA 300 mg Sitagliptin 100 mg	Number of subjects treated by treatment group: CANA 300 mg (N=377) Sitagliptin 100 mg (N=378)
Duration of Run-in Period	2-week single-blind placebo run-in period	
Duration of treatment	52 weeks	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline to Week 52
	Key secondary	Change from Baseline to Week 52 in: Fasting plasma glucose (FPG) Proportion of subjects with HbA_{1c} <7.0% Body weight
Database lock date	14 March 12	
Primary analysis description	Analysis of covariance (ANCOVA) model with treatment and stratification factors as fixed effects and HbA_{1c} baseline value as covariate. The upper bound of the 95% CI of the treatment difference in LS means was used in the non-inferiority testing of the comparison with the non-inferiority margin 0.3%.	
Analysis population	Number of subjects in mITT population: CANA 300 mg (N=377); Sitagliptin 100 mg (N=378)	
Primary efficacy results	Baseline	Week 52
	Mean (SD): CANA 300 mg 8.12 (0.910); Sitagliptin: 8.13 (0.916)	Sitagliptin-subtracted LS mean (SE): CANA 300 mg -0.37 (0.064)
	95% CI:	CANA 300 mg (-0.500; -0.250)
Key Secondary Results	FPG: Change from Baseline to Week 52 (LOCF): Sitagliptin-subtracted LS Mean (SE): CANA 300 mg -1.34 (0.164)	
	Proportion of Subjects with HbA_{1c} <7.0%: CANA 300 mg 47.6; Sitagliptin: 35.3	
	Body Weight: Percent Change from Baseline to Week 52 (LOCF): Sitagliptin-subtracted LS Mean (SE): CANA 300 mg -2.8 (0.3)	

Cardiovascular assessment study with efficacy substudies (DIA3008 and substudies)

Study DIA3008: CANVAS is a placebo-controlled, 3 parallel-group study to evaluate the safety, tolerability, and CV risk with CANA plus standard of care relative to placebo plus standard of care in subjects with T2DM, on a wide range of current antihyperglycaemic agents (AHAs), who had either a history or high risk of CV disease.

Subjects were randomized to treatment with CANA (100 mg or 300 mg) or placebo in a 1:1:1 randomization ratio. CANVAS is an event-driven study, with the study duration based on the occurrence of sufficient events to evaluate the study hypothesis and objectives. It is planned to enrol approximately 4500 subjects in the study. The sample size was determined based upon a sufficient number of MACE plus hospitalised unstable angina events (assuming a per annum event rate of 2.25%) to support a planned meta-analysis of CV data from this study (and other CANA phase III studies).

With the CANVAS study the Applicant addressed the requirement as set out in CPMP/ EWP/1080/00 Rev.1 that the development programme of drugs for the treatment of T2DM "provides sufficient information supporting the lack of a drug induced excess cardiovascular risk". Cardiovascular high risk patients will be followed for a minimum of 4 years in this event driven study and blinded data will be monitored for MACE. Results of the interim safety analysis (data

cut off 15 September 2011) are presented in the safety section of this report. Notably, interim results showed no meaningful differences in the incidence of death, with a lower frequency of death in the combined CANA groups (0.7%) relative to the placebo group (0.9%).

Key features of this study are summarised in the following table:

Title: A Randomized, Multicenter, Double-blind, Parallel, Placebo-controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus (CANVAS: CANagliflozin Cardiovascular Assessment Study)		
Study identifier	28431754-DIA3008 (Interim Safety)	
Study design	Randomized, double-blind, placebo-controlled, parallel-group study	
Primary objectives	To assess the effect of CANA plus standard of care relative to placebo plus standard of care on CV risk as measured by the hazard ratio for a composite endpoint (MACE including CV death, nonfatal MI, and nonfatal stroke); the safety and tolerability of CANA plus standard of care relative to placebo plus standard of care	
Hypothesis	No efficacy hypothesis for this interim safety report	
Treatments groups	CANA 100, 300 mg Placebo	Number of subjects treated by treatment group: CANA 100 mg (N=1,445), CANA 300 mg (N=1,441), Placebo (N=1,441)
Duration of Run-in Period	2-week single-blind placebo run-in period	
Duration of treatment	Event driven	
Endpoints and definitions	Primary	Not applicable
	Key secondary	Not applicable
Database lock date	Study is ongoing; data cutoff for report is 15 September 2011	
Primary analysis description	Not applicable	
Analysis population	Safety Analysis Set: Placebo (N=1,441), CANA 100 mg (N=1,445), CANA 300 mg (N=1,441)	
Primary efficacy results	Not applicable	

DIA3008 (Insulin substudy): the aim of this substudy was to investigate the add-on use of CANA to insulin in CV high risk subjects with inadequate glycaemic control, either as monotherapy or in combination with metformin or any other AHA(s).

Most of the 1,718 randomized and dosed subjects (population 2 = subjects on insulin ≥30IE/day) completed the 18 week substudy (93%), and the proportion of subjects who were discontinued prior to week 18 was modestly higher in the placebo group (9%) than in the pooled canagliflozin group (7%). The overall mean insulin dose at baseline was 83 IU/day, and 70% of subjects were on a background of basal (ie, long-acting) plus bolus (short-acting) insulin prior to baseline, while 20% of subjects were on a background of basal insulin alone and 9% were on a background of bolus insulin alone (not specified for 1%). Approximately 90% of subjects remained on stable doses of insulin during the 18-week substudy, as specified by the protocol, unless down-titration was considered necessary to avoid hypoglycaemia, or if rescue criteria were met.

Clinically relevant reductions in HbA1c at week 18 compared to placebo were observed with both doses of CANA (placebo-adjusted changes from baseline: -0.72% and -0.63% for CANA 300 mg and 100 mg, respectively, population 2). The other glycaemic endpoints tested (FPG lowering, proportion of subjects achieving HbA1c <7%) were statistically significantly superior to placebo for both CANA doses. Of note, albeit smaller compared to effects in other phase III studies, some

reductions of body weight were seen with both CANA doses in the presence of ongoing insulin therapy.

Significant, dose-dependent reductions from baseline to week 26 were achieved in SBP with the 100 mg and 300 mg CANA doses compared to placebo (SBP: -4.57mmHg and -6.94 mmHg with the 100 mg and 300 mg dose, respectively, placebo -2.47mmHg). Reductions in DBP were less pronounced: -1.86 mmHg and -2.95 mmHg with CANA 100 mg and 300 mg, respectively (placebo:-1.23mmHg).

In the CANA groups background insulin dose could be decreased in a greater proportion of patients as compared to placebo (12% and 10% in the CANA 300 mg and 100 mg group, respectively, compared to 4% in the placebo group). Reduction of insulin requirements and alleviation of insulin induced weight gain are considered desirable effects of CANA in the frequently obese population of patients with T2M. Sustainability of the decrease in insulin requirements was, however, comparable between the CANA and the placebo groups. Glycaemic control (HbA1c) in the subgroup of patients who decreased their insulin dosage was comparable to the results of the primary analysis. Reduction of insulin requirements and alleviation ofinsulin induced weight gain are considered desirable effects of CANA in the frequently obese population of patients with T2M

Overall, this study supports the efficacy of both doses of CANA in combination with insulin with or without other AHAs, predominantly metformin.

Key features and efficacy results are summarised in the following table:

Title: A Randomized, Multicenter, Double-blind, Parallel, Placebo-controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus (CANVAS: CANagliflozin Cardiovascular Assessment Study)		
Study identifier	28431754-DIA3008 (Insulin Substudy)	
Study design	Randomized, double-blind, placebo-controlled, parallel-group substudy	
Primary objectives	To assess the HbA_{1c} -lowering efficacy (change from baseline in HbA_{1c}) of CANA relative to placebo after 18 weeks of treatment; the safety and tolerability of canagliflozin	
Hypothesis	Superiority	
Treatments groups	CANA 100, 300 mg Placebo	Number of subjects treated by treatment group: CANA 100 mg (N=566), CANA 300 mg (N=587) Placebo (N=565)
Duration of Run-in Period	2-week single-blind placebo run-in period	
Duration of treatment	18 weeks	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline to Week 18
	Key secondary	Change from Baseline to Week 18 in: Fasting plasma glucose (FPG) Proportion of subjects with HbA_{1c} <7.0% Body weight
Database lock date	Study is ongoing; data cutoff for report is 15 September 2011	
Primary analysis description	Analysis of covariance (ANCOVA) model with treatment and stratification factors as fixed effects and HbA_{1c} baseline value as covariate	
Analysis population	Number of subjects in mITT population: Placebo (N=565), CANA 100 mg (N=566), CANA 300 mg (N=587)	
Primary efficacy results	Baseline	Week 18
	Mean (SD): Placebo 8.20 (0.837); CANA 100 mg 8.33 (0.905);	Placebo-subtracted LS Mean (SE): CANA 100 mg -0.65 (0.044); CANA 300 mg -0.73 (0.043)

	CANA 300 mg 8.27 (0.894)	
	P value:	CANA 100 mg <0.001; CANA 300 mg <0.001
Key Secondary Results	FPG: Change from Baseline to Week 18 (LOCF): Placebo-subtracted LS Mean (SE): CANA 100 mg -1.25 (0.150); CANA 300 mg -1.61 (0.150)	
	Proportion of Subjects with HbA_{1c} <7.0%: Placebo 7.7; CANA 100 mg 19.8; CANA 300 mg 24.7	
	Body Weight: Percent Change from Baseline to Week 18 (LOCF): Placebo-subtracted LS Mean (SE): CANA 100 mg -1.9 (0.2); CANA 300 mg -2.4 (0.2)	

Study 3008 (SU substudy) the aim of this substudy was to investigate the add-on use of CANA in CV high risk subjects with inadequate glycaemic control in the subgroup of subjects receiving **SU** monotherapy at a protocol pre-specified dose. However, due to misstratification population 1 was the pre-specified population of interest which is acceptable. For this study a total of 127 patients in population 1 were randomised to CANA 100mg, 300 mg or placebo. About 7% of patient discontinued with the majority in the placebo group (patients in need for rescue therapy).

Clinically relevant reductions in HbA1c at week 18 compared to placebo were observed with both doses of CANA (% changes from baseline compared to placebo -0.83% and -0.74% for CANA 300 mg and 100 mg, respectively, population 1). The other glycaemic endpoints tested (FPG lowering, proportion of subjects achieving HbA1c <7%) generally supported the findings on HbA1c. Numerically superior effects on body weight were shown. As regards systolic blood pressure statistically non-significant, dose-dependent reductions from baseline to week 18 were achieved with the 100 mg and 300 mg CANA groups compared to placebo (SBP: -4.04mmHg and -4.22 mmHg with the 100 mg and 300 mg dose, respectively, placebo -3.70 mmHg). Reductions in DBP were as follows: -3.48 mmHg (baseline 82 mmHg) and -1.88 mmHg (baseline 76 mmHg) with CANA 100 mg and 300 mg, respectively (placebo:-0.9 mmHg).

During the 18-week substudy, 100% and 98% of subjects in Population 1 and 2, respectively, remained on stable doses of the SU agent that they were on at randomization, as specified by the protocol. In population 2 there were 3 decreases in the combined CANA group and no decrease in the placebo group.
Results on HbA1c in the subgroup of moderately renally impaired patients in population 1 were not presented in the study report and should be submitted by the Applicant.

Overall, this study supports the efficacy of both doses of CANA as add-on to SU.

Key features and results of this study are summarised in the following table:

Title: A Randomized, Multicenter, Double-blind, Parallel, Placebo-controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus (CANVAS: CANagliflozin Cardiovascular Assessment Study)		
Study identifier	28431754-DIA3008 (SU Substudy)	
Study design	Randomized, double-blind, placebo-controlled, parallel-group substudy	
Primary objectives	To assess the HbA_{1c} -lowering efficacy (change from baseline in HbA_{1c}) of CANA relative to placebo after 18 weeks of treatment; the safety and tolerability of canagliflozin	
Hypothesis	Superiority	
Treatments groups	CANA 100, 300 mg Placebo	Number of subjects treated by treatment group: CANA 100 mg (N=42), CANA 300 mg (N=40)

		Placebo (N=45)
Duration of Run-in Period	2-week single-blind placebo run-in period	
Duration of treatment	18 weeks	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline to Week 18
	Key secondary	Change from Baseline to Week 18 in: Fasting plasma glucose (FPG) Proportion of subjects with HbA_{1c} <7.0% Body weight
Database lock date	Study is ongoing; data cutoff for report is 15 September 2011	
Primary analysis description	Analysis of covariance (ANCOVA) model with treatment and stratification factors as fixed effects and HbA_{1c} baseline value as covariate	
Analysis population	Number of subjects in mITT population: Placebo (N=45), CANA 100 mg (N=42), CANA 300 mg (N=40)	
Primary efficacy results	Baseline	Week 18
	Mean (SD): Placebo 8.49 (1.130); CANA 100 mg 8.29 (0.831); CANA 300 mg 8.28 (1.005)	Placebo-subtracted LS Mean (SE): CANA 100 mg -0.74 (0.206); CANA 300 mg -0.83 (0.207)
	P value:	CANA 100 mg <0.001; CANA 300 mg <0.001
Key Secondary Results	FPG: Change from Baseline to Week 18 (LOCF): Placebo-subtracted LS Mean (SE): CANA 100 mg -2.07 (0.464); CANA 300 mg -2.66 (0.465)	
	Proportion of Subjects with HbA_{1c} <7.0%: Placebo 5.0; CANA 100 mg 25.0; CANA 300 mg 33.3	
	Body Weight: Percent Change from Baseline to Week 18 (LOCF): Placebo-subtracted LS Mean (SE): CANA 100 mg -0.4 (0.7); CANA 300 mg -1.8 (0.7)	

Clinical studies in special populations *(DIA3004 and DIA3010)*

Study DIA3004: this study aimed to investigate the add-on use of canagliflozin in patients with T2DM with inadequate glycaemic control and having moderate renal impairment with an GFR of ≥30 and <50 mL/min/1.73 m^2 while either not receiving background therapy with an AHA or on a stable AHA regimen that could have included oral agents and/or insulin therapy. A high proportion of 269 randomized and dosed subjects (87%) completed 26 weeks of treatment, and the proportion that were discontinued prior to the week 26 visit was lower in the canagliflozin 300 mg group (8%) than in the placebo (14%) or canagliflozin 100 mg (17%) groups. Most subjects (98%) were taking at least 1 AHA agent, and nearly 60% were on 2 or more classes of AHA agents; 74% of subjects were treated with insulin alone or in combination with another AHA.

Concerning the primary efficacy endpoint mean change in HbA1c was statistically significantly higher in both CANA groups compared to placebo. The reductions at both doses were -0.30% and -0.40% for CANA 300 mg and 100mg, respectively, placebo-subtracted change from baseline at week 26). The smaller effect size on HbA1c in patients with lower baseline GFR is expected in view of CANA`s mechanism of action (rate of UGE linearly related to GFR).

CANA treatment was associated by a greater proportion of subjects who achieved goal HbA1c <7% compared to placebo. Results on FPG were numerically in favour of CANA. The results for body weight are numerically in favour of CANA. Nearly the full effect on body weight was achieved at week 6 with only minimal further reduction observed for both CANA doses. As

regards systolic and diastolic blood pressure reductions from baseline to week 26 were achieved with the 100 mg and 300 mg CANA groups compared to placebo. The reduction in SBP and DBP were more pronounced in the 300 mg relative to the 100 mg group (SBP: placebo -0.32mmHg, CANA 100 mg -6.05mmHg, CANA 300 mg -6.44mmHg; DBP: placebo -1.39mmHg, CANA 100mg -2.57mmHg, CANA 300 mg-3.46mmHg).

Key features and results are summarised in the following table:

Title: A Randomized, Double-Blind, Placebo-Controlled, 3-arm, Parallel-Group, 26-Week, Multicenter Study With a 26-Week Extension, to Evaluate the Efficacy, Safety and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus who Have Moderate Renal Impairment		
Study identifier	28431754-DIA3004	
Study design	Randomized, double-blind, placebo-controlled, parallel-group study (with a 26-week, core double-blind period plus a 26-week, extension double-blind period)	
Primary objectives	To assess the effect of CANA relative to placebo on HbA_{1c} after 26 weeks of treatment; the safety and tolerability of CANA	
Hypothesis	Superiority	
Treatments groups	CANA 100, 300 mg Placebo	Number of subjects treated by treatment group: CANA 100 mg (N=90), CANA 300 mg (N=89) Placebo (N=90)
Duration of Run-in Period	2-week single-blind placebo run-in period	
Duration of treatment	26 weeks (core double-blind period)	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline to Week 26
	Key secondary	Change from Baseline to Week 26 in: Fasting plasma glucose (FPG) Proportion of subjects with HbA_{1c} <7.0% Body weight
Database lock date	19 January 2012	
Primary analysis description	Analysis of covariance (ANCOVA) model with treatment and stratification factors as fixed effects and HbA_{1c} baseline value as covariate	
Analysis population	Number of subjects in mITT population: Placebo (N=90), CANA 100 mg (N=90), CANA 300 mg (N=89)	
Primary efficacy results	Baseline	Week 26
	Mean (SD): Placebo 8.02 (0.917); CANA 100 mg 7.89 (0.898); CANA 300 mg 7.97 (0.805)	Placebo-subtracted LS mean (SE): CANA 100 mg -0.30 (0.117); CANA 300 mg -0.40 (0.117)
	P value:	CANA 100 mg 0.012; CANA 300 mg <0.001
Key Secondary Results	FPG: Change from Baseline to Week 26 (LOCF): Placebo-subtracted LS Mean (SE): CANA 100 mg -0.85 (0.368); CANA 300 mg -0.67 (0.371)	
	Proportion of Subjects with HbA_{1c} <7.0% at Week 26: Placebo 17.2; CANA 100 mg 27.3; CANA 300 mg 32.6	
	Body Weight: Percent Change from Baseline to Week 26 (LOCF): Placebo-subtracted LS Mean (SE): CANA 100 mg -1.6 (0.4); CANA 300 mg -1.8 (0.4)	

Study DIA3010: this study was designed to assess the efficacy and safety of canagliflozin in older subjects not adequately controlled on current glucose lowering therapy (HbA_{1c} of ≥7.0 to ≤10.0%), and to assess body composition and bone safety using DXA in a subset of subjects. The mITT analysis set was comprised of 714 subjects (median age of 63 years, range 55 to 80 years,

while a total of 211 subjects participated in the body composition substudy. A high proportion of subjects (89%) completed 26 weeks of double-blind treatment, and the proportion of subjects who were discontinued prior to week 26 was higher in the placebo group versus the pooled canagliflozin group (17% vs. 9%). The design of the study differs from most of the other phase III studies in that it examines the add-on use of CANA to existing diabetes treatment rather than add-on to a predefined AHA regimen. Almost all subjects (98%) were taking at least 1 AHA agent (49% on a SU and 33% on insulin), and 76% of subjects were on 2 or more classes of AHA agents.

Overall, CANA showed statistically significant and clinically relevant as well as dose-dependent improvement in glycaemic control in patients with T2DM on various antidiabetic background therapies. The primary efficacy endpoint mean change in HbA1c was statistically significantly higher in both CANA groups compared to placebo (change from baseline in HbA1c at week 26 for CANA 300 mg relative to placebo -0.7% for 300 mg and -0.57% for 100 mg). Other antihyperglycaemic efficacy parameters (FPG, responder analysis) supported these results.

Results of the subgroup analysis investigating the effect on HbA1c according to age group (<65 years versus ≥65 years) showed a marked decrease in effect in the older patient group (reduction in HbA1c with 300 mg CANA -0.50% and with CANA 100 mg -0.45% compared to -0.82% and -0.65% in the younger age group). This difference might be partly explained by a slightly lower baseline HbA1c in the older age group (7.8% vs 7.6%) and – to a greater extent – by a lower baseline GFR in this group. Age per se was not found to be a factor influencing efficacy of another SGLT2-inhibitor and also did not affect the efficacy of CANA (see section 3.6).

The age distribution in this study does not differ markedly from the one in the other phase III studies and – despite the study's goal to investigate the efficacy and safety of CANA in older patients with T2DM - less than 3% of patients were between 65 and 75 years of age, below 1% between 75 and 85 years and no patient was above 85 years.

However, in the whole phase III population a sufficient number of older patients was included, and results on HbA1c reduction showed clinically relevant effects even in the patients above 75 years of age (age group ≤75 years: CANA 100 mg -0.77%, CANA 300 mg -0.68%, placebo -0.13%; age group<75 years CANA 100 mg -0.69%, CANA 300 mg -0.85%, placebo -0.15%, see section 3.6).

Results of subgroup analyses on study DIA3010 investigating the effect on HbA1c according to baseline GFR values showed results comparable to those of study 3004: the antihyperglycaemic efficacy in moderately renally impaired patients was of borderline clinical significance.

As regards systolic and diastolic blood pressure reductions from baseline to week 26 were achieved with the 100 mg and 300 mg CANA groups compared to placebo. The reduction in SBP and DBP were more pronounced in the 300 mg relative to the 100 mg group (SBP change from baseline to week 26 [mmHg]: CANA 100 mg -3.96, CANA 300 mg -7.47, placebo 0.30; DBP change from baseline to week 26[mmHg] : CANA 100 mg -1.97, CANA 300 mg -3.48, placebo -0.49).

Body weight was significantly reduced with CANA in a dose dependent fashion. Body composition measurements performed in a subgroup of patients showed that fat mass loss accounted for approximately two-thirds of overall body mass reduction. This finding showed that, albeit a

portion of the weight loss with CANA could be attributed to fluid loss (osmotic diuresis accompanying the increase in UGE), the majority of the total absolute weight loss was through loss of fat mass. The results are in line with those of study DIA 3009 and those observed for another SGLT2-inhibitor, and the relative reduction in fat and lean mass are similar to those achieved with dieting.

Overall, this study supports the efficacy of CANA in combination with various background therapies but does not specifically contribute to the evaluation of efficacy and safety of CANA in older patients. However, the whole phase III program included enough older patients with results showing clinically relevant antihyperglycaemic efficacy of both doses of CANA.

Key features and efficacy results from this study are summarised in the following table:

Title: A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety, and tolerabilty of canagliflozin compared with placebo in the treatment of older subjects with type 2 diabetes mellitus inadequetly controlled on glucose lowering therapy		
Study identifier	28431754-DIA3010	
Study design	Randomized, double-blind, placebo-controlled, parallel-group study (with a 26-week, core double-blind period plus a 78-week, extension double-blind period)	
Primary objectives	To assess the effect of addition of treatment with CANA relative to placebo on HbA_{1c} after 26 weeks of treatment; the safety and tolerability of CANA	
Hypothesis	Superiority	
Treatments groups	CANA 100, 300 mg Placebo	Number of subjects treated by treatment group: CANA 100 mg (N=241), CANA 300 mg (N=236) Placebo (N=237)
Duration of Run-in Period	2-week single-blind placebo run-in period	
Duration of treatment	26 weeks (core double-blind period)	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline through Week 26
	Key secondary	Change from Baseline to Week 26 in: Fasting plasma glucose (FPG) Proportion of subjects with HbA_{1c} <7.0% Body weight
Database lock date	09 December 2011	
Primary analysis description	Analysis of covariance (ANCOVA) model with treatment and stratification factors as fixed effects and HbA_{1c} baseline value as covariate	
Analysis population	Number of subjects in mITT population: Placebo (N=237), CANA 100 mg (N=241), CANA 300 mg (N=236)	
Primary efficacy results	Baseline	Week 26
	Mean (SD): Placebo 7.76 (0.785); CANA 100 mg 7.77 (0.773); CANA 300 mg 7.69 (0.779)	Placebo-subtracted LS Mean (SE): CANA 100 mg -0.57 (0.069); CANA 300 mg -0.70 (0.070)
	P value:	CANA 100 mg <0.001; CANA 300 mg <0.001
Key Secondary Results	FPG: Change from Baseline to Week 26 (LOCF): Placebo-subtracted LS Mean (SE): CANA 100 mg -1.41 (0.175); CANA 300 mg -1.54 (0.176)	
	Proportion of Subjects with HbA_{1c} <7.0%: Placebo 28.0; CANA 100 mg 47.7; CANA 300 mg 58.5	
	Body Weight: Percent Change from Baseline to Week 26 (LOCF): Placebo-subtracted LS Mean (SE): CANA 100 mg -2.3 (0.3); CANA 300 mg -3.0 (0.3)	

Summary of main efficacy results in the phase III program

The following tables summarise the efficacy results from the phase III program supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10: Overview of Key Efficacy Results (LS Mean Difference From Placebo) in Phase III Placebo-Controlled Studies of Canagliflozin (LOCF Analysis; Modified Intent-to-Treat Analysis Set)

Efficacy Endpoint	Mono-therapy	Dual Therapy		Triple Therapy		Add-on to Insulin	Special Populations	
	DIA3005	DIA3006 Add-on to Metformin	DIA3008 SU Substudy	DIA3002 Add-on to Metformin + SU	DIA3012 Add-on to Metformin + pioglitazone	DIA3008 Substudy	DIA3004 Moderate Renal Impair-ment	DIA3010 Older Adults
Primary assessment timepoint	Week 26	Week 26	Week 18	Week 26	Week 26	Week 18	Week 26	Week 26
Total number subjects	584`	1284	127	469	342	1718	269	714
	Results of Pairwise Comparisons of Canagliflozin Dose Group with Placebo[a]							
Primary Endpoint								
Change from BL in HbA_{1c} (%)								
CANA 300 mg	-1.16[§]	-0.77[§]	-0.83[§]	-0.92[§]	-0.76[§]	-0.73[§]	-0.40[§]	-0.70[§]
CANA 100 mg	-0.91[§]	-0.62[§]	-0.74[§]	-0.71[§]	-0.62[§]	-0.65[§]	-0.30[*]	-0.57[§]
Other Key Glycaemic Endpoints								
Change from BL in FPG (mmol/L)								
CANA 300 mg	-2.41[§]	-2.23[§]	-2.66[§]	-1.92[§]	-1.98[§]	-1.61[§]	-0.67	-1.54[§]
CANA 100 mg	-1.97[§]	-1.65[§]	-2.07[§ ¥]	-1.24[§]	-1.63[§]	-1.25[§]	-0.85[* ¥]	-1.41[§]
Proportion achieving HbA_{1c} <7.0%[b]								
CANA 300 mg	41.7[§]	27.9[§]	28.3[†]	38.6[§]	31.8[§]	17.0[§]	15.3[* ¥]	30.5[§]
CANA 100 mg	23.9[§]	15.6[§]	20.0[† ¥]	25.2[§]	14.4[†]	12.1[§]	10.0	19.7[§]
Other Key Efficacy Endpoints								
Percent change from BL in Body Wgt.								
CANA 300 mg	-3.3[§]	-2.9[§]	-1.8[*]	-2.0[§]	-3.7[§]	-2.4[§]	-1.8[c]	-3.0[§]

Efficacy Endpoint	Mono-therapy	Dual Therapy		Triple Therapy		Add-on to Insulin	Special Populations	
	DIA3005	DIA3006 Add-on to Metformin	DIA3008 SU Substudy	DIA3002 Add-on to Metformin + SU	DIA3012 Add-on to Metformin + pioglitazone	DIA3008 Substudy	DIA3004 Moderate Renal Impair-ment	DIA3010 Older Adults
Primary assessment timepoint	Week 26	Week 26	Week 18	Week 26	Week 26	Week 18	Week 26	Week 26
Total number subjects	584`	1284	127	469	342	1718	269	714
CANA 100 mg Change from BL in SBP (mmHg)	-2.2§	-2.5§	-0.4	-1.4§	-2.7§	-1.9§	-1.6c	-2.3§
CANA 300 mg	-5.42§	-6.58§	-1.77	-1.62	-3.46*	-4.38§	-6.12c	-7.89§
CANA 100 mg	-3.71§	-5.36§	-0.10	-2.24	-4.07†	-2.58§	-5.73c	-4.63§
Percent change from BL in HDL-C (mmol/L)								
CANA 300 mg	6.1†	8.4§	0.9	3.5*¥	6.5§	4.7§	1.5d	4.7§
CANA 100 mg	6.8§	6.6§	2.7	2.6	4.8*	0.8	2.5d	5.3§
Percent change from BL in TG (mmol/L)								
CANA 300 mg	-10.2*¥	-4.6	12.0	-3.1	-17.0†	-2.0	3.9d	0.7
CANA 100 mg	-5.4	-1.6	-13.0	-6.2	-12.1*¥	0.2	-1.7d	-4.8

- [a] Based on the ANCOVA model with treatment, study specific stratification factors and baseline value as a covariate. § p<0.001; † p<0.01; * p<0.05, ¥ nominal significance.
- [b] Difference (%) minus placebo
- [c] Endpoint not associated with hypothesis testing for DIA3004, but 95% CI excluded '0'.
- [d] Endpoint not associated with hypothesis testing for DIA3004, but 95% CI included '0'
- KEY: BL = baseline, CANA = canagliflozin, FPG = fasting plasma glucose, HDL-C = high density lipoprotein-cholesterol, S = significant, NS = not significant, SBP = systolic blood pressure, TG = triglycerides, Wgt = weight.
- Note: Data for DIA3008 SU Substudy presented for Population 1 (subjects on protocol-specified doses of SU monotherapy regardless of stratification). Data for DIA3008 Insulin substudy presented for Population 2 (subjects receiving insulin dose ≥30 U/day).
- Source: Mod5.3.5.3\ISE\Tab23, Tab25, Tab24, Tab29, Tab34, Tab36, and Tab37.Table107.

Analysis performed across trials (pooled analyses and meta-analysis)

To assess how subgroup factors impact glycaemic responses to CANA subgroup analyses were performed: the **overall pooled population of placebo-controlled studies** for subgroup analyses of efficacy endpoints comprised 4158 subjects from the ITT analysis sets of DIA3005 main study, DIA3006, DIA 3008 SU substudy, DIA3002, DIA3012, and DIA3008 insulin substudy.

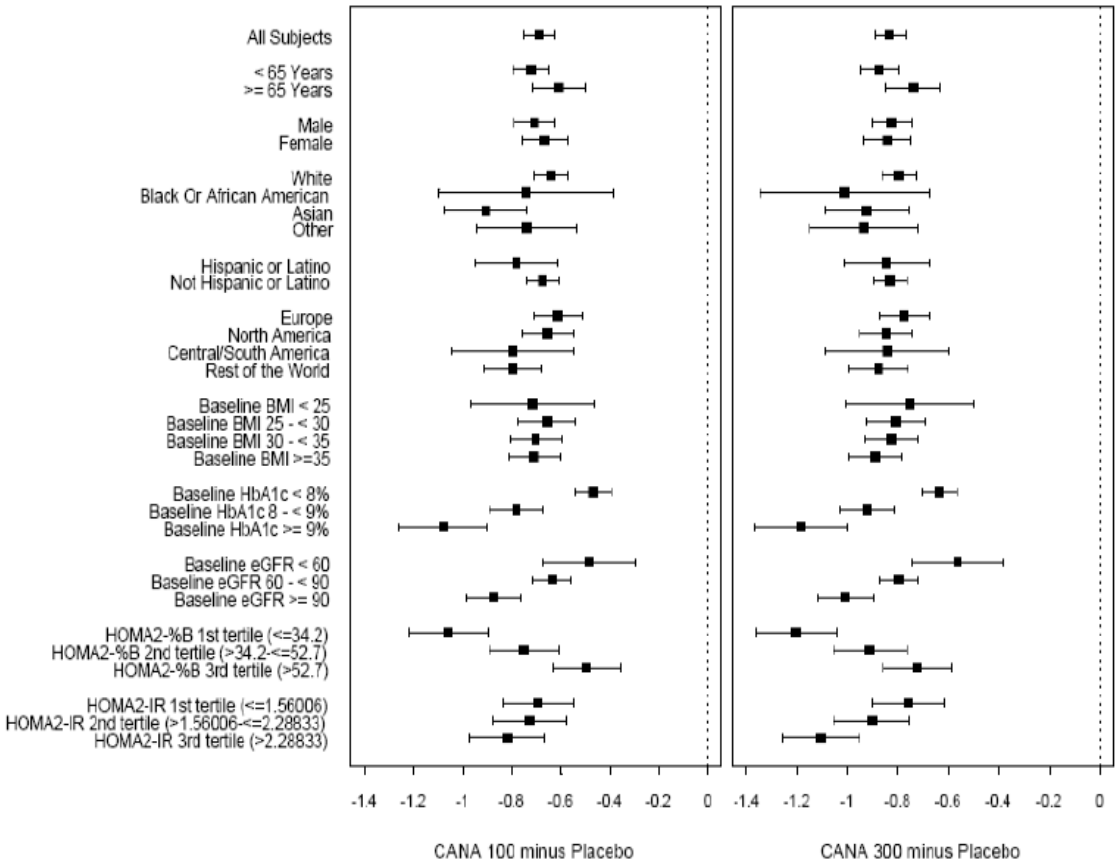
Baseline characteristics were generally similar across the pooled CANA 100 mg, CANA 300 mg group, and placebo treatment group. In each pooled treatment group, there was a slightly higher proportion of males compared with females. The median age was 60 years, a total of 1031 (25%) patients was 65-<75 years of age, and a total of 183 subjects (4%) were 75 years or older, with one subject being ≥85 years of age. Approximately three-quarters of pooled population subjects were white, 4% black or African American, and 13% Asian; 18% of subjects were Hispanic-Latino.

A total of 63% of subjects were obese, as indicated by a baseline BMI of ≥30 kg/m^2. The mean HbA1c at baseline was 8.1% and the duration of diabetes was 10 years in each pooled treatment group. At baseline 12% of subjects had moderate renal impairment; the mean eGFR value in the pooled population was 82.1 mL/ min/ 1.73m^2. No baseline imbalances occurred with respect to anthropometric and disease characteristics.

Subgroup analyses of change in HbA1c

The change from baseline in HbA1c within each of the predefined subgroups for the pooled population of placebo-controlled studies is presented in the following forest plot:

Figure 4-1: HbA_{1c} (%) 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)



Key: BMI = body mass index, CANA = canagliflozin, CI = confidence interval, eGFR = estimated glomerular filtration rate, EU = Europe (includes EU, EEA, EFTA), ISE = Integrated Summary of Efficacy, LS = least squares, mITT = modified intent-to-treat.
Note: Pairwise comparison: CIs are based on the ANCOVA model with factor(s) treatment, study and baseline HbA_{1c}.
Note: Predefined timepoint of primary endpoint: Week 18 (DIA3008 SU and Insulin substudies) or Week 26 (DIA3002, DIA3005, DIA3006, DIA3012).
Note: Studies include DIA3002, DIA3005 (excluding High Glycemic substudy), DIA3006 (excluding active comparator), DIA3008 SU and Insulin substudies, DIA3012.
Source: attachment 1.2, FEFF03_PC.

Overall, the mean change from baseline in HbA1c at the primary assessment time point, relative to placebo, was -0.83% (95%CI: [-0.892;-0.771] for the 300 mg dose and -0.69% (95%CI:[-0.749;-0.627] for the 100 mg dose. Hence, results in the pooled dataset are generally consistent with results of the individual studies.

Results on body weight in the pooled dataset of placebo controlled studies

In the pooled dataset of placebo controlled studies the mean percent change from baseline in body weight at the primary assessment timepoint, relative to placebo, was -2.7% (95% CI: [-2.9;-2.4]) for the 300 mg dose and -2.0% (95% CI: [-2.3;-1.8]) for the 100 mg dose. Corresponding placebo-subtracted LS mean absolute reductions in body weight for the 300 mg

and 100 mg groups for the pooled population of placebo-controlled studies were -2.43 kg (95% CI: [-2.652;-2.199]) and -1.84 kg (95% CI: [-2.064;-1.611]), respectively.

The treatment-by-subgroup interactions were not significant (p >0.10) for subgroups defined by sex, age, baseline BMI, ethnicity and region. Subgroup analyses of particular interest which demonstrated an impact on the magnitude of HbA1c lowering response to CANA were the subgroup analyses by baseline HbA1c and the subgroup analysis by baseline GFR.

Subgroup analysis by baseline HbA1c: Unsurprisingly, there was a significant interaction observed with HbA1c baseline values: the most prominent effect occurred in patients with high baseline values. The effect (placebo substracted LS mean change) was -0.63% and -0.47% for CANA 300 mg and 100 mg, respectively, in the HbA1c <8% subgroup, -1.15% and -1.01%, respectively, in the HbA1c 8-9% subgroup, and -1.6% and -1.08% in the HbA1c ≥9% subgroup.

Subgroup analysis by baseline GFR: Reductions in HbA1c were reduced in a stepwise manner with lower baseline GFR: -0.56% and -0.48% for the <60 mL/min/1.73 m^2 subgroup, -0.80% and -0.63%, for 60-<90 mL/min/1.73 m^2 subgroup, and -1.01% and -0.87% for ≥90 mL/min/1.73m^2 subgroup, for CANA 300 mg and 100mg, respectively. The mean baseline GFR values at baseline were 50.6, 75.4, and 104.5 in the <60, 60 to <90, and ≥90 mL/min/1.73 m^2 groups, respectively, of the overall pooled population of placebo controlled studies. The HbA1c reduction observed in pooled datasets were higher as compared to the results in study DIA3004 (-0.3% and -0.4% placebo corrected change from baseline for CANA 100 mg and CANA 300 mg, respectively), which is likely due to the difference in baseline GFR values (39.4 mL/min/1.73m^2 in study DIA3004 and 50.6 mL/min/1.73m^2 in the pooled population of placebo controlled studies).

Efficacy of CANA was also evaluated in the **pooled population of patients with moderate renal impairment** (all subjects from placebo-controlled phase III studies with GFR ≥30 to<60 mL/min/1.73 m^2). This population comprised a total of 1085 treated subjects. Baseline characteristics were similar across treatment groups. In this population HbA1c decreased from baseline by -0.47% and -0.38% for CANA 300 mg and 100 mg, respectively, compared to placebo.

Results were provided for 2 subgroup classifications defined by baseline GFR (<45 and ≥45 mL/min/1.73 $m^2$and <50 and ≥50 mL/min/1.73 m^2). In this population the subgroup of patients with GFR< 45 mL/min/1.73m^2 showed clinically questionable to insufficient HbA1c reductions of -0.39% and -0.23% with CANA 300 mg and 100 mg, respectively. Results are given in the following table:

Table 76: HbA_{1c} (%) by eGFR Category: Change From Baseline to Primary Assessment Timepoint - LOCF: Pooled Population of Subjects With Moderate Renal Function (ISE Phase 3 Studies: Modified Intent-to-Treat Analysis Set)

Blood hemoglobin A_{1c} (%)	Placebo	CANA 100 mg	CANA 300 mg
Baseline eGFR group: <45 mL/min/1.73 m^2			
Value at baseline			
N	108	118	122
Mean (SD)	8.10 (0.933)	8.08 (0.972)	8.10 (0.898)
Change from baseline			
LS mean (SE)	0.05 (0.190)	-0.18 (0.189)	-0.34 (0.194)
Diff. of LS means (SE)		-0.23 (0.113)	-0.39 (0.113)
95% CI[a]		(-0.452;-0.006)	(-0.612;-0.168)
Baseline eGFR group: ≥45 mL/min/1.73 m^2			
Value at baseline			
N	248	208	232
Mean (SD)	7.98 (0.880)	8.11 (0.920)	8.10 (0.965)
Change from baseline			
LS mean (SE)	-0.10 (0.066)	-0.57 (0.068)	-0.62 (0.066)
Diff. of LS means (SE)		-0.47 (0.075)	-0.52 (0.073)
95% CI[a]		(-0.613;-0.318)	(-0.665;-0.379)
Baseline eGFR group: <50 mL/min/1.73 m^2			
Value at baseline			
N	163	164	175
Mean (SD)	8.02 (0.869)	8.10 (0.945)	8.07 (0.855)
Change from baseline			
LS mean (SE)	-0.12 (0.104)	-0.46 (0.108)	-0.56 (0.107)
Diff. of LS means (SE)		-0.34 (0.090)	-0.44 (0.088)
95% CI[a]		(-0.514;-0.162)	(-0.614;-0.267)
Baseline eGFR group: ≥50 mL/min/1.73 m^2			
Value at baseline			
N	193	162	179
Mean (SD)	8.01 (0.922)	8.10 (0.934)	8.13 (1.020)
Change from baseline			
LS mean (SE)	-0.09 (0.084)	-0.50 (0.085)	-0.58 (0.085)
Diff. of LS means (SE)		-0.42 (0.089)	-0.50 (0.086)
95% CI[a]		(-0.593;-0.245)	(-0.669;-0.330)

Results for HbA1c after completion of the 52-weeks extension periods (submitted on day 120)

The Applicant submitted 52-week data for 4 of the phase 3 studies (DIA3005, DIA3006, DIA3002, DIA3004). Percent changes from baseline to week 52 in HbA1c, FPG, body weight, SBP and DBP, and fasting plasma lipids (including LDL-C, HDL-C, non-HDL-C, total cholesterol, ratio of LDL-C to HDL-C, and triglycerides) for the mITT, extension mITT and the 52-week completer's analysis sets were summarized with descriptive statistics. No treatment differences were estimated. Results for HbA1c change from baseline to week 52 for the mITT set are given in the following table:

Table 9: HbA_{1c} (%) Change from Baseline to Week 52 - LOCF: Study by-Study Comparison - Modified Intent-to-Treat (mITT) Analysis Set

	Placebo	Cana 100 mg	Cana 300 mg	Sitagliptin
DIA3006[b] - Add-on to metformin				
N		365	360	354
Baseline, mean (SD)		7.94(0.879)	7.95(0.931)	7.92(0.875)
Change from baseline, LS mean (SE)		-0.73(0.047)	-0.88(0.047)	-0.73(0.047)
Diff of LS mean (SE) (minus Sitagliptin)		0.00(0.061)	-0.15(0.062)	
95% CI[a]		(-0.119;0.122)	(-0.273;-0.031)	
DIA3002 - Add-on to metformin and SU				
N	150	155	152	
Baseline, mean (SD)	8.12(0.896)	8.13(0.926)	8.13(0.942)	
Change from baseline, LS mean (SE)	0.01(0.077)	-0.74(0.077)	-0.96(0.078)	
Diff of LS mean (SE) (minus Placebo)		-0.75(0.099)	-0.97(0.100)	
95% CI[a]		(-0.945;-0.554)	(-1.165;-0.772)	
DIA3005[b] - Monotherapy				
N		191	194	
Baseline, mean (SD)		8.06(0.959)	8.01(0.988)	
Change from baseline, LS mean (SE)		-0.75(0.067)	-1.04(0.067)	
95% CI[a]		(-0.887;-0.623)	(-1.166;-0.904)	
DIA3004 – Moderate renal impairment				
N	87	89	89	
Baseline, mean (SD)	8.02(0.917)	7.88(0.886)	7.97(0.805)	
Change from baseline, LS mean (SE)	0.07(0.104)	-0.19(0.104)	-0.33(0.103)	
Diff of LS mean (SE) (minus Placebo)		-0.27(0.135)	-0.41(0.135)	
95% CI[a]		(-0.532;0.001)	(-0.676;-0.142)	

Key: AHA=antihyperglycemic agent, Cana=canagliflozin, CI=confidence interval, Diff=difference, LOCF=last observation carried forward, LS=least squares, N=number, SD=standard deviation, SE=standard error, SU=sulphonylurea, Met=metformin, IR=immediate release, FDC= fixed dose combination

[a] CIs are based on the ANCOVA model with treatment, study specific stratification factors, and baseline HbA_{1c}
[b] For DIA 3005 and 3006, there is no placebo-controlled group provided in the table since the placebo group in the core period (first 26 weeks) changed therapy to sitagliptin in the extension period (remaining 26 weeks). Hence, the 52-week efficacy results do not represent the effects in the original randomized population.

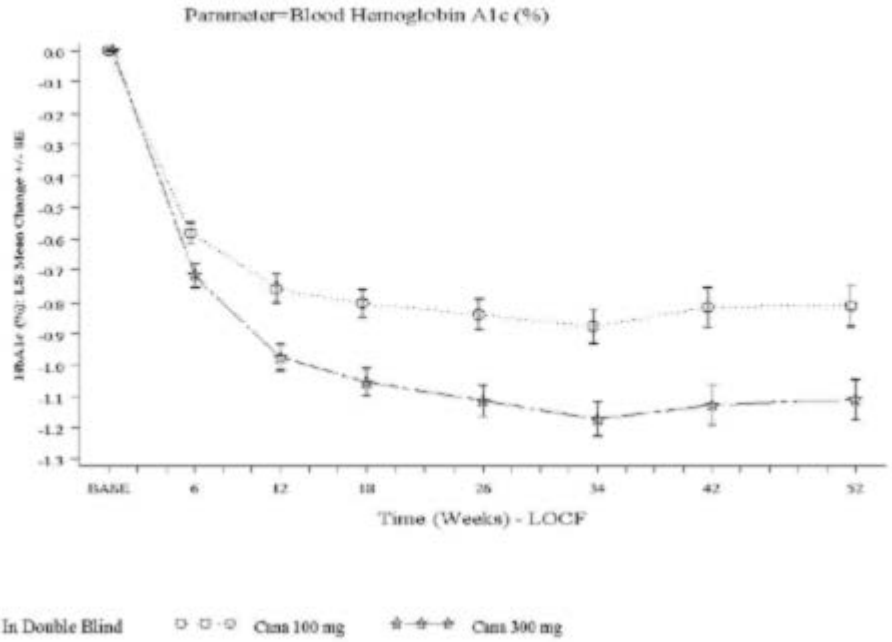
Note 1: The table includes only the subjects who had both baseline and post baseline HbA_{1c} values.
Note 2: The mITT analysis set includes all randomized subjects who took at least one dose of double blind study medication.
Sources: Mod5.3.5.1\DIA3002\Tab 12; Mod5.3.5.1\DIA3004\Tab 13; Mod5.3.5.1\DIA3006\Tab 12; Mod5.3.5.1\DIA3005\Tab 12

In studies DIA 3005, DIA 3006, DIA 3002 durability of the anti-hyperglycaemic effect could be demonstrated for CANA over the 52 week period. Clinical relevant anti-hyperglycaemic effects were corroborated in the extension mITT analysis set (all patients in the mITT analysis set who did not receive rescue therapy) in each of the three studies (DIA 3005, DIA 3002, DIA3006):

In study DIA 3005 in the extension mITT analysis set (166 patients on CANA 100 mg, 166 patients on CANA 300 mg) the LS mean change from baseline in HbA1c at Week 52 was -1.11%

for the canagliflozin 300 mg group and -0.81% for the canagliflozin 100 mg group. In both treatment groups, decreases from baseline were most rapid through Week 12, and were more gradual through Week 34, with small changes subsequently observed.

Figure 3: HbA_{1c}: LS Mean Change From Baseline Over Time – LOCF
(Study 28431754-DIA3005: Extension mITT Analysis Set)



In study DIA 3002 in the extension mITT analysis set (125 patients on CANA 100 mg, 125 patients on CANA 300 mg) the LS mean change from baseline in HbA1c at Week 52 was -0.87% for the canagliflozin 300 mg group and -0.63% for the canagliflozin 100 mg group.

In study DIA 3006 in the extension mITT analysis set (311 patients on CANA 100 mg, 320 patients on CANA 300 mg, 295 patients on sitagliptin) the LS mean change from baseline in HbA1c at Week 52 was -0.93% for the canagliflozin 300 mg group, -0.77% for the canagliflozin 100 mg group and -0.75% for sitagliptin.

Effects on blood pressure, body weight and fasting plasma lipids were maintained through week 52 in studies DIA3005, DIA 3006 and DIA 3002.

In study DIA3004 (subpopulation of renally impaired subjects, mean baseline GFR 39.4 ml/ min/ 1.73m2, range 24.0-61.0 ml/ min/ 1.73 m2) the antihyperglycaemic efficacy at week 26 was of borderline clinical relevance (-0.3% and -0.4% placebo corrected change from baseline for CANA 100 mg and CANA 300 mg, respectively). The 52 week data showed no further decline in antihyperglycaemic efficacy (-0.27% and -0.41% placebo corrected change from baseline for CANA 100 mg and CANA 300 mg). The clinical relevant effects on SBP and DBP observed at week 26 were maintained through week 52. Body weight reduction was about 1-2% for both doses at week 26 and did not change through week 52.

The antihyperglycaemic efficacy demonstrated for both CANA doses in studies DIA3002, DIA3005 and DIA 3006 during the core study periods (26 week) is maintained through week 52. Likewise, effects in blood pressure, body weight and fasting plasma lipids were maintained.

Antihyperglycaemic efficacy in study DIA3004 was of borderline clinical relevance at week 26. There was no further decline through week 52.

Overall, durability of action of both CANA doses is not a concern.

Clinical studies in special populations

Placebo-controlled Study in Moderate Renal Impairment– DIA3004

DIA3004 was designed to support the add-on use of canagliflozin in patients with T2DM with inadequate glycaemic control (HbA1c of ≥7.0% to ≤10.5%) and having moderate renal impairment with an eGFR of ≥30 and <50 mL/min/1.73 m2 while either not receiving background therapy with an AHA or on a stable AHA regimen that could have included oral agents and/or insulin therapy. A high proportion of 269 randomized and dosed subjects (87%) completed 26 weeks of treatment, and the proportion that were discontinued prior to the Week 26 visit was lower in the canagliflozin 300 mg group (8%) than in the placebo (14%) or canagliflozin 100 mg (17%) groups. Thus, discontinuation rates in the study including patients with moderate renal impairment were low, indication that canagliflozin was well tolerated.

Most subjects (98%) were taking at least 1 AHA agent, and nearly 60% were on 2 or more classes of AHA agents; 74% of subjects were treated with insulin alone or in combination with another AHA.

The LS mean change from baseline in HbA1c at Week 26 for canagliflozin 300 mg relative to placebo was –0.40% ($p<0.001$), and -0.30% for canagliflozin 100 mg relative to placebo ($p=0.012$). Thus the change in HbA1c from baseline was statistically significant but the clinical relevance of the effect is debatable.

The 300 mg dose of canagliflozin did not achieve statistical significance with respect to the secondary endpoint related to FPG ($p=0.070$), although numerical improvement was observed with canagliflozin relative to placebo. Treatment with both doses of canagliflozin provided meaningful, albeit moderate, increases in the proportion of subjects achieving an HbA1c <7.0% at Week 26 relative to placebo (10 % and 15 % for the 100mg and 300 mg dose respectively, placebo adjusted). In addition to improvements in glucose control, weight loss and decreases in SBP were seen with canagliflozin 300 mg and 100 mg. Small increases in HDL-C were seen in both canagliflozin groups, but there were no notable changes from baseline in TG with canagliflozin relative to placebo in this population with moderate renal improvement.

The lower efficacy of canagliflozin in this population is also reflected in a lower proportion achieving target as well as by the failure of achieving statistically significant outcomes with regards to the secondary endpoints. The need for rescue medication was lower in the canagliflozin groups compared to placebo.

Older Adults – Placebo-controlled Study – DIA3010

DIA3010 was designed to assess the efficacy and safety of canagliflozin in older subjects not adequately controlled on current glucose lowering therapy (HbA1c of ≥7.0 to ≤10.0%), and to

assess body composition and bone safety using DXA in a subset of subjects. The mITT analysis set was comprised of 714 subjects (median age of 63 years), while a total of 211 subjects participated in the body composition substudy. This study included patients above the age of 55, with almost 40 % of patients being older than 65 years. The mean age was similar to that of the two CANVAS substudies and lower than observed in study DIA3004 (renal impairment). The study addition to the knowledge of the use of canagliflozin in elderly patients is therefore limited, especially the age group > 75 years of age.

A high proportion of subjects (89%) completed 26 weeks of double-blind treatment, and the proportion of subjects who were discontinued prior to Week 26 was higher in the placebo group versus the pooled canagliflozin group (17% vs. 9%). Discontinuations rates were lower in the canagliflozin groups, indicating that canagliflozin was well tolerated.

Almost all subjects (98%) were taking at least 1 AHA agent (49% on a SU and 33% on insulin), and 76% of subjects were on 2 or more classes of AHA agents.

The change from baseline in HbA1c at Week 26 for canagliflozin 300 mg relative to placebo was -0.70% ($p<0.001$), and -0.57% for canagliflozin 100 mg relative to placebo ($p<0.001$). Both doses of canagliflozin achieved statistical significance with respect to the major secondary endpoints related to FPG, proportion with HbA1c <7.0% (20 % and 30 % for the 100 mg and 300 mg dose respectively, placebo adjusted), body weight, SBP, HDL-C, and body FM. Statistical significance was not achieved for percent change from baseline in fasting TG for either dose of canagliflozin. The change in HbA1c from baseline was in the same range as observed in the overall population. The need for rescue medication was lower in the canagliflozin groups compared to placebo.

Supportive study

An independent clinical development programme was conducted by Misubishi Tanabe Pharma Cooperation (MTPC) in Japan. One dose-finding study from this development program is submitted with this application (Study TA-7284-04). This was a placebo-controlled study in adults with T2DM investigating a dose range of 50 to 300 mg CANA as monotherapy. The LS mean differences, compared to the placebo group, in the change from baseline to Week 12 in HbA1c were -0.72%, -0.90%, -0.90%, and -0.99% the CANA 50 mg, 100 mg, 200 mg, and 300 mg groups, respectively. No phase III study from this programme has been submitted.

The study results showed a dose response relationship, and as such supported the findings of study DIA2001. However, since it was stated that “methodologies used for collecting and analyzing key efficacy and safety endpoints in this study were different from those for the JRD-sponsored studies”, this study is considered supportive only.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is supported by a comprehensive study program consisting of 9 phase III studies. The study program is in line with the adopted EMA Guideline “Note for Guidance on the Clinical Investigation of Medicinal Products for the treatment of diabetes mellitus (CPMP/EWP/1080/00

Rev.1)" and is generally in line with the CHMP Scientific Advice given. The phase III program for CANA evaluated CANA efficacy in a broad population of 10,285 T2DM subjects, including subjects who had: (1) inadequate glycaemic control while on diet and exercise (DIA3005[monotherapy]), (2) inadequate glycaemic control on a single oral AHA or dual oral AHA therapy (DIA3006 [metformin], DIA3009 [metformin], DIA3008 [SU Substudy]), or a dual combination of AHAs (DIA3002 [metformin/SU], DIA3015 [metformin/SU], and DIA3012 [metformin/pioglitazone]), and (3) inadequate glycaemic control on treatment with insulin, alone or in combination with oral AHA therapy (in particular, in combination with metformin) (DIA3008 Insulin substudy). Other phase III studies examined add-on use of CANA in subjects with inadequate glycaemic control while remaining on their specific AHA background therapy (whether diet and exercise, or oral, or parenteral AHAs, alone or in combinations), including study DIA3004 in subjects with moderate renal impairment (with a GFR ≥30 to <50 mL/min/1.73m^2) and DIA3010 in older adults (age >55 and <80 years). The DIA3008 substudies examined add-on use of CANA in subjects on insulin or on SU monotherapy in subjects with a history of or a high risk for CV disease.

The placebo controlled phase III studies DIA3002, DIA3004, DIA3005, DIA3006, DIA3010 and DIA3012 had a core double blind period for the primary endpoint of 26 weeks. For the DIA3008 Insulin and SU substudies, the primary efficacy evaluation was at 18 weeks. In the two active comparator non-inferiority studies (DIA3009 glimepiride, DIA3015 sitagliptin) the primary efficacy endpoint was at 52 weeks. Each of the phase III studies except DIA3015, the DIA3005 high glycaemic substudy, and the DIA3008 substudies, had long-term extension treatment periods of up to 78 additional weeks. With this submission data were provided for the core double blind periods.

HbA1c was chosen as the primary endpoint in all phase II/III studies, which is in line with "Note for Guidance on the Clinical Investigation of Medicinal Products for the treatment of diabetes mellitus (CPMP/EWP/1080/00)". The range of doses for the phase III program (100 mg and 300 mg CANA) was chosen based on the data from the phase I studies and the phase IIb study and is justified.

The primary and secondary endpoints chosen for the phase III program were appropriate. Further to the evaluation of CANA on glycaemic endpoints, the effect of CANA on body weight, blood pressure and lipid parameters were investigated. Pharmacodynamic endpoints assessed in selected phase III studies to characterise the mechanism of action included RT_G and beta-cell function/ insulin secretion PD endpoints.

The patients included in the studies were representative for the target population. Patients with long-standing disease and diabetic complications such as (mild to moderate) renal impairment or CV disease were adequately represented in the study population. Inadequate glycaemic control was defined in most of the studies as an HbA1c level of ≥7.0 and ≤10.5%, which is appropriate.

Of the 4994 subjects exposed to CANA across the phase III studies, 1390 were at least 65 years of age, including 1149 who were 65 to<75 years of age, 234 who were 75 to <85 years, and 7 subjects who were ≥85 years. Hence, more than 100 geriatric patients were included in the phase III program and, as such, the requirement as outlined in EMA/ CHMP/ ICH/604661/2009 (ICH topic E7 Studies in Support of special populations: Geriatrics Q and A) is met.

All phase 3 studies were multicenter studies with European sites included and the majority of patients were white.

With this MAA no studies including patients below the age of 18 were submitted. Studies to be conducted in this population targeting at the indication *treatment of T2DM* in pediatric patients above 10 years of age were granted deferral.

Although drug naïve (in addition to pretreated) subjects were included in the monotherapy study DIA3005 to support the restricted first line indication applied for, this is acceptable since the effect of CANA is not expected to be different in patients intolerant compared to those tolerant to metformin. The most frequent contraindication to metformin is relevant renal insufficiency (usually defined as creatinine clearance < 60 mL/min/1.73 m^2). Since patients may remain on treatment with CANA down to an eGFR of 45 ml/min/1.73 m^2 (see section on benefit/risk), the inclusion of "contraindications to metformin" in the indication appears justified.

Patients in the add-on studies were on adequate background therapy. Treatment failure was an inclusion criterion and adequately defined. The non-inferiority, active comparator studies were adequately designed, with almost all patients being treated with the target dose of both glimepiride and sitagliptin. The non-inferiority margin was selected with reference to values suggested by FDA guidance and to CHMP SA (EMEA/H/SA/1252/2008/III).

The statistical methods used in the superiority and non-inferiority studies are well described and considered appropriate. ANCOVA with baseline covariate adjustment to analyse change from baseline for the primary and several secondary efficacy endpoints as used across the phase III studies is appropriate. Stratification factors were correctly implemented in the models. Primary analyses in all studies were supported by a number of sensitivity analyses. Control of family-wise type I error rate was adequately implemented in all phase III studies. Of note, test for superiority after establishing non-inferiority in the non-inferiority studies was not part of the hierarchical test sequence. A considerable impact of missing data on results is very unlikely and additional MMRM sensitivity analyses support this conclusion.
Overall, 90% of subjects from the mITT analysis set for the pooled total CANA group completed the double-blind treatment period through the primary efficacy assessment, and this percentage was higher than that of the pooled placebo group (87%). The low number of discontinuations is reassuring.

Efficacy data and additional analyses
In the phase III studies, efficacy of CANA appeared generally dose-dependent. Results demonstrated the efficacy of CANA in reducing HbA1c on a range of different background AHA therapies. A clinically meaningful improvement in glycaemic control was seen when CANA was given as monotherapy and when given in dual combinations (add-on to metformin or to SUs), in triple oral AHA combinations (add-on to metformin plus a SU or metformin plus pioglitazone), in combinations with insulin (alone or in combination with other oral agents, especially metformin), or as an add-on to individual pre-existing diabetes therapy (any approved oral or parenteral therapy).

Across the placebo-controlled phase III studies examining add-on combination uses, the efficacy of CANA in lowering HbA1c, relative to placebo, was generally consistent and ranged from -0.70% to -0.92% with the 300 mg dose and from -0.57% to -0.74% with the 100 mg dose. Greater efficacy was observed when CANA was evaluated as monotherapy use, with HbA_{1c} reductions of -1.16% and -0.91% (placebo-adjusted) for CANA 300 mg and 100 mg, respectively.

In a 52-week active comparator-controlled study, non-inferiority of CANA 300 mg and 100 mg to glimepiride (maximum dose, 6 to 8 mg/day) was demonstrated. Clinically relevant glycaemic improvements were observed with both CANA and glimepiride at week 52: the adjusted mean changes from baseline in HbA1c to Week 52 were -0.93% and -0.82% for the CANA 300 mg and 100 mg groups, respectively, and -0.81% for the glimepiride group. A step-down to an assessment of superiority was pre-specified; the upper limit of 95% CI between CANA 300 mg and glimepiride was <0%, demonstrating superiority for CANA 300mg to glimepiride. The HbA_{1c}-lowering response to CANA 100 mg was not superior to that of glimepiride in this study.

CANA 300 mg was also shown to have non-inferior efficacy compared to sitagliptin 100 mg. Clinically relevant glycaemic improvements were observed with both agents: the change from baseline in HbA1c to week 52 was -1.03% for the CANA 300 mg group and -0.66% for the sitagliptin group. A step-down to an assessment of superiority was pre-specified; the upper limit of 95% CI between CANA 300 mg and sitagliptin was <0%, demonstrating superiority of CANA 300 mg to sitagliptin 100 mg. The 100 mg dose was not tested in this study.

The favourable results on HbA1c were generally supported by the results on secondary glycaemic endpoints (FPG, postprandial glucose excursion for the two phase III studies that included a MMTT) and discontinuation rates due to rescue therapy.

Considering the mechanism of action of CANA and the CANA-induced UGE being proportional to renal function, unsurprisingly, the efficacy of CANA was dependent upon baseline GFR. Therefore, the efficacy in renally impaired patients was of particular interest. Patients with mild renal impairment were generally included in the phase III program and, compared to patients with normal renal function, showed a slightly reduced but clearly clinically relevant effect with CANA. Patients with moderate renal impairment were investigated within a separate study (DIA 3004). This study demonstrated HbA1c reductions of borderline to insufficient clinical relevance in patients with GFR values of ≥30 to <50 mL/min/1.73m^2: the change from baseline in HbA1c at week 26 relative to placebo was -0.4% and -0.3% for CANA 300 mg and 100 mg, respectively. The Applicant also performed an analysis in the pooled patient population with moderate renal impairment (N=1085) from all placebo-controlled studies. In the pooled analysis in moderately impaired renal patients overall HbA1c reductions compared to placebo were- 0.47% and -0.38% for CANA 300 mg and 100 mg, respectively. The small differences in results on HbA1c reduction between study DIA3004 and the pooled datasets may be explained by differences in baseline GFR, which were 39.4 mL/min/1.73m^2 on average in study DIA3004 and 50.6 mL/min/1.73m^2 in the pooled population of placebo controlled studies (since in most of the phase III studies a GFR <55 mL/min/1.73m^2 was an exclusion criterion).

The Applicant provided further subgroup analyses in patients with moderate renal impairment using eGFR cut-offs of 45 and 50 mL/min/1.73m^2. In the subgroup of patients with GFR >45 to <60 mL/min/1.73m^2, borderline clinically relevant reductions in HbA1c of -0.52% and – 0.47% with the 300 mg and 100 mg dose, respectively, were observed, while in the subgroup with eGFR <45 mL/min/1.73m^2 insufficient HbA1c reductions of only -0.39% and -0.23%, respectively, were observed. The higher dose appears slightly more effective, however, is also associated with an increased rate of adverse events (e.g. related to water and electrolyte imbalance), especially in patients with an eGFR < 45 ml/min/1.73m^2 (see safety part). Therefore, the benefit/ risk profile of CANA is considered negative for patients with an eGFR ≤45ml/min/1.73m^2.

As outlined above elderly patients were adequately represented in the phase III program. Of note, in study DIA3010, aiming at investigating the efficacy and safety of CANA in the elderly, the age distribution does not differ markedly from that in the other phase III studies with the majority of patients being below 65 years of age (55-65 years), less than 3% of patients were between 65 and 75 years of age, below 1% between 75 and 85 years and no patient was above 85 years. In this study HbA1c response was more pronounced in subjects below 65 years of age compared to subjects above 65 years (which could be explained by a higher baseline GFR in the younger group). However, the glucose-lowering effect was clinically relevant in the elderly group. This was confirmed by the results of the pooled placebo-controlled population for subgroup analyses: across the subgroups, defined by a cut-off of either 65 and 75 years clinically relevant reductions in HbA1c could be observed for both doses of CANA (in the oldest subgroup, comprising 175 subjects, adjusted mean changes of -0.65% for CANA 100 mg and -0.55% for CANA 300 mg). Hence, efficacy seems to be maintained in the elderly. It is also known from another SGLT2-inhibitor that age per se does not influence efficacy.

Overall, the effect of CANA appeared to be maintained over time. Although in some of the placebo-controlled phase III studies, the initial effect on HbA1c lowering appeared to slightly wane through the primary assessment timepoint, in other studies the effect was maintained or even appeared not to have been fully achieved at the time of the primary evaluation. Furthermore, examination of the slope of the HbA1c curve over time in the two non-inferiority studies from Week 26 to Week 52, referred to as the coefficient of durability, showed a markedly slower rate of rise for CANA relative to either SU or sitagliptin. Durability of effect seems not to be of concern based on the available data. Results of the extension periods of placebo controlled studies may further help to evaluate the sustainability of the glucose-lowering effect of CANA.

Results of subgroup analyses performed in the pooled population of the placebo-controlled phase III studies found no important differences when comparing the effect of CANA in lowering HbA_{1c} based on age, sex, race, and ethnicity, baseline BMI, or geographic region. As expected, greater reductions (significant interaction at an $\alpha=0.10$ level) in HbA_{1c} relative to placebo were observed with CANA among subjects with higher baseline HbA_{1c} and higher GFR values compared to subjects with lower baseline values. A baseline HbA1c-dependent glucose-lowering effect is also known from other anti-hyperglycaemic agents.

Treatment with CANA resulted in a dose-dependent reduction in total body weight relative to placebo. The effect was generally consistent across placebo-controlled phase III studies. In the pooled dataset of placebo controlled studies the mean percent change from baseline in body weight at the primary assessment timepoint, relative to placebo, was -2.7% (95% CI: [-2.9;-2.4]) for the 300 mg dose and -2.0% (95% CI: [-2.3;-1.8]) for the 100 mg dose. Correspondingly, placebo-subtracted LS mean absolute reductions in body weight for the 300 mg and 100 mg groups for the pooled population of placebo-controlled studies were -2.43 kg (95% CI: [-2.652;-2.199]) and -1.84 kg (95% CI: [-2.064;-1.611]), respectively. Statistically significant reductions from baseline in percent change in body weight, relative to glimepiride (DIA3009, mean differences 5.2 to 5.7 kg), for both doses of CANA, and sitagliptin (DIA3015), for the CANA 300 mg dose, were observed ($p<0.001$ for all comparisons). Results of specialized body composition investigations using dual energy x-ray absorptiometry (DXA) in 2 of the phase III studies (DIA3009, DIA3010) indicated that the body weight reduction with CANA was attributable to a greater decrease in body fat mass relative to lean body mass (with

approximately 2/3 as fat mass loss). Hence, it was demonstrated that weight loss was predominantly due to loss of calories rather than dehydration. The effect on body weight and composition is likely to favourably influence CV risk in the frequently obese patients with T2DM.

Across all phase III studies, clinically relevant lowering of SBP and DBP was observed, which is a desirable additional effect of CANA in the frequently hypertensive patients with T2DM. Since a BP-lowering effect is not usually expected for a glucose-lowering drug, appropriate labelling is warranted to create awareness among physicians and patients and to minimize risks in vulnerable patients (see safety section).

Overall, by improving glycaemic control, reducing weight/fat mass and BP CANA treatment may favourably influence CV risk in patients with T2DM. However, longer term data (extension periods of ongoing studies, CANVAS study) will further help to elucidate the impact of CANA on CV risk (also see safety section).

For all placebo controlled phase III studies, results of the core double blind period and subsequent extension periods were submitted. These data showed good durability of the antihyperglycaemic effect up to 52 weeks.

2.5.4. Conclusions on the clinical efficacy

The clinical program supports the efficacy of CANA as monotherapy in patients intolerant to metformin, and when given in dual combinations (add-on to metformin or to SUs), in triple oral AHA combinations (add-on to metformin plus a SU or metformin plus pioglitazone), in combinations with insulin (alone or in combination with other oral agents, especially metformin), or as an add-on to existing diabetes therapy (any approved oral or parenteral therapy). The effect size with the selected doses of 100 mg and 300 mg is considered clinically relevant and was consistent in all studies. In addition to the glycaemic improvement, weight reduction and a clinically relevant reduction in blood pressure was observed across the study program. These results support the benefit of CANA.

Both a restricted monotherapy indication and the add-on indications were considered approvable from an efficacy point of view. The efficacy of CANA in patients with eGFR 45-60 mL/min/1.73m^2 is clearly reduced compared to patients with normal renal function but still clinically relevant. However, efficacy is clearly insufficient in patients with eGFR < 45 mL/min/1.73m^2. Due to the very small effect size and safety concerns (see safety section), the benefit-ratio ratio of CANA in patients with a GFR <45 mL/min/1.73m^2, is considered negative. Therefore the recommendation to discontinue the treatment when eGFR is persistently below 45 mL/min/1.73m^2 has been added to the product information.

In the clinical program, both the 100 mg and 300 mg dose were shown to be efficient. The Applicant proposes that the higher dose should be used in patients who need tighter glycaemic control. The lower dose is proposed as the general starting dose with the option of up-titration when a higher dose is needed and tolerated; as a precautionary measure, 300 mg should not be used in patients with eGFR below 60 mL/min/1.73 m^2.

Durability of antihyperglycaemic effect has been demonstrated following submission of the results of the extension periods for studies DIA 3002, 3004, 3005 and 3006.

2.6. Clinical safety

The general safety assessment is mainly based on the phase III trials. In all phase III trials two different doses of CANA were tested, 100 mg and 300 mg per day. Dose selection should be based on glycaemic control. The 300 mg dose can be used by all patients if tolerated and needed, no special restrictions are made; it is recommended to use 100 mg per day as starting dose. Hence, the observations made with the 300 mg dose will be most relevant for safety assessment; the 100 mg dose can reveal dose-dependency of an effect. Special safety aspects were investigated mechanistically in smaller trails. The phase III studies were performed in patients with different background therapies, were either placebo-controlled or using an active comparator (glimepride or sitagliptin). A large trial was performed in patients with increased CV risk (DIA3008). Smaller phase III (sub-)trials investigated the effects of CANA in patients with moderate renal impairment (DIA3004, eGFR between 30 and 60 mL/min/1.73m^2 at baseline) and in patients with poor glycaemic control (part of DIA3005). The larger phase II trials were for dose finding (DIA2001) and for investigating CANA in patients with obesity (no diabetics, OBE2001); in these studies also parameters relevant for bone safety were measured.

For all of the phase III studies, safety evaluations included the collection of adverse events, safety laboratory tests (including hematology, chemistry, and urinalysis), 12-lead electrocardiograms (ECGs), vital signs (blood pressure and pulse rate), body weight, physical examinations, self-monitored blood glucose (SMBG), and collection of potential hypoglycaemic episodes (e.g., from the subject diary provided to subjects). In study DIA3010, bone mineral density was assessed at the lumbar spine, hip, and forearm using dual-energy X-ray absorptiometry (DXA) technology. Serum collagen type 1 carboxy-telopeptide (CTx) and propeptide amino terminal of type I procollagen (P1NP) were measured in this study. Quantitative computed tomography (CT) of the spine and hip were used to assess trabecular and cortical bone density changes, geometric properties and material properties (using finite element analysis [FEA]) in a subset of subjects (approximately 50 per treatment group).

Several safety monitoring committees were commissioned for the phase III program:

- An independent Endpoint Adjudication Committee (EAC) reviewed blinded data for selected adverse events, including major adverse cardiovascular events plus events of unstable angina (MACE-plus), hospitalized congestive heart failure, venous thromboembolism/pulmonary embolism, and all deaths.
- Independent assessment committees reviewed blinded data for assessment of fracture (Fracture Adjudication Committee [FAC]), hepatic (Hepatic Events Assessment Committee [HEAC]), and renal events (Clinical Events Committee [CEC]).
- An Independent Data Monitoring Committee (IDMC) reviewed unblinded serious adverse events and CV events.

In total, four different safety data sets (DS1 - DS4) were created by compiling different patient populations, see table below. Phase II trials were not included in these data pools because the largest phase II trials were dose finding studies so that most patients received different CANA doses than in the phase III trials.

Table 11: Data sets (DS) created by pooling different patient populations

Dataset Name	Dataset Description	Studies Pooled	Objectives
Placebo-Controlled Studies Dataset (ISS Dataset 1 [**DS1**])	Includes the 26-week placebo-controlled Phase III studies	DIA3002, DIA3005,[a] DIA3006,[b] DIA3012	Evaluate the safety and tolerability of canagliflozin based upon a large subject sample by pooling placebo-controlled Phase III studies of generally similar design
Moderate Renal Impairment Dataset[c] (ISS Dataset 2 [**DS2**])	Subjects with baseline eGFR ≥30 to <60 mL/min/1.73m2	DIA3004 and subgroups from DIA3005, DIA3008, DIA3010	Evaluate safety and tolerability within a special population of subjects with renal insufficiency with eGFR ≥30 to <60 mL/min/1.73m2
Broad Dataset (ISS Dataset 3 [**DS3**])	All Active- and Placebo-controlled studies	DIA3002, DIA3004, DIA3005,[a] DIA3006, DIA3008, DIA3009, DIA3010, DIA3012	Large pooled dataset from controlled clinical studies (active and placebo-controlled) to identify less common safety signals, and to support safety assessments in the Placebo-Controlled Studies Dataset (DS1).
Longer-term Exposure Broad Dataset (ISS Dataset 4 [**DS4**])	All Active- and Placebo-controlled studies	DIA3002, DIA3004, DIA3005,[a] DIA3006, DIA3008, DIA3009 DIA3010, DIA3012	Longer-term exposure dataset to provide information on safety with longer exposure, and to support safety assessments in the Placebo-Controlled Studies Dataset (DS1); to evaluate selected adverse events occurring with low incidence (eg, skin photosensitivity, specific malignancies) and events undergoing adjudication (including CV events).

a DIA3005: Excluding the high glycaemic substudy
b DIA3006: Excluding sitagliptin treatment group

Patient exposure

The following table summarises the patient exposure in the Phase III programme, stratified for treatment duration.

Table 12: Overall Exposure in Canagliflozin Phase III Program (Canagliflozin Phase III Program: Safety Analysis Set)

	Non-CANA	CANA 100 mg	Cana300 mg
Total Number of Subjects in Phase III Program	3640	3139	3506
6-month Exposure	3162	2844	3092
12-month Exposure	2392	2260	2463
18-month Exposure	569	604	596
24-month Exposure	64	73	71

Note: The cut-off of Study DIA3015 is end of the study and the cut-off of the rest of the Phase III 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.
Thus, up to 18 month the number of exposed patients is considered high enough to allow meaningful conclusions.

Adverse events

In DS4, the following (Table 41 below) incidences of AEs were observed in the different treatment group. In DS1 (placebo-controled pool) the absolute numbers of AE incidence were lower in all groups (obviously due to different baseline characteristics), but the overall picture was the same.

Table 13: Overall Summary of Adverse Events - Regardless of Use of Rescue Medication (ISS Phase III Longer-term Exposure Broad Dataset: Safety Analysis Set)

	All Non-CANA	**CANA 100 mg**	**CANA 300 mg**
	(N=3262)	(N=3092)	(N=3085)
	n (%)	n (%)	n (%)
Any adverse events	2355(72.2)	2274(73.5)	2274(73.7)
Adverse events leading to discontinuation	142(4.4)	147(4.8)	201(6.5)
Adverse events related to study drug	661(20.3)	850(27.5)	991(32.1)
Adverse events related to study drug and leading to discontinuation	59(1.8)	94(3.0)	131(4.2)
Serious adverse events	377(11.6)	329(10.6)	330(10.7)
Serious adverse events leading to discontinuation	59(1.8)	49(1.6)	44(1.4)
Serious adverse events related to study drug	25(0.8)	24(0.8)	31(1.0)
Serious adverse events related to study drug and leading to discontinuation	7(0.2)	12(0.4)	11(0.4)
Deaths	• 26(0.8)	• 18(0.6)	• 17(0.6)

The overall rate of AEs is fairly balanced between the treatment groups. This is also true for serious AEs and AEs leading to discontinuation. Merely the number of AEs related to study drug (according to investigator) was dose-dependently increased in the CANA groups. But reassuringly, related serious AEs were again fairly balanced.

The AEs considered related were often genital or urinary tract infections, a known side effect of SGLT2 inhibitors (see also section on discontinuation due to AEs below).

Although the overall incidence in AEs was balanced between the treatment groups, some individual AEs or AEs in certain organ systems had markedly different incidences in DS4, see table below. Most salient and important findings are marked with incidences in **bold**.

Table 14: AEs by organ system or syndrome - DS4

	Non-CANA	CANA 100mg	CANA 300mg
Body System Or Organ Class	(N=3262)	(N=3092)	(N=3085)
Dictionary-Derived Term	n(%)	n(%)	n(%)
Blood and lymphatic system disorders	79(2.4)	65(2.1)	62(2.0)
Anaemia	51(1.6)	34(1.1)	28(0.9)
Cardiac disorders	189(5.8)	156(5.0)	162(5.3)
Cardiac failure	12(0.4)	2(0.1)	7(0.2)
Coronary artery disease	23(0.7)	10(0.3)	12(0.4)
Myocardial ischaemia	14(0.4)	6(0.2)	2(0.1)
Palpitations	10(0.3)	15(0.5)	23(0.7)
General disorders and administration site conditions	355(10.9)	346(11.2)	387(12.5)
Asthenia	20(0.6)	23(0.7)	37(1.2)

Oedema peripheral	98(3.0)	50(1.6)	45(1.5)
Thirst	**2(0.1)**	**42(1.4)**	**68(2.2)**
Hepatobiliary disorders	54(1.7)	48(1.6)	50(1.6)
Cholelithiasis	23(0.7)	8(0.3)	11(0.4)
Infections and infestations	1229(37.7)	1234(39.9)	1216(39.4)
Acute sinusitis	10(0.3)	6(0.2)	2(0.1)
Balanitis candida	5(0.2)	9(0.3)	16(0.5)
Genital infection fungal	**4(0.1)**	**20(0.6)**	**27(0.9)**
Pyelonephritis chronic	0	4(0.1)	4(0.1)
Urinary tract infection	164(5.0)	191(6.2)	185(6.0)
Vaginal infection	9(0.3)	38(1.2)	32(1.0)
Vulvitis	0	11(0.4)	8(0.3)
Vulvovaginal candidiasis	5(0.2)	43(1.4)	40(1.3)
Vulvovaginal mycotic infection	**21(0.6)**	**70(2.3)**	**72(2.3)**
Vulvovaginitis	2(0.1)	25(0.8)	26(0.8)
Investigations	278(8.5)	247(8.0)	266(8.6)
Blood creatine phosphokinase increased	59(1.8)	23(0.7)	26(0.8)
Blood creatinine increased	13(0.4)	37(1.2)	33(1.1)
Blood glucose increased	13(0.4)	7(0.2)	3(0.1)
Blood potassium increased	**2(0.1)**	**12(0.4)**	**13(0.4)**
Blood pressure increased	***32(1.0)***	***10(0.3)***	***11(0.4)***
Blood urea increased	10(0.3)	18(0.6)	21(0.7)
Blood uric acid increased	15(0.5)	4(0.1)	5(0.2)
Liver function test abnormal	12(0.4)	3(0.1)	6(0.2)
Urine output increased	**1(<0.1)**	**19(0.6)**	**15(0.5)**
Weight decreased	8(0.2)	23(0.7)	33(1.1)
Metabolism and nutrition disorders	496(15.2)	402(13.0)	406(13.2)
Gout	25(0.8)	10(0.3)	16(0.5)
Hypercalcaemia	**4(0.1)**	**3(0.1)**	**14(0.5)**
Hyperglycaemia	***103(3.2)***	***44(1.4)***	***38(1.2)***
Polydipsia	1(<0.1)	11(0.4)	6(0.2)
Musculoskeletal and connective tissue disorders	647(19.8)	613(19.8)	611(19.8)
Arthralgia	152(4.7)	130(4.2)	106(3.4)
Foot deformity	0	5(0.2)	2(0.1)
Synovial cyst	7(0.2)	0	5(0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	82(2.5)	78(2.5)	90(2.9)
Colon adenoma	0	3(0.1)	4(0.1)
Thyroid neoplasm	0	5(0.2)	5(0.2)
Nervous system disorders	429(13.2)	408(13.2)	437(14.2)
Carotid artery stenosis	8(0.2)	1(<0.1)	10(0.3)
Polyneuropathy	0	2(0.1)	6(0.2)
Tremor	4(0.1)	15(0.5)	10(0.3)
Renal and urinary disorders	192(5.9)	317(10.3)	332(10.8)
Micturition urgency	6(0.2)	17(0.5)	15(0.5)
Nephrolithiasis	18(0.6)	21(0.7)	6(0.2)
Pollakiuria	31(1.0)	110(3.6)	132(4.3)
Polyuria	**10(0.3)**	**30(1.0)**	**33(1.1)**
Reproductive system and breast disorders	110(3.4)	237(7.7)	291(9.4)
Balanitis	**13(0.4)**	**70(2.3)**	**67(2.2)**
Balanoposthitis	**5(0.2)**	**25(0.8)**	**51(1.7)**
Genital discomfort	0	4(0.1)	6(0.2)
Pruritus genital	10(0.3)	21(0.7)	17(0.6)
Vulvovaginal discomfort	1(<0.1)	4(0.1)	7(0.2)

Vulvovaginal pruritus	**5(0.2)**	**42(1.4)**	**58(1.9)**
Respiratory, thoracic and mediastinal disorders	347(10.6)	293(9.5)	288(9.3)
Cough	120(3.7)	105(3.4)	85(2.8)
Skin and subcutaneous tissue disorders	246(7.5)	287(9.3)	314(10.2)
Erythema	5(0.2)	13(0.4)	12(0.4)
Skin ulcer	16(0.5)	26(0.8)	30(1.0)
Vascular disorders	228(7.0)	181(5.9)	191(6.2)
Haematoma	13(0.4)	3(0.1)	3(0.1)
Hypertension	***125(3.8)***	***64(2.1)***	***48(1.6)***
Hypertensive crisis	***10(0.3)***	***1(<0.1)***	***3(0.1)***
Hypotension	**17(0.5)**	**40(1.3)**	**54(1.8)**
Orthostatic hypotension	**4(0.1)**	**8(0.3)**	**21(0.7)**

Most of the imbalances displayed in the table above reflect the known physiological actions of CANA as an SGLT2 inhibitor or known side effects resulting from them. These comprise e.g. thirst, polyuria, hypotension (due to increased diuresis), weight decrease and all signs of urogenital infection. Also increased serum creatinine can be most likely explained by elevated diuresis (for detailed discussion, see section on changes on renal function below). Reduced incidence of increased blood pressure and hyperglvcaemia in the CANA groups can also be explained by SGLT2 inhibition.

There is a small increase in AEs related to skin and subcutaneous tissue, most pronounced for erythema and skin ulcer. The reason for this finding (if true and not due to chance) is not obvious. Phototoxicity of CANA was observed in non-clinical studies but clear phototoxicity was not observed in dedicated studies of the Applicant (see below).

All other imbalances are not considered meaningful, either because of being too small or because the absolute number of patients affected is very low.

AEs of special interest:

Hypoglycaemia was defined as an AE of special interest by the Applicant. In this analysis, only documented hypoglycaemias were included: Either by measured fingerstick glucose of ≤70 mg/dL (3.9 mmol/L) or a severe episode requiring assistance or leading to consciousness. The observed incidences in patients **without** hypoglycaemic background therapy are displayed in the table below.

Table 15: Documented Hypoglycemia - Prior to Use of Rescue Medication (ISS Phase III Placebo-Controlled Studies Dataset Excluding DIA3002: Safety Analysis Set)

	Placebo	CANA 100mg	CANA 300mg
	(N=490)	(N=676)	(N=678)
	n (%)	n (%)	n (%)
Incidence rate per subject-year exposure	0.05	0.08	0.09
Subjects with any documented hypoglycemia	11(2.2)	26(3.8)	29(4.3)
Biochemically documented hypoglycemia	11(2.2)	26(3.8)	28(4.1)
Severe hypoglycemia	0	1(0.1)	1(0.1)

There is a small and dose-dependent increase in hypoglycaemic events in the CANA groups as compared to placebo. Reassuringly, severe hypoglycaemias were rare.

In the **presence** of hypooglycaemic background therapy (i.e. insulin or SU) the incidence was increased by CANA. The table below provides the actual figures.

Table 16: Treatment-Emergent Documented Hypoglycemia (Biochemically Documented and/or Severe) - Prior to Rescue Medication

	Placebo	**CANA 100 mg**	**CANA 300 mg**	**Comparator sitagliptin**
DIA3002 (background: **met+SU**)	(N=156)	(N=157)	(N=156)	NA
Subjects with any documented hypoglycemia	24(15.4)	43(27.4)	47(30.1)	NA
Biochemically documented hypoglycemia	24(15.4)	42(26.8)	47(30.1)	NA
Severe hypoglycemia	1(0.6)	1(0.6)	0	NA
DIA3008 **Insulin** Substudy	(N=565)	(N=566)	(N=587)	NA
Subjects with any documented hypoglycemia	208(36.8)	279(49.3)	285(48.6)	NA
Biochemically documented hypoglycemiaa	208(36.8)	279(49.3)	283(48.2)	NA
Severe hypoglycemia	14(2.5)	10(1.8)	16(2.7)	NA
DIA3008 **Sulphonylurea** Substudy	(N=69)	(N=74)	(N=72)	NA
Subjects with any documented hypoglycemia	4(5.8)	3(4.1)	9(12.5)	NA
Biochemically documented hypoglycemia	4(5.8)	3(4.1)	9(12.5)	NA
Severe hypoglycemia	0	0	0	NA
DIA3015 (comparator sitagliptin, background **met+SU**)	NA	NA	(N=377)	(N=378)
Subjects with any documented hypoglycemia	NA	NA	163(43.2)	154(40.7)
Biochemically documented hypoglycemia	NA	NA	162(43.0)	152(40.2)
Severe hypoglycemia	NA	NA	15(4.0)	13(3.4)

SU and insulin are known to have a rather high hypoglycaemic propensity themselves. CANA further increases the hypoglycaemia incidence of a hypoglycaemic background therapy which includes insulin or an insulin secretagogue. However, hypoglycaemic events were not meaningfully different for CANA + metformin +SU compared to sitagliptin + metformin + SU. Furthermore, no relevant imbalances (CANA vs. plac) were observed with severe hypoglycaemias.

The incidence of **urinary tract infections** (UTI) hardly differed between CANA and placebo. Merely in the low-dose CANA group the incidence is somewhat higher for unknown reasons, see table below. Serious events were rare.

Table 17: Urinary Tract Infection Adverse Events Regardless of Use of Rescue Medication (ISS Phase III Placebo-Controlled Studies Dataset: Safety Analysis Set)

	Placebo	CANA 100mg	CANA 300mg
	(N=646)	(N=833)	(N=834)
Dictionary-Derived Term	n(%)	n(%)	n(%)
Total no. subjects WITH ANY UTIs	26(4.0)	49(5.9)	36(4.3)
Incidence Rate Per Subject-Year Exposure	0.09	0.13	0.09
Cystitis	0	2(0.2)	2(0.2)
Kidney Infection	0	0	1(0.1)
Urinary Tract Infection	26(4.0)	46(5.5)	34(4.1)
Urosepsis	0	1(0.1)	0
Serious adverse events of UTI	0	2(0.2)	1(0.1)

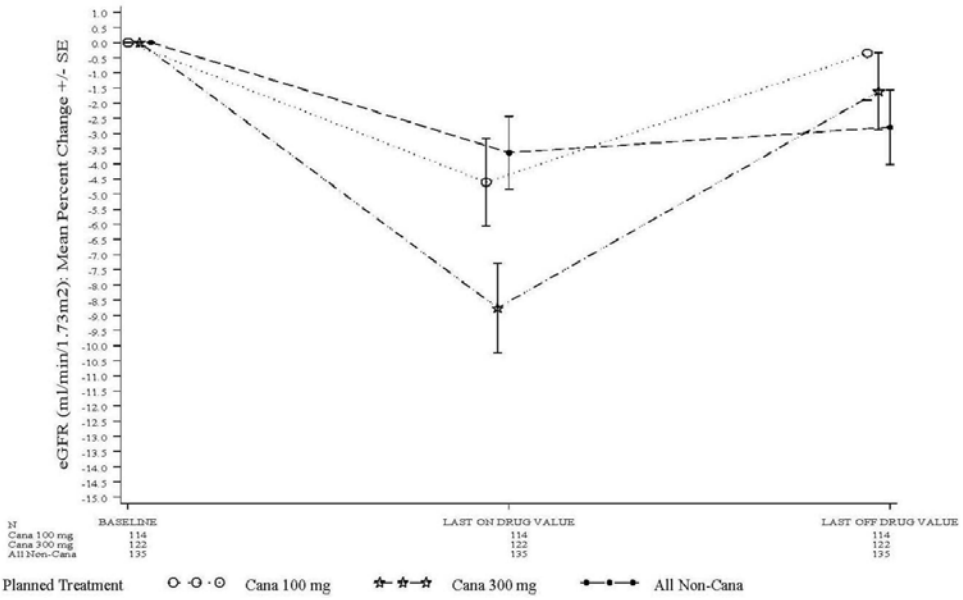
This picture is in line with other SGLT2 inhibitors. SGLT2 inhibitor intake more often leads to genital infection. The incidence of female **genital infection** is shown in the table below:

Table 18: Overall Summary of Vulvovaginitis Adverse Events - Regardless of Use of Rescue Medication (ISS Phase III Placebo-Controlled Studies Dataset: Safety Analysis Set)

	Placebo	Cana100mg	Cana300mg
	(N=312)	(N=425)	(N=430)
Number (%) of Subjects with at least one AE of following Types	n(%)	n(%)	n(%)
Any vulvovaginitisa	10(3.2)	44(10.4)	49(11.4)
Vulvovaginitisa leading to discontinuation	0	4(0.9)	2(0.5)
Vulvovaginitisa related to study drug	8(2.6)	33(7.8)	45(10.5)
Serious adverse events of vulvovaginitis	0	0	0

There was a clearly and highly increased incidence of female genital infection in both CANA groups, slightly dose-dependent, as compared to placebo. Most of these events were considered related to study drug by the investigator, most likely because this is an expected side effect of SGLT2 inhibition. Part of these events also led to discontinuation of study drug. Reassuringly, no serious AEs related to genital infection were observed. Many of the infections were caused by fungi. This may explain the different incidence pattern as compared to UTIs. The picture in males was similar although the absolute numbers of incidence were lower since genital infections in men are generally less frequent than in women.

Regarding markers of **renal function**, there was a consistent decrease in eGFR associated with CANA use, caused by an increase in serum creatinine. This may either reflect decreased renal function and renal damage or may simply be a consequence of the haemoconcentration that is known to occur with SGT2 inhibitors. To exclude renal damage the Applicant collected post-treatment data of eGFR from 371 patients who discontinued treatment, shown in the figure below.



Mean Percent Change (+/-SE) in eGFR For Subjects Who Discontinued and Have a Post Treatment Value (>5 to <60 Days After the Last Study Medication) – Regardless of Use of Rescue Medication (ISS Phase III Broad Dataset: Safety Analysis Set)

Data from more than 100 patients per group of the broad dataset (including high CV risk patients) clearly show that eGFR returns to baseline values after cessation of CANA therapy. This observation largely excludes renal damage by CANA and strongly argues for dehydration as the cause for the observed decrease in eGFR during CANA therapy, at least in this data set (DS3). No information is available how many patients with renal impairment were included in this analysis. This special population is discussed in the respective section below.

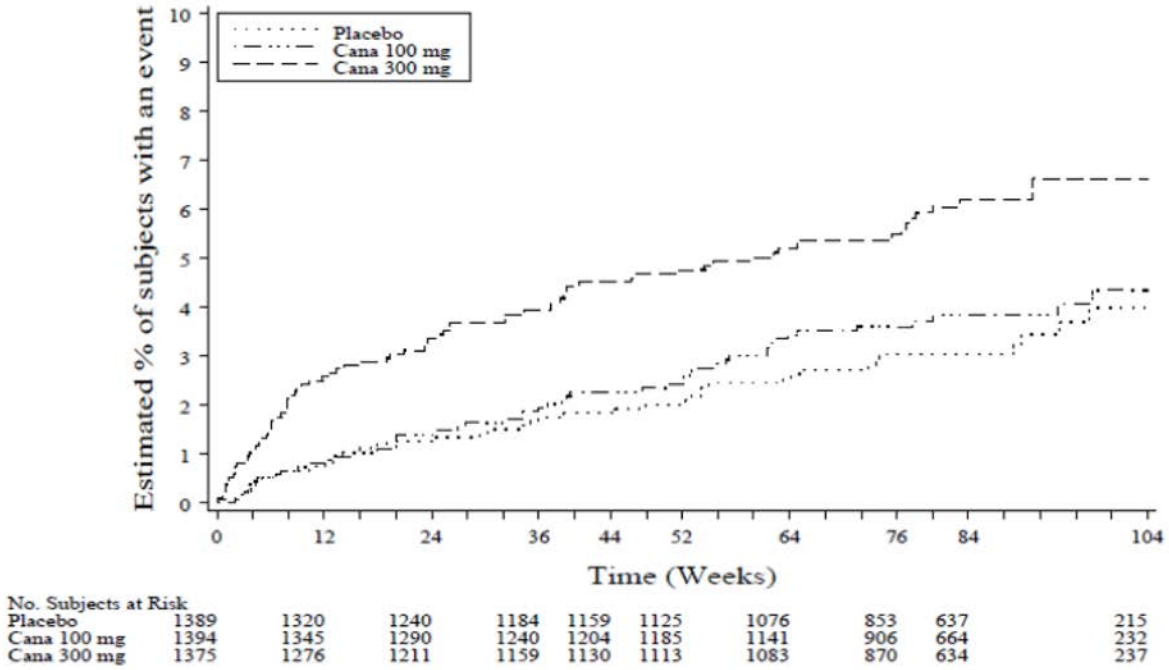
SGLT2 inhibition causes water and sodium loss because of glucose-induced osmotic diuresis and because SGLT2 is also a sodium carrier. Thus, signs of **volume depletion** and AEs related to volume depletion may be expected with CANA therapy. The following table lists the incidence of AEs related to dehydration in general as well as the most frequent individual events. Results from DS3 are shown; the picture was similar in DS1 (placebo-controlled studies).

Table 19: Volume Depletion Adverse Events - Regardless of Use of Rescue Medication (ISS Phase III Broad Dataset: Safety Analysis Set)

	All Non-CANA	Cana100mg	Cana300mg
	(N=3262)	(N=3092)	(N=3085)
Dictionary-Derived Term	n(%)	n(%)	n(%)
Total no. subjects With adverse eventsa	49(1.5)	71(2.3)	105(3.4)
Incidence Rate Per 1000 Person-Years Exposure	21.56	31.41	47.61
Blood Pressure Decreased	1(<0.1)	2(0.1)	2(0.1)
Dehydration	7(0.2)	5(0.2)	11(0.4)
Dizziness Postural	13(0.4)	18(0.6)	24(0.8)
Hypotension	13(0.4)	34(1.1)	47(1.5)
Orthostatic Hypotension	4(0.1)	7(0.2)	19(0.6)
Orthostatic Intolerance	0	1(<0.1)	0
Presyncope	5(0.2)	3(0.1)	2(0.1)
Syncope	10(0.3)	6(0.2)	12(0.4)
Serious adverse events of volume depletion	9(0.3)	6(0.2)	4(0.1)

CANA clearly increased the incidence in dehydration-related events in a dose-dependent manner to more than twofold the comparator level for the high dose group, most pronounced for hypotension. Nevertheless, the absolute number of events was still low and serious AEs were not increased with CANA. The influence of concomitant therapy with diuretics and antihypertensive drugs is presented in the section on interactions below.

The first AEs related to volume depletion occurred early after start of treatment, mostly in the first 8 to 12 weeks (see Kaplan-Meier plot below). Thereafter, the tolerabilty of CANA in respect to volume depletion related AEs did remain essentially constant as identified by the nearly parallel curves of the CANA and placebo groups from week 12 onward.



Kaplan-Meier Plot of Time to the First Treatment-Emergent Volume Depletion Adverse Event for Subjects with Baseline GFR ≥45 mL/min/1.73 m2 in DIA3008 Study through July 1, 2012

A serious complication of dehydration and haemoconcentration is **venous thrombosis**. Therefore the Applicant summarised all relevant AEs that are related to venous thrombosis. The percentage of VTE was very low (0.2 to 0.3%) so that even the large dataset does not allow firm conclusions. It cannot be fully excluded that 300 mg CANA increase the risk of total VTE and serious VTE but the very low absolute number of events indicates that VTE is no major problem of CANA therapy.

A meta-analysis for **cardiovascular (CV) events** of phase II and III canagliflozin studies in subjects with T2DM was performed in accordance with FDA Guidance Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. Prospectively adjudicated major adverse cardiovascular events (MACE, including CV death, nonfatal myocardial infarction [MI], and nonfatal stroke) and events of hospitalized unstable angina (collectively referred to as MACE-plus) are included in the meta-analysis. An independent Endpoint Adjudication Committee (EAC), composed of external specialists classified the outcome events while blinded to treatment assignment. The meta-analysis was based upon a pooled population of subjects with T2DM receiving at least one dose of CANA (mITT set) 100 or 300 mg in the well-controlled, randomized studies of at least 12 weeks in duration. Study DIA3015 is not included because of the later database lock.

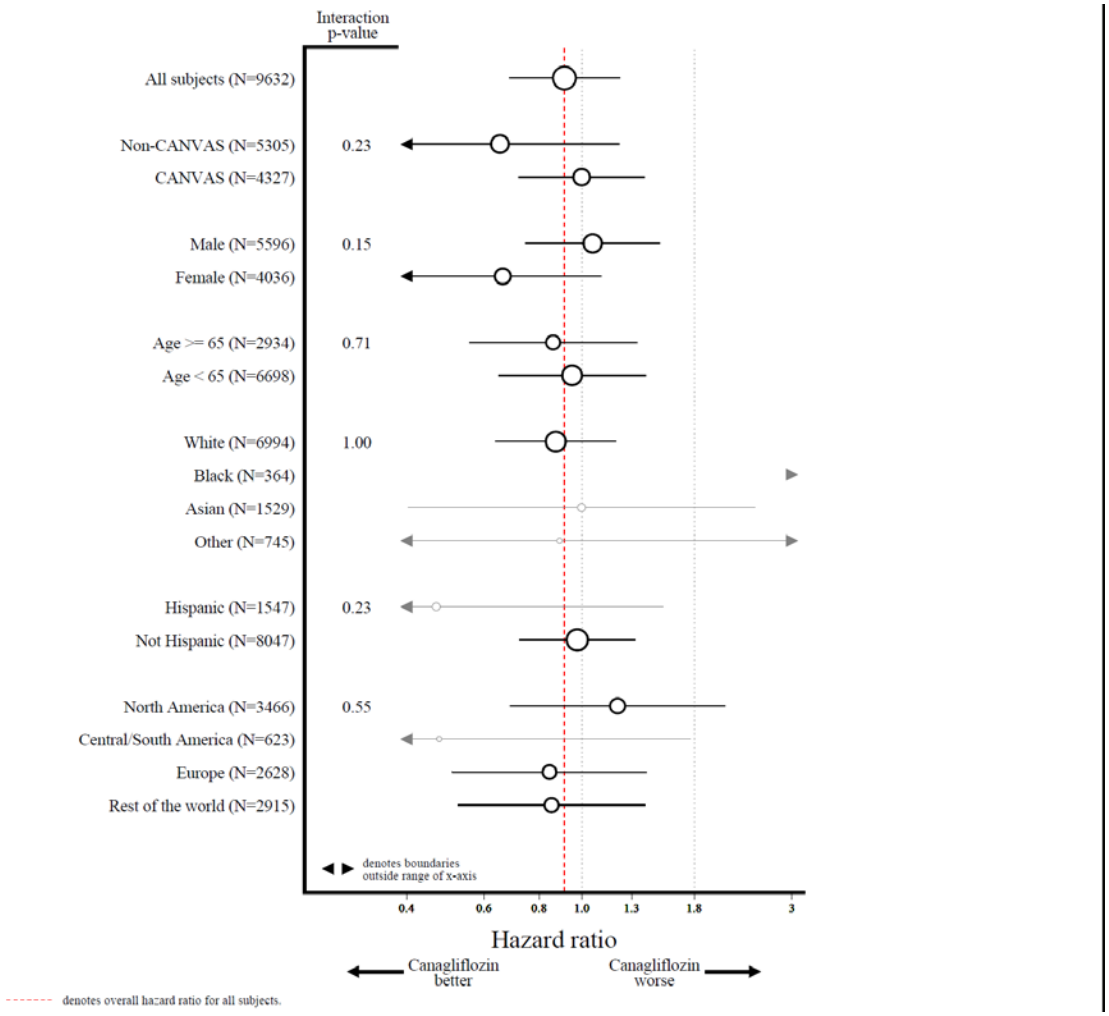
The following table summarise the main results for MACE events:

Table 20: MACE Events (All Phase II/III Studies: mITT Analysis Set)

	Non-CANA	CANA 100 mg	CANA 300 mg	All CANA	Ratio (95% CI)
	N = 3327	N = 3156	N = 3149	N = 6305	
MACE[c]					
Subjects with an event (%)	53(1.6)	55(1.7)	49(1.6)	104(1.6)	**HR: 0.98 (0.70, 1.37)**
Number of events	54	57	51	108	
Patient-years of exposure to first event	3478	3453	3383	6835	
Total patient-years of exposure	3495	3480	3408	6888	
Event rate (/1,000 patient-yrs)	15.4	16.4	15.0	15.7	
Event accounting[d]					
Cardiovascular death	16(0.5)	11(0.3)	10(0.3)	21(0.3)	
Nonfatal MI	25(0.8)	22(0.7)	19(0.6)	41(0.7)	
Nonfatal stroke	12(0.4)	22(0.7)	20(0.6)	42(0.7)	

In the meta-analysis performed, the CV events are fairly balanced between the treatment groups in both evaluations. The event rate for MACE was nearly identical between the All CANA and the comparator group and the upper limit of the 95% CI of the HR is rather low (1.37), reasonably excluding a relevant increase in cardiovascular risk of CANA.

The Applicant provided a graphical overview (Forrest plot below) of the contribution of important subpopulations to the mean HR of MACE-plus (the latter is shown as the red dotted line).



Forest Plot of MACE-Plus Events Stratified by CANVAS/Non CANVAS Studies (All Phase II/III Studies: mITT Analysis Set)

The Applicant also summarised the incidence of AEs related to **congestive heart failure**. In the Non-CANA group of the broad, long-term DS4, **0.31%** of patients presented with this diagnosis. There was a lower incidence in the two CANA groups, **0.13%** and **0.16%** for 100 and 300 mg CANA, respectively.

Rather pronounced differences become obvious from the figure (Forrest plot) above between participants of the CV outcome study CANVAS (DIA3008) and participants of the other phase III trials. The confidence intervals are largely overlapping so that it is not clear whether these differences are true. Nevertheless, these currently limited data suggest that patients with lower CV risk (majority of patients included in the non-CANVAS studies) may potentially derive a CV benefit from treatment with CANA whereas this may not be the case for patients with known CV disease or a clearly increased risk thereof (CANVAS population). Importantly, the HR data do not indicate a detrimental effect of CANA in either population.

In order to obtain a broader database, a subpopulation of "high CV risk patients" was defined within the broad data set DS3, consiting of patients who meet the inclusion criteria for the CV outcome trial CANVAS (DIA3008). The results are tabulated below, for MACE and MACEPlus:

Table 21: MACE Events for CANVAS Subjects and Selected Non-CANVAS Subjects (mITT)
JNJ-28431754 Phase 2/3 Studies (results through 31 Jan 2012)

	Control k/N (%)	CANA 100 mg k/N (%)	CANA 300 mg k/N (%)	CANA Pooled k/N (%)	Hazard Ratio (95% CI)[a]
CANVAS	38/1441(2.6)	46/1445(3.2)	40/1441(2.8)	86/2886(3.0)	1.11 (0.76,1.63)
Non-CANVAS(with CV risk similar to CANVAS)[b,c]	10/643(1.6)	7/580(1.2)	4/549(0.7)	11/1129(1.0)	0.61 (0.26,1.44)
Overall CV high risk population (CANVAS + non-CANVAS)[d]	48/2084(2.3)	53/2025(2.6)	44/1990(2.2)	97/4015(2.4)	**1.01** (0.71,1.43)
Non-CANVAS(without high CV risk)	5/1243(0.4)	2/1131(0.2)	5/1159(0.4)	7/2290(0.3)	**0.73** (0.23,2.29)

Table 22: MACE Plus Events for CANVAS Subjects and Selected Non-CANVAS Subjects (mITT) (JNJ-28431754 Phase 2/3 Studies (results through 31 Jan 2012)

	Control k/N (%)	CANA 100 mg k/N (%)	CANA 300 mg k/N (%)	CANA Pooled k/N (%)	Hazard Ratio (95% CI)
CANVAS	53/1441(3.7)	56/1445(3.9)	52/1441(3.6)	108/2886(3.7)	1.00 (0.72,1.39)
Non-CANVAS(with CV risk similar to CANVAS)	11/643(1.7)	8/580(1.4)	7/549(1.3) 15/1129(1.3)	0.76 (0.35,1.66)	
Overall CV high risk population (CANVAS + non-CANVAS)	64/2084(3.1)	64/2025(3.2)	59/1990(3.0)	123/4015(3.1)	**0.96** (0.71,1.30)
Non-CANVAS(without high CV risk)	7/1243(0.6)	2/1131(0.2)	5/1159(0.4)	7/2290(0.3)	**0.52** (0.18,1.49)

Note: k is number of subjects with MACE events; N is the number of all subjects in the treatment group.

[a] Hazard ratio of pooled canagliflozin subjects versus control subjects with events is from Cox proportional hazards model.

[b] Non-CANVAS subjects who had 'Prior CV history as defined by selected MedDRA terms'.

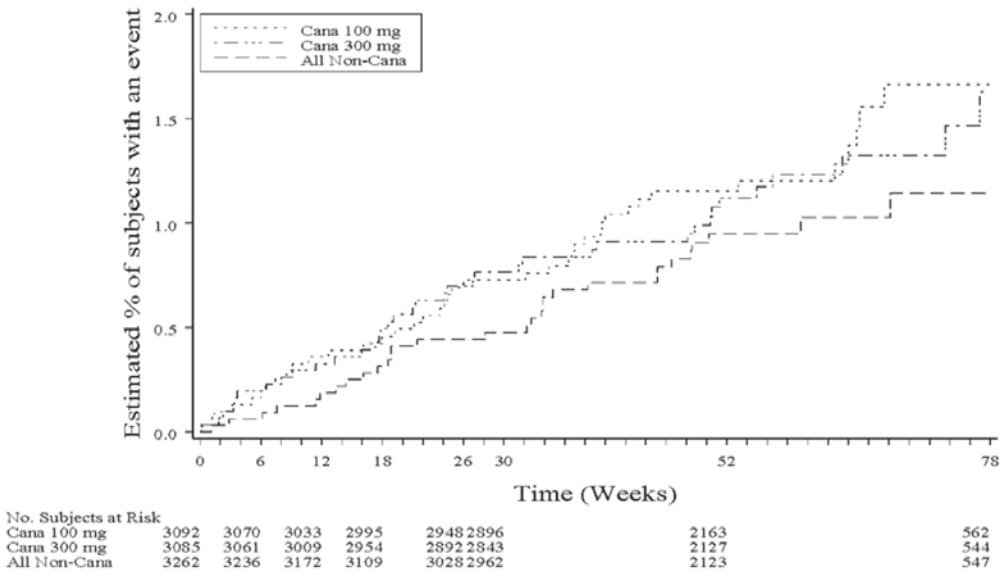
[c] Non-CANVAS subjects with 2 or more defined CV risk factors at baseline.

[d] Combining all CANVAS subjects and selected non-CANVAS subjects as specified in footnote b and c.

A markedly different HR in patients with vs. without high CV risk is obvious with the HR being higher in the latter. However, even in the patients with high baseline CV risk, the HR is very close to unity for MACE as well as for MACEPlus suggesting absence of of excess CV risk of CANA. CV event rates were also similar for both CANA doses.

The following table shows the incidence of **bone fractures** (all and low-trauma) in DS4, and the Kaplan-Meier plot illustrate the time to first event of low-trauma fracture.

	Non-CANA	CANA 100 mg	CANA 300 mg
Total no. subjects with adverse events n(%)	47 (1.4)	58 (1.9)	54 (1.8)
Low Trauma	31 (1.0)	41 (1.3)	39 (1.3)



Kaplan-Meier Plot of Time to First Low Trauma Fracture Adverse Event (ISS Phase III Longer term Exposure Broad Dataset: Safety Analysis Set)

The Kaplan-Meier plot indicates a questionable increase in low-trauma fractures with CANA (both doses). The difference became obvious very early in treatment (after around 6 weeks). Thus, it remains unclear whether this effect could be caused by CANA. Usually bone changes (e.g. noticeable decrease in bone density) need more time to develop. On the other hand, the increase in fractures (if true) may be due to increased falls related to CANA-induced dizziness or hypotension. A causal relationship cannot be excluded because most fractures that occured briefly after onset of CANA therapy were located in the upper extremity and were related to falls. At least in one case a temporal relationship between low blood pressure and fall could be established.

Bone mineral density (BMD) was measured by DXA up to 52 weeks in study DIA3010.The results were as follows:

% Change from Baseline	Placebo (N=237)	Cana 100 mg (N=241)	Cana 300 mg (N=236)
N	170	201	190
Lumbar spine			
LS Mean (SE)	0.6 (0.33)	0.2 (0.34)	-0.1 (0.34)
Diff. (%) of LS Means (minus Placebo) 95% CI		**-0.4 (-1.0;0.3)**	**-0.7 (-1.4;-0.1)**
Femoral neck			

LS Mean (SE)	-1.5 (0.36)	-1.4 (0.36)	-0.9 (0.36)
Diff. (%) of LS Means (minus Placebo) 95% CI		**0.1 (-0.6;0.8)**	**0.6 (-0.1;1.4)**
Distal forearm			
LS Mean (SE)	-0.6 (0.32)	-0.1 (0.33)	-0.5 (0.33)
Diff. (%) of LS Means (minus Placebo) 95% CI		**0.5 (-0.1;1.2)**	**0.1 (-0.6;0.7)**

These data reveal only small (<1%) and inconsistent changes in BMD in the bone regions tested. Hence, there is no hint for CANA-induced bone loss.

Nonclinical studies and phase I/II trials demonstrated that CANA has **phototoxic potential**, although only at high light intensity which is considered clinically irrelevant. In phase III studies the incidence of all AEs potentially related to photosensitivity was numerically increased in the CANA groups than in the non-CANA group, see table below, but the absolute number of events was low so that no firm conclusions can be drawn.

Table 23: Photosensitivity Skin Adverse Events - Regardless of Use of Rescue Medication (ISS Phase III Longer-term Exposure Broad Dataset: Safety Analysis Set)

	AllNon-CANA	Cana100mg	Cana300mg
	(N=3262)	(N=3092)	(N=3085)
Dictionary-Derived Term	n(%)	n(%)	n(%)
Total no. subjects With adverse events	5(0.2)	9(0.3)	8(0.3)
Incidence Rate Per Subject-Year Exposure	0.0015	0.0027	0.0024
Photodermatosis	0	0	1(<0.1)
Photosensitivity Reaction	2(0.1)	6(0.2)	4(0.1)
Polymorphic Light Eruption	0	0	1(<0.1)
Sunburn	3(0.1)	3(0.1)	3(0.1)

Overall, phototoxicity is rare, even in the presence of CANA. This is in agreement with the findings of the phase I and phase II studies. There was a marked increase in the incidence of skin ulcer in the broad dataset DS3/DS4. However, these ulcers were located on leg and foot, and the imbalance in their incidence was most likely due to the observed imbalance in the baseline rate of microvascular disorders.

Serious adverse event / deaths / other significant events

There was no increase in overall death rate or **deaths** considered related to study drug in the CANA groups as compared to control: 1 death in the placebo and one death (cardiac death) in the CANA 300 mg group were considered possibly related to study drug by the investigator in DS4.

Serious AEs (SAEs) were overall balanced between the CANA and non-CANA groups. Furthermore, no individual SAE or organ system was markedly imbalanced between the groups. An exception could be the term “Reproductive System and Breast Disorders” with an SAE incidence of 0.1% in the non-CANA and 0.4% in the high-dose CANA group. However, no predominant entity of SAEs in this organ system could be identified and the absolute number of events is low. No such imbalance was observed in the other datasets (DS1 and DS2). Hence, this finding is most likely due to chance.

In the non-clinical 2-year rat carcinogenesis study (see Non-Clinical AR for details) three types of **neoplasms** became obvious which were apparently related to CANA administration. These were phaeochromocytomas, Leydig cell tumours of the testis and renal tumours. Far the most of the

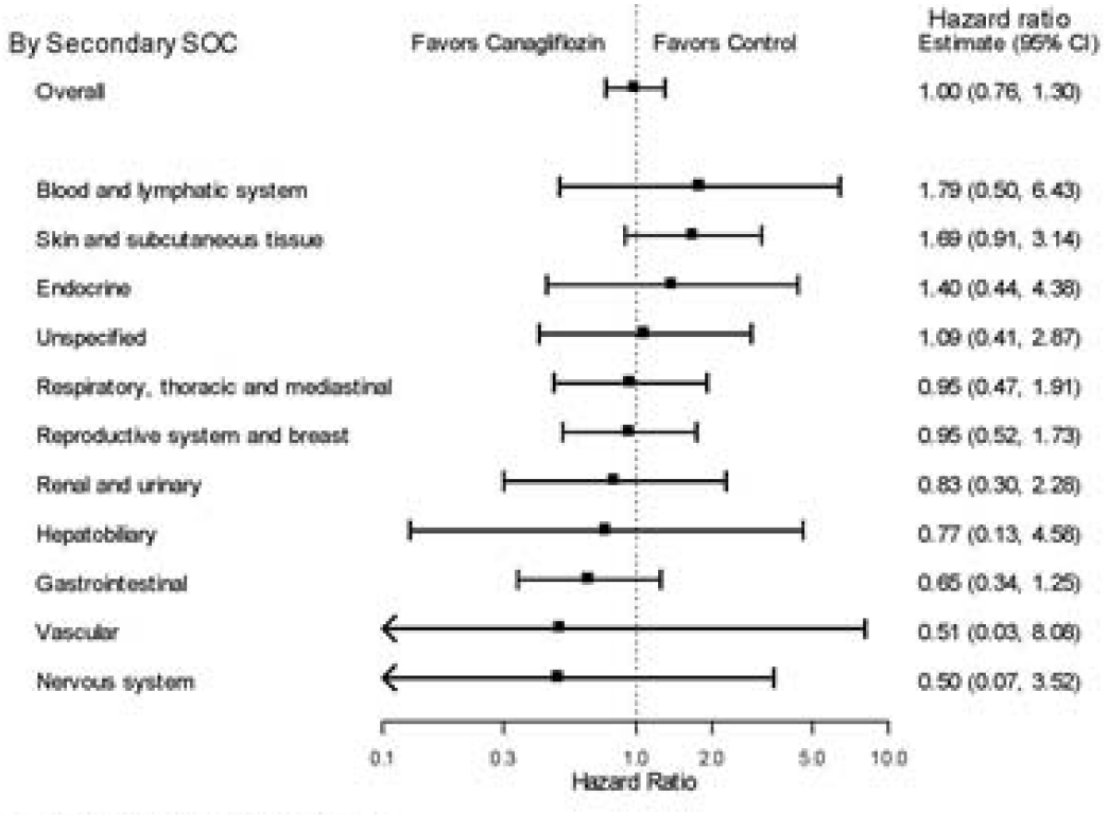
phaeochromocytomas and all Leydig cell tumours were benign. The kidney tumours were benign or malignant but were highly differentiated and displayed a histopathological picture that markedly differed from known spontaneous kidney tumours in rats (and also humans). In the mouse carcinogenicity study no CANA-related neoplasms became obvious.

The Applicant conducted mechanistic studies in the rat strain which had revealed the tumours and concluded that SGLT1 inhibition by CANA at high doses in the small intestine with consecutive glucose malabsorption plays a crucial role. According to this hypothesis the reduced pH in the gut lumen leads to the absorption of higher than usual amounts of calcium from food. To keep the calcium serum level within the normal range the kidney has to excrete this excessively resorbed calcium. The need to excrete high amounts of calcium (nearly 10-fold the normal amount) could be responsible for the observed kidney changes (hyperplasia, inflammation, tumours). The inflammation may be caused by the observed mineralisation (probably calcium phosphate crystals) in the renal cortex. This mechanism appears plausible. It also appears irrelevant for humans since there are no hints for major carbohydrate malabsorption in humans as determined in the clinical trials DIA1007 and DIA1022. It should be noted that the oral bioavailability of CANA is markedly lower in rats than in humans (around 35% in rats compared to 65% in humans). Therefore, with a given CANA dose a markedly higher fraction remains in the gut in rats and is able to block SGLT1 transporters locally. Kidney changes were markedly reduced when the rats received a glucose-free diet which sharply reduced renal calcium excretion. Simultaneously, cell division and hypertrophy in the adrenal cortex were no longer observed with glucose-free diet, leading to the coclusion that the phaeochromocytomas were also caused by malabsorption (although the mechanism is not fully clear).

Leydig cell tumours were explained by the Applicant by increased LH (luteinising hormone) levels caused by CANA in rats. The reason why CANA influenced LH (and testosterone) levels in rats is not clear, but no such changes were observed in humans as determined in the dedicated phase I trial DIA2001.

In the most relevant long-term, broad data set 4, there was a slight imbalance in neoplasms (combined benign and malignant). **2.5%**, **2.5%** and **2.9%** of the patients in the **comparator**, **CANA 100 mg** and **CANA 300 mg** group, respectively, had a finding of neoplasm. Phaeochromocytomas and Leydig cell tumours (as seen in the non-clinical carcinogenicity study) were not observed in the phase III programme.

In the DS3 data set (shorter observation time), there was a slight imbalance in the overall neoplasm incidence, i.e., 2.17% (67/3085) neoplasms in the CANA 300 mg group vs. 1.68% (55/3262) in the non-CANA group (ratio **1.29**)**.** However, in the DS4 data set (longer observation time of the same patients), this imbalance was diminished, i.e., 2.92% (90/3085) neoplasms in the CANA 300 mg vs. 2.51% (82/3262) neoplasms in the CANA 300 vs. non-CANA group (ratio of **1.16**). In the latest evaluation (cut-off date 31 Dec 2012) the ratio further dropped to **1.04** (2.56% in the All CANA and 2.45% in the comparator group). The imbanlance in bladder tumours found with another SGLT-2 inhibitor was not observed for CANA. Thus, there is no hint from clinical data that the rat findings could be relevant for humans or that CANA is generally associated with an increased tumour risk. For further reassurance the Applicant also provided a Forrest Plot showing the hazard ratios (HRs) for individual tumour types:



Hazard Ratio for AEs in the Primary SOC of Neoplasms Benign, Malignant and Unspecified (Pooled Dataset DS3, through a cut-off date of 31 December 2012)

It can be derived from the figure that the HRs for the individual tumour types scatter around unity, with some types having HRs above (e.g. blood and skin tumours) and others revealing HRs below one (e.g. gastrointestinal and renal/urinary). There are no outliers and no tumour type has a HR which is different from 1 in a statistically significant way. Thus, this pattern fits the assumption of a random distribution with the mean (overall) HR of 1.

Laboratory findings

Decrease in **blood pressure** and slight and dose-dependent increases in **haemoglobin (hb)**, **haematocrit (hct)**and **serum electrolytes** were observed with CANA and are apparently linked to its pharmacodynamic action (water and salt loss). The regularly observed hb and hct increase (Hb: mean increase -0.8, 6.9 and 7.6 g/L for placebo, CANA 100 and CANA 300 mg, respectively) did not lead to an increased incidence of hb or hct being above the upper limit of normal. Serum creatinine also increased with CANA treatment. The significance of this finding is discussed above in the section on renal function as AE of special interest.

The following table displays the changes in **blood pressure** from baseline to week 26.

		Systolic blood pressure (mmHg)		**Diastolic blood pressure (mmHg)**	
	N	**Change from Baseline**		**Change from Baseline**	
		Mean	SD	**Mean**	SD
All Non-CANA	2786	**-1.4**	13.36	**-0.9**	8.18
CANA 100 mg	2739	**-5.2**	13.13	**-2.4**	8.07
CANA 300 mg	2691	**-6.7**	13.81	**-3.2**	8.28

No relevant changes in liver parameters were observed, and there was no hint that CANA induces liver injury.

Apart from the PD-related laboratory findings outlined above CANA also induced small but consistent changes in **serum lipids**; most pronounced were increases in LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C). The LDL-C/HDL-C ratio remained essentially unchanged. A post-hoc performed NMR-spectroscopy to assess LDL-C particle number showed that the increase in the total LDL-C particle number was driven primarily by a large increase in particle number of the large LDL-C subfraction with little or no change in the small LDL-C particle number, hence leading to an increase in the less atherogenic subfraction. The increase in serum lipoproteins could also be due to haemoconcentration. This would be in line with the finding that LDL-C and HDL-C increased to around the same amount.

CANA also caused slight and dose-dependent mean changes in serum bicarbonate (decrease), serum magnesium (increase) and serum sodium (increase) which became obvious shortly after onset of treatment (within 6 weeks). The observed changes were small and the serum levels of these electrolytes usually remained within the normal range. They somewhat more frequently exceeded the normal range in patients with moderate renal impairment, especially with CANA 300 mg (see section on special populations, renal impairment, below).

Safety in special populations

The following AE incidences, tabulated below, were observed in the patient population pool with **moderate renal insufficiency** (i.e. eGFR between 30 and 60 mL/min/1.73m^2).

Table 24: Volume Depletion Adverse Events - Regardless of Use of Rescue Medication (ISS Phase III Moderate Renal Impairment Dataset: Safety Analysis Set)

	Placebo	Cana100mg	Cana300mg
	(N=382)	(N=338)	(N=365)
Dictionary-Derived Term	n(%)	n(%)	n(%)
Total no. subjects with adverse eventsa	10(2.6)	17(5.0)	31(8.5)
Incidence Rate Per 1000 Person-Years Exposure	38.40	70.16	118.78
Dehydration	2(0.5)	1(0.3)	4(1.1)
Dizziness Postural	2(0.5)	7(2.1)	7(1.9)
Hypotension	3(0.8)	7(2.1)	14(3.8)
Orthostatic Hypotension	1(0.3)	1(0.3)	3(0.8)
Presyncope	1(0.3)	0	1(0.3)
Syncope	2(0.5)	1(0.3)	3(0.8)
Serious adverse events of volume depletion	5(1.3)	1(0.3)	3(0.8)

Table 25: Number of Subjects with Serum Chemistry / Haematology Laboratory Values Outside Pre-Defined Limits - Regardless of Use of Rescue Medication (ISS Phase III Moderate Renal Impairment Dataset: Safety Analysis Set)

	Placebo	CANA 100mg	CANA 300mg
	N=366	N=332	N=351
	n(%)	n(%)	n(%)
eGFR <80 mL/min/1.73m2 and decrease >30% from baseline	18(4.9)	31(9.3)	43(12.2)

Phosphate > ULN and >25% increase from baseline	1(0.3)	9(2.7)	18(5.1)
Potassium > ULN and >15% increase from baseline	29(7.9)	24(7.2)	42(12.0)
Sodium > ULN and increase of >5 mmol/L from baseline	8(2.2)	15(4.5)	17(4.8)
Hemoglobin ≥20 g/L increase from baseline	9(2.6)	27(8.4)	19(5.7)

Since clinically relevant efficacay was still observed in a subgroup of patiens with moderate renal impairment who had an eGFR of ≥45 mL/min/1.73m^2 (see efficacy section), the Applicant provided a safety evaluation for this subgroup (patients with eGFR between 45 and 60 mL/min/1.73m^2). The incidence of AEs related to volume depletion and serum electrolyte imbalance was slightly increased as compared to patients with eGFR ≥60 mL/min/1.73m^2 but the incidence of severe or serious events did not increase and the type of events remained the same.

Table 26: Post Randomization Fracture Adverse Events - Regardless of Use of Rescue Medication For Subjects with Moderate Renal Impairment (Subset of ISS Phase III Longer-term Exposure Broad Dataset: Subjects with Moderate Renal Impairment: Safety Analysis Set)

	All Non-CANA	CANA 100mg	CANA 300mg
	(N=382)	(N=338)	(N=365)
	n(%)	n(%)	n(%)
Total no. subjects with adverse events a	5(1.3)	9(2.7)	4(1.1)
Incidence rate per 1000 person-years exposure	13.33	25.59	10.57

There is a numerical increase in fracture rate in renally impaired patients in the low-dose but not in the high-dose CANA group. The relevance of this observation is unclear. This could reflect random fluctuation due to the low number of events. Specific studies on bone turnover markers and calcium metabolism in renally impaired patients are not available. In study DIA3004 (subjects with moderate renal impairment), relative to placebo, moderate percent reductions in PTH (-10.3% and -16.1%) were seen with canagliflozin 100 mg and 300 mg, respectively, which do not indicate an increased renal loss of calcium with CANA use.

Renally impaired patients more often display alterations of eGFR (reduced), serum phosphate (increased), serum sodium (increased) and serum potassium (increased) in response to CANA than the overall study population, especially with 300 mg CANA. Hyperkalaemia may adversely affect cardiac function.

Furthermore, the incidence of AEs related to dehydration and the incidence of vascular disorders (including hypotension) was markedly increased in this population. Taken together, this indicates that the effects of CANA on water and electrolyte balance are less well tolerated in patients with relevant renal impairment and that the renal safety of CANA in this patient population has not been clarified.

In the **older population** (over 75 years) the incidence of AEs was rather high in all groups, probably because of background disease. Dehydration is in general more frequently observed in the older population, e.g. because of physiologically reduced thirst and often reduced water intake. In patients aged 75 or more, 2.6% in the Non-CANA vs. 4.9% in the 100 mg and 8.7% in

the 300 mg CANA group had AEs related to dehydration. Furthermore, the organism may have reduced ability to compensate for the changes in water and electrolyte balance induced by CANA. It is reassuring that serious AEs and AEs leading to discontinuation were not increased with CANA as compared to control. It can be assumed that most diabetic patients over 75 years of age will have some degree of renal impairment. Thus, it is not known whether old age is a risk factor *per se* or if the imbalance is mainly due to the expected higher incidence of renal impairment. The Applicant is therefore asked to clarify how many of the older patients did have impaired renal function and whether this influenced the AE profile.

Immunological events

The adverse event of hypersensitivity was reported in 9 (0.3%) subjects in the canagliflozin 100 mg (1 subject had 2 events), 6 (0.2%) subjects in the canagliflozin 300 mg and 1 (<0.1%) subject in the non-CANA groups. In 6 subjects in the combined canagliflozin group, reported terms suggested environmental allergies and in 9 subjects reported terms were non-specific hypersensitivity. The majority of the events were considered by the investigator as mild or moderate in severity and not related to the study drug. Two of 15 subjects in the combined canagliflozin group had events of hypersensitivity that led to discontinuation of study drug. In both subjects who discontinued, the events were considered by the investigator as related to study drug, and in 1 of the 2 subjects who discontinued the event was serious (Type I allergic reaction on Day 1, 1 hour after CANA intake). No other subjects had serious events of hypersensitivity or events that were considered related to study drug.

Safety related to drug-drug interactions and other interactions

The most relevant interactions of CANA are expected with diuretics and blood pressure lowering agents. As shown in the table below, adverse events related to volume depletion were markedly increased with CANA 300 mg in patients with a background therapy of loop diuretics or antihypertensive drugs of the ACE/ARB class. The effect was less pronounced with other diuretics.

Table 27: Number of Subjects with Volume Depletion Adverse Events by Selected Baseline Characteristics - Regardless of Use of Rescue Medication (ISS Phase III Broad Dataset: Safety Analysis Set)

	%(n) in population	Incidence		
		All Non-CANA	CANA 100 mg	CANA 300 mg
	%(n/N)	%(n/N)	%(n/N)	%(n/N)
Use of ACE/ARB	N=9439			
No	31.4%(n=2961)	1.0%(10/1022)	1.2%(12/970)	1.5%(15/969)
Yes	68.6%(n=6478)	1.7%(39/2240)	2.8%(59/2122)	**4.3%**(90/2116)
Use of Loop Diuretics	N=9439			
No	92.4%(n=8717)	1.2%(37/3006)	2.2%(64/2876)	2.9%(83/2835)
Yes	7.6%(n=722)	4.7%(12/256)	3.2%(7/216)	**8.8%**(22/250)

Other conditions that increased the risk for CANA to induce dehydration included low systolic blood pressure, diabetes duration, diabetes complications and, rather pronounced, age 75 or above. This indicates that poorer general health may decrease the tolerability of CANA.

Discontinuation due to adverse events

There was some imbalance in the incidence of AEs leading to discontinuation between CANA and control, most pronounced in the high-dose CANA group (3.7%, 4.2% and 5.6% for Non-CANA, CANA 100 mg and CANA 300 mg, respectively). This imbalance was largely due to various terms related to genital infection and polliakiuria, but no predominant single condition became obvious.

2.6.1. Discussion on clinical safety

The safety profile of CANA is largely consistent with the expected safety profile for an SGLT2 inhibitor. This includes water and sodium loss which may lead to dehydration with all its sequels including hypotension and syncope in vulnerable patients. The mean arterial blood pressure decreased with CANA by around 7 mm Hg (systolic) and around 3 mm Hg (diastolic). The blood pressure lowering effect is a desirable effect in the frequently hypertensive, overweight patient with type 2 diabetes but such an effect is not usually expected for a glucose-lowering agent; therefore a warning has been included in the product information. Caution should be exercised in patients for whom a canagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension, elderly patients or patients with (intercurrent) conditions that may lead to volume depletion.

Glucose in urine favours urogenital infections. As with other SGLT2 inhibitors, the most pronounced increase in AEs was observed for genital infections, mainly of mycotic origin. Severe, ascending urinary tract infections were rare and not apparently increased with the use of CANA. Urogenital infections are considered manageable if the patient and prescriber are aware of the risk. Therefore, these events are not regarded as a major safety concern.

CANA was phototoxic in non-clinical tests. Dedicated phase I and phase II clinical trials revealed that acute or delayed photosensitivity reaction are unlikely at the light intensities of normal sunlight. However, the incidence of adverse events of skin and subcutaneous tissue was increased in CANA-treated patients, but this increase was due to probably diabetes-related skin ulcers located at the leg or foot and could be explained by a baseline imbalance in pre-existing microvascular disease.

In the clinical Phase 3 program, an increased incidence of photosensitivity reactions occurred in the combined canagliflozin group (0.28%; 17/6177) and in comparison to the non-canagliflozin group (0.15%; 5 /3262). Of the events assessed as related to study medication by the investigator, photosensitivity reaction occurred in 10 (0.16%) subjects in the combined canagliflozin group and 2 (0.06%) subjects in the non-canagliflozin group. However, no event was serious or severe, and the number of events was low. Thus, photosensitivity is not considered as a clinically relevant concern.

Bone fractures were slightly increased with CANA. The early occurrence, locations (upper extremity) and circumstances (most often falls) of the observed fractures suggest that CANA-induced drop in blood pressure may have been the reason for the slightly increased fracture rate. In order to minimise the risk of hypotension and potential sequelae, a start of CANA therapy with the low dose (100 mg) is recommended in the product information. DXA measurements up to 52 weeks of therapy reveal only very small and inconsistent changes in BMD with CANA compared

to placebo. Serum markers of bone formation and turnover changed slightly with no clear net effect. Based on these data, there is currently no concern regarding bone safety of CANA. For further reassurance the 104-week BMD data should be submitted as soon as available.

CANA caused hypoglycaemia (≤70 mg/dL [3.9 mmol/L]) in rare cases, even in the absence of a hypoglycaemic background therapy, but the incidence of clinically more relevant hypoglycaemia (blood glucose below 56 mg/dL [3.1 mmol/L]) was not different from placebo. CANA markedly increased the incidence of documented hypoglycaemia if the background therapy included insulin or sulphonylureas. Thus, care should be taken when CANA is added to insulin or sulphonylureas and dose reduction of the latter medications may be considered, as recommended in the SmPC. Reassuringly, the incidence of severe hypoglycaemia was not increased with CANA, even in the presence of insulin or sulphonylurea background therapy.

Analysing the safety data from patients with moderate renal impairment (eGFR between 30 and 60 mL/min/1.73m2) pooled from the whole phase III programme revealed some differences to the overall study population. In particular, hyperkalaemia and AEs related to dehydration and hypotension were more often induced by CANA in this special population, particularly with the higher dose and in patients with more severe renal insufficiency (i.e. eGFR < 45 ml/min/1.73 m^2). However, in the subgroup of patients with eGFR 45 to < 60 mL/min/1.73m^2 (stage 3A chronic kidney disease, CKD) the incidence of adverse events was close to placebo level with 100 mg CANA; 300 mg increased the incidence of volume depletion related AEs and serum electrolyte imbalances (mainly decreased bicarbonate and increased magnesium) in this group, but the events were not serious. Both types of AEs, volume depletion related and electrolyte imbalances, occurred early after onset of treatment so that treatment of patients with stage 3A CKD appears safe, at least in patients who are on stable treatment, initiated before the onset of moderate renal impairment. Since AE incidence was clearly lower with 100 mg than with 300 CANA mg and was nearly at comparator level in stage 3A CKD patients (patients with eGFR 45 to < 60 mL/min/1.73m^2), as a precautionary measure, the dose in this patient population should be limited to 100 mg/d.

It should be noted that CANA, due to its induction of osmotic diuresis, could consecutively activate the renin-angiotensin system (RAS). This could be a disadvantage because RAS activation may accelerate decrease of renal function. On the other hand, ACE inhibitors (or agiotensin receptor agonists) are recommended for renally impaired patients anyway to slow disease progression. Accordingly, strict blood pressure control is recommended in these patients and is achieved in practice often by use of thiazide diuretics. It is expected that the latter activate RAS to at least the same extent as CANA does but no renal adverse effects were noted to date. Hence, it is unlikely that CANA accelerates the progression of renal insufficiency. The finding of attenuation of the initial CANA-induced eGFR decrease over time and the complete reversibility upon treatment discontinuation, also in patients with moderate renal insufficiency, as well as the decrease in urinary albumin/creatinine ratio in patients with microalbuminuria and macroalbuminuria during CANA treatment provide further reassurance regarding renal safety of CANA.

Adverse events were more pronounced in patients over 75 years of age. It can be assumed that most diabetic patients over 75 years of age will have some degree of renal impairment. A dedicated analysis revealed that CANA-related AEs relevantly increased in patients ≥75 years if they had moderate renal impairment but not in patients of this age group with normal or only

mildly impaired renal function. Therefore, old age per se should not be a criterion to discourage use of CANA. With the general starting dose of 100 mg/day most of the relevant AEs (e.g. due to the initial drop in blood pressure) can be avoided.

A pronounced effect of loop diuretics, 8.8% vs. 2.9% (i.e. increase by around factor 3) on dehydration- related adverse events with 300 mg CANA is obvious. Therefore, use of CANA in patients on loop diuretics is not recommended.

In a CV meta analysis across trials there was no increased risk of CANA vs. comparator (active or placebo) for the combined CV endpoint MACE or MACE-plus (the latter including MACE and hospitalisation for CV events). The hazard ratio (HR) for MACE was close to unity with an acceptable upper limit of the 95% CI (HR: 0.98, 95% CI: 0.70, 1.37). Remarkably, there was a rather pronounced numerical difference in HR of MACE and MACE-plus between patients with high CV risk (CANVAS CV outcome study inclusion criteria) and patients not meeting the CANVAS inclusion criteria. Nevertheless, even in the patients with high CV risk, the HR with CANA did not exceed 1. Therefore, no increased CV risk due to CANA is expected. Taken together, the data suggest that patients with lower CV risk may potentially derive a CV benefit from treatment with CANA, whereas this may not to be the case for patients with established CV disease or a clearly increased risk thereof (CANVAS population). The data also suggest that patients on CANA are at lower risk to develop congestive heart failure compared to patients on comparator, which may be explained by the diuretic effect of CANA.

There was a slight trend for a higher risk for strokes, HR was 1.47 (95% CI: 0.83, 2.59). The majority were non-fatal ischemic strokes and occurred in both CANA groups (100 mg and 300 mg). It is not yet clear whether this finding is due to chance. Thus, strokes will be further followed post-marketing in the CV outcome study CANVAS and in the PSURs.

Carcinogenicity studies in animals revealed neoplastic findings in rats but not in mice. Benign and malignant tumours of the renal cortex and the adrenal medulla (phaechromcytomas) were observed as well as benign Leydig cell tumours of the testes. For the renal tumours the Applicant provided the following explanation, which was considered reasonable. CANA is not well absorbed in the gut of rats and therefore causes a rather high local inhibition of SGLT1 in the intestine. In consequence, less glucose but more calcium (because of reduced luminal pH) becomes absorbed. These high amounts of calcium have to be excreted by the kidney which in turn leads to hyperplasia, inflammation and tumours. A glucose-free diet could prevent these changes. Although the mechanism for the induction of phaeochromocytomas is unknown, this diet also prevented hypertrophy of the adrenal medulla. Since no relevant carbohydrate malabsorption with CANA was observed in humans, the rat findings are considered not relevant for humans.

For further assurance the Applicant provided an analysis of the broadest data set with a late data cut-off (31 Dec 2012) and calculated hazard ratios (HRs) also for each type of tumour (according to the location in an organ system). This analysis revealed a HR of 1.00 for all neoplasms and showed that the HRs of the individual tumour types are randomly distributed around one, without outlier. Thus, the expected pattern of a random distribution resulted, strongly indicating that CANA is not associated with tumours.

There was an increase in serum LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C). The LDL-C/HDL-C ratio remained essentially unchanged. Reassuringly, the LDL-C increase was mainly driven by the less atherogenic subfraction of large particles. So far, there is no evidence for an

increased CV risk associated with CANA. The CV outcome study is still ongoing and will provide further long-term data particularly on patients with high CV risk.

2.6.2. Conclusions on the clinical safety

CANA demonstrated largely a safety profile as expected of an SGLT2 inhibitor. Due to enhanced renal glucose and sodium excretion, CANA may lead to dehydration and its sequelae, to low blood sugar levels (mainly in combination with insulin or insulin secretatogues) and urogenital infections (particularly genital mycoses). In general, these safety issues appear manageable.

Based on its mechanism of action, CANA decreases blood pressure which could be favourable in many type 2 diabetics. Because these effects are unexpected for a diabetes drug, caution should be taken in potentially vulnerable patients.

Thus, some conditions exist in which a starting dose of 100 mg should be used for safety reasons since drop in blood pressure and volume depletion or its sequelae could be more pronounced upon onset of treatment. Therefore a starting dose of 100 mg is recommended for all patients as a precautionary measure and to simplify posology.

The frequencies of AEs, especially those related to dehydration, were increased in patients with moderate renal impairment, particularly with the higher dose and in patients with more severe renal impairment. Simultaneously, efficacy depends on renal function and is therefore markedly decreased in patients with relevantly reduced eGFR. Due to insufficient efficacy and more pronounced safety concerns, the B/R ratio of CANA is considered unfavourable in patients with an eGFR below 45 mL/min/1.73m2. In patients with eGFR ≥45 and <60 ml/min/1.73m^2 there is also an increased reporting of adverse events related to water and electrolyte imbalance compared to comparator, predominantly with CANA 300 mg. However, no relevant differences in AE incidence or serum electrolyte imbalances were observed with 100 mg CANA in this patient population. Furthermore, AEs related to osmotic diuresis and drop in blood pressure usually occured within approximately the first eight weeks of commencement of treatment. Hence, as precautionary measures, CANA treatment should not be initiated in patients with eGFR <60 mL/min/1.73m^{2}or CrCl < 60 mL/min. However patients already under well-tolerated treatment may continue therapy with dose adjustment to 100 mg/d as long as eGFR remains at or above 45 mL/min/1.73 m^2; below this value efficacy becomes too low and AEs are expected to increase so that CANA should then be discontinued.

CANA enhances diuresis which leads to volume reduction and to counter-regulatory effects, manifesting themselves as reduced albuminuria and reversible decrease in eGFR which does not reflect renal damage. Similar mechanisms are at work when these patients are treated with thiazide diuretics. It is established that tight blood pressure control retards spontaneous deterioration of the diabetic kidney disease in the long term, and this BP control is often achieved with diuretics (also in combination with other agents). This argues against the assumption that diuretics, or agents that act as diuretics such as CANA, accelerate progression of diabetic nephropathy.

Based on currently available data, cardiac safety of CANA is reasonably well demonstrated. Further data from the CV outcome study are awaited post-marketing.

The slight imbalance in low-trauma bone fractures (not favouring CANA) cannot be explained by renal calcium loss or otherwise adverse effects of CANA on bone. Fractures were mainly due to falls which could have been a consequence of CANA-induced drop in blood pressure.

Non-clinical data indicate phototoxicity of CANA but clinical data indicate that this would play only a role at artificially high light intensities. Phase III trials indicate that serious photosensitivity reactions are highly unlikely and are therefore not regarded as a relevant concern.

In non-clinical studies malignant neoplasms (in the kidney and adrenal gland of rats) were observed which were most likely species-specific. In patients, there was no imbalance in the incidence of neoplasms in the CANA vs. comparator group in the latest safety evaluation.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

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

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 2.2, the PRAC considers by consensus decision that the risk management system for canagliflozin (Invokana) in the treatment of in adults aged 18 years and older with T2DM to improve glycaemic control is acceptable. The following points should be taken into account in the next update.

The RMP needs revision with the next RMP update to include consistent wording about toxicology results of the juvenile rat study on pregnancy and lactation. However, the preliminary view is that the RMP is approvable as the requested revision concerns minor issues that do not require immediate action or would preclude RMP approval.

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	Vulvovaginal candidiasis Balanitis or balanoposthitis Urinary tract infections Hypoglycaemia in combination with insulin or glucose-independent insulin secretagogues Volume depletion
Important potential risks	Renal impairment/Renal failure Clinical consequences of increased haematocrit Bone fractures Photosensitivity Hypoglycaemia in the absence of insulin or glucose-independent insulin secretagogues Off-label use for weight loss
Missing information	Long-term cardiovascular safety in patients Use in patients with congestive heart failure defined as NYHA class IV Use in paediatric patients between 10 and 18 years of age Use in pregnancy Use in nursing mothers Use in very elderly patients (≥ 85 years) Use in patients with severe hepatic impairment Use in patients with severe renal impairment (eGFR<30mG/min/1.73m^2)

The PRAC agreed.

- **Pharmacovigilance plans**

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports** (planned or actual)
DIA3010 Category 3	To evaluate the efficacy, safety, and tolerability of canagliflozin compared with placebo in the treatment of older subjects with T2DM inadequately controlled on glucose lowering therapy	Bone safety, cardiovascular safety, Safety in older subjects with T2DM	12 April 2010	4Q 2013
DIA3008 Category 3	To evaluate of cardiovascular outcomes in adult subjects with T2DM	Cardiovascular safety, Renal impairment/Renal failure Clinical consequences of increased haematocrit Bone fractures Photosensitivity	16 Nov 2009	IDMC Status Reports: Twice annually until study completion Final report: 2Q 2018
DIA 4003 Category 3	To assess the effects of canagliflozin major cardiovascular events (MACE) in adult subjects with T2DM	Cardiovascular safety	Planned	2Q 2018

Cardiovascular metaanalysis (including DIA3008 and DIA4003) Category 3	Establish the upper bound of the 2-sided 95% CI of the MACE events hazard ratio for the combined canagliflozin group compared to the placebo group excludes 1.3 post approval.	Cardiovascular safety		Final report: 4Q 2017
DIA1055 Category 3	To evaluate the single- and multipledose pharmacokinetics, pharmacodynamics, and safety of canagliflozin in older children and adolescents 10 to <18 years of age with T2DM on metformin monotherapy	Initial tolerability and safety in paediatric patients	3Q 2013	4Q 2015
Paediatric Phase 3 trial Category 3	To evaluate the efficacy, safety, and tolerability of the addition of canagliflozin to the treatment of older children and adolescents (10 and <18 years of age) with T2DM with inadequate glycaemic control on metformin monotherapy.	Safety and tolerability in paediatric patients	1Q 2015	4Q 2018

The PRAC, having considered the data submitted, was of the opinion that the proposed post-

authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

- **Risk minimisation measures**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Vulvovaginal candidiasis	*SPC 4.4, 4.8*	*NONE*
Balanitis or balanoposthitis	*SPC 4.4, 4.8*	*NONE*
Urinary tract infections	*SPC 4.8*	*NONE*
Hypoglycaemia in combination with insulin or glucose-independent insulin secretagogues	SPC 4.2, 4.5, 4.8	*NONE*
Volume depletion	SPC 4.2, 4.4, 4.8	*NONE*
Important potential risks		
Renal impairment/Renal failure	SPC 4.2, 4.4, 4.8	*NONE*
Clinical consequences of Increased haematocrit	NONE	*NONE*
Bone fractures	NONE	*NONE*
Photosensitivity	NONE	*NONE*
Hypoglycaemia in the absence of insulin or glucose-independent insulin secretagogues	SPC 4.8	*NONE*
Off-label use for weight loss	SPC 4.1	*NONE*
Missing information		
Long-term cardiovascular safety in patients	NONE	*NONE*
Use in patients with congestive heart failure defined as New York Heart Association (NYHA) class IV	SPC 4.4	NONE
Use in paediatric patients	SPC 4.2	NONE

between 10 and 18 years of age		
Use in pregnancy	SPC 4.6	NONE
Use in nursing mothers	SPC 4.6	NONE
Use in very elderly patients (≥85 years)	SPC 4.2, 4.4, 4.8, 5,1	NONE
Use in patients with severe Hepatic impairment	SPC 4.2, 5.2	NONE
Use in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2)	SPC 4.2, 4.4	NONE

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

CANA 100 mg and 300 mg, compared to placebo, provided consistent, statistically significant and clinically relevant improvements in glycaemic control when given as monotherapy in patients intolerant or with contraindications to metformin or as add-on to other AHAs including insulin.

CANA was shown to have non-inferior antihyperglycaemic efficacy compared to glimepiride and sitagliptin after 52 weeks of treatment with both active comparators titrated to a sufficiently high dose to achieve full glucose lowering potential. For CANA 300mg even superiority over both active comparators was demonstrated.

Durability of effect of both CANA doses has convincingly been shown, especially based on the 52-week data from the extension periods of studies DIA 3002, 3004, 3005, 3006 as well as data from the active controlled studies (DIA 3009 and 3015). Over the course of one year, CANA demonstrated better durability of effect than the active comparators glimepiride and sitagliptin.

The effect of CANA strongly depends on renal function. The efficacy of CANA in patients with eGFR 45- 60 mL/min/1.73m^2 is reduced but still considered clinically relevant, whereas in patients with an eGFR < 45 mL/min/1.73m^2 it is clearly insufficient.

CANA was associated with a consistent decrease in body weight from baseline. This effect was especially evident in comparison to SU (difference in weight 5.2% and 5.7% for 100 mg and 300 mg CANA, respectively). Body composition investigations indicated that the body weight reduction with CANA was attributable to a greater decrease in body fat mass relative to lean body mass (with approximately 2/3 as fat mass loss). The weight loss can be explained by the CANA-induced renal nutrient loss. Fluid loss appears to play only a minor role.

Across all phase III studies clinically relevant lowering of SBP and DBP was observed, which is considered a beneficial additional effect of CANA in the frequently hypertensive patients with T2DM. This is addressed by appropriate labelling.

CANA itself has low propensity to cause hypoglycaemia. This was especially evident in comparison to glimepiride (hypoglycaemia incidence 3.1 vs. 1.9 vs. 12.7% in the CANA 100 mg, CANA 300 mg and glimepiride, respectively).

CANA has also been shown to be efficacious in elderly patients, who were adequately represented in the study program.

Uncertainty in the knowledge about the beneficial effects

By decreasing serum glucose levels through renal glucose elimination, CANA lowers endogenous insulin requirements thereby decreasing the burden on beta cells and potentially slowing exhaustion of beta cells/diabetes progression.

Risks

Unfavourable effects

According to its mechanism of action, CANA leads to dose- and blood glucose-dependent osmotic diuresis with increased urine volume and glucosuria. Resulting adverse events observed in the clinical trials are genital infection, haemoconcentration/dehydration, electrolyte disturbances and arterial hypotension. These are established AEs for SGLT2 inhibitors. In line with the observed haemoconcentration increases in serum creatinine and, consequently, decreases in calculated eGFR are observed upon treatment initiation, which are in general attenuated with continued treatment and reversible after cessation of treatment and do not indicate renal damage.

Older patients and patients with relevant impairment of their renal function appear more vulnerable to the effects of CANA on water and electrolyte balance, resulting in more frequent dehydration-related AEs, especially at the 300 mg dose.

The risk of dehydration is markedly increased in patients concomitantly taking loop diuretics. Therefore, this combination is not recommended. A potential canagliflozin-induced drop in blood pressure could pose a risk in patients with known cardiovascular disease, patients on antihypertensive therapy with a history of hypotension, elderly patients or patients with (intercurrent) conditions that may lead to volume depletion. As a precautionary measure, a

starting dose of 100 mg is recommended for all patients. In case of concomitantly taken antihypertensive agents, dose adjustments may be necessary.

Genital infections, mainly fungal infections, are clearly increased with CANA use, especially in females. There was only a slight increase in UTIs and no imbalance in serious/severe urogenital infections.

Similar to other glucose-lowering agents that have low hypoglycaemic potential themselves, CANA increases the frequency of hypoglycaemic events when given in combination with insulin or an insulin secretagogue. Even then, however, severe hypoglycaemic events were rare and of similar frequency as observed with placebo.

Uncertainty in the knowledge about the unfavourable effects

CV safety of CANA has been reasonably well established (MACE events in the meta-analysis including all patients from the phase II/III trials: HR 0.98, upper limit of the 95%CI 1.37). However, there was a concern that haemodynamic changes as induced by CANA, especially upon treatment initiation, could be less well tolerated in patients with pre-existing CV disease. An additional meta-analysis including all patients with increased CV risk (i.e. meeting the CANVAS inclusion criteria) was provided showing that the HR (CANA vs. non-CANA group) did not exceed 1 with an acceptable upper limit of the 95% CI of around 1.4 for MACE and MACE-plus, which is reassuring. Final data from the ongoing CV outcome study will be submitted post-authorisation.

There was a small, questionable increase in bone fractures, starting rather soon after commencement of CANA treatment. Measurements of BMD (52-week data), bone markers, urinary calcium and PTH do not indicate urinary calcium loss or an otherwise detrimental effect of CANA on bone. Based on the information obtained, the small excess rate of fractures could be due to a higher frequency of falls related to CANA-induced decrease in blood pressure.

Benefit-risk balance

Importance of favourable and unfavourable effects

Favourable effects

The most important effect of an antihyperglycaemic agent is its ability to improve glycaemic control. CANA, at the proposed dose of 100 mg and 300 mg has clearly been shown to effectively lower HbA1c when given alone or in combination with various AHAs including insulin with the effect being similar or even superior to that of glimepiride and sitagliptin. The effect of CANA appears to be maintained based on week 52 data in studies DIA 3006, 3002, 3005, 3004, 3009 and 3015. However, due to its dependency on renal function, the effect is only clinically relevant in patients with eGFR values ≥ 45 ml/min/1.73 m^2.

The reduction in body weight is an additional benefit in the usually obese patients with T2DM. The majority of the weight loss appears to be due to loss of fat mass including visceral fat and is sustained over time. CANA was superior in reducing body weight as compared to glimepiride and sitagliptin.

CANA appears to reduce insulin requirements by reducing glucose load. This is considered favourable since insulin-induced weight gain is alleviated. In addition, the reduced burden on

beta cells may have long-term benefits with regard to beta-cell function/diabetes progression, which would, however, need to be further investigated and confirmed.

The observed reduction in blood pressure is beneficial in the frequently hypertensive patients with T2DM as it may, together with weight loss, contribute to a reduction in CV risk.

The low propensity of CANA to cause hypoglycaemia is considered a beneficial effect which may be particularly relevant in patients at increased risk of hypoglycaemia.

Unfavourable effects

The most important risk of CANA is dehydration and its potential sequelae in vulnerable patients. Since dehydration is not usually expected for a glucose-lowering agent, this has been appropriately labelled.

The small excess rate in bone fractures are unlikely to reflect direct effects of CANA on bone but a causal relationship with CANA-induced drop in blood pressure cannot be excluded. As a precautionary measure, a starting dose of 100 mg/day is recommended in all patients.

Efficacy and tolerability decrease with decreasing renal function. Therefore, patients with a certain degree of renal impairment (eGFR below 45 mL/min/1.73m2) should no longer receive CANA.

Genital infections were usually not serious and were manageable. Thus, genital infections, although frequent and unpleasant, are no important risk. The same is true for urinary tract infections, the frequencies of which were nearly balanced between CANA and comparator.

Benefit-risk balance

CANA could be a valuable asset to the already existing treatment options for T2DM. The overall treatment effect is clinically relevant and can be achieved in monotherapy or in combination with other antihyperglycaemic agents of different product classes including insulin. Adverse events are in most cases a consequence of the pharmacologic action of CANA and appear in general manageable in the overall patient population.

However, due to the mechanism of action of CANA, its efficacy declines with decreasing renal function. Due to decreasing efficacy and tolerability (especially regarding water and electrolyte imbalance) in patients with profound renal impairment, the benefit/risk balance of CANA is considered unfavourable in patients with a GFR < 45 mL/min/1.73m^2. In patients with eGFR ≥45 and <60 ml/min/1.73m^2 the benefit is modest but still clinically relevant and similar for the 100 and 300 mg dose (placebo-adjusted HbA1c reduction of approx. 0.5%). However, with 300 mg there is also a clearly increased reporting of adverse events related to water and electrolyte imbalance compared to comparator. In contrast, with 100 mg, the AE incidence is close to comparator level so that use of this dose in patients who are already on well-tolerated CANA therapy and whose eGFR drops below 60 mL/min/1.73 m2 appears be justified as long as eGFR remains above 45 mL/7min/1.73m^2.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Invokana in the treatment of:

adults aged 18 years and older 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 glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that canagliflozin is qualified as a new active substance.