20 February 2014
EMA/179391/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vokanamet

International non-proprietary name: CANAGLIFLOZIN / METFORMIN

Procedure No. EMEA/H/C/002656/0000

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:	Vokanamet
Applicant:	Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse BELGIUM
Active substance:	CANAGLIFLOZIN / METFORMIN HYDROCHLORIDE
International Nonproprietary Name/Common Name:	CANAGLIFLOZIN / METFORMIN
Pharmaco-therapeutic group (ATC Code):	A10BD16
Therapeutic indication(s):	Canagliflozin/Metformin is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control: • in patients not adequately controlled on their maximally tolerated doses of metformin alone or those who are being treated with co-administered canagliflozin and metformin • as add on therapy in patients on their maximally tolerated doses of metformin along with other anti-hyperglycaemic 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:	50 mg / 1000 mg, 50 mg / 850 mg, 150 mg / 850 mg and 150 mg / 1000 mg
Route of administration:	Oral use
Packaging:	bottle (HDPE)
Package sizes:	20 tablets, 60 tablets and 180 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	antihyperglycemic 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	Canagliflozin
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 II
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 Glycemic 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
MET	Metformin
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
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 4 March 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Vokanamet, 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 Canagliflozin/Metformin is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control:

- in patients not adequately controlled on their maximally tolerated doses of metformin alone or those who are being treated with co-administered canagliflozin and metformin
- as add on therapy in patients on their maximally tolerated doses of metformin along with other anti-hyperglycaemic 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).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that canagliflozin was considered to be a new active substance.

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/138/2011 on the granting of a (product-specific) waiver.

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 was not a constituent of a product previously authorised within the Union at the time of submission of the application.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 March 2009, 22 October 2009 and 21 October 2010. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

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 SpA
Via C. Janssen
Borgo San Michele
04100 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: Karsten Bruins Slot

- The application was received by the EMA on 4 March 2013.
- The procedure started on 27 March 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 June 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2013.
- During the meeting on 25 July 2013, 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 26 July 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 October 2013.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 November 2013.
- During the CHMP meeting on 19 December 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 January 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 January 2014.
- During the meeting on 20 February 2014, 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 Vokanamet.

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 glycemic control, requiring combinations of agents, and often eventually insulin therapy. Underlying this progressive deterioration in glycemic 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 50 mg/850 mg, 50 mg/1000 mg, 150 mg/850 mg, and 150 mg/1000 mg of canagliflozin and metformin hydrochloride as active substances. The film coated tablets are capsule-shaped and can be differentiated by their colour and embossing.

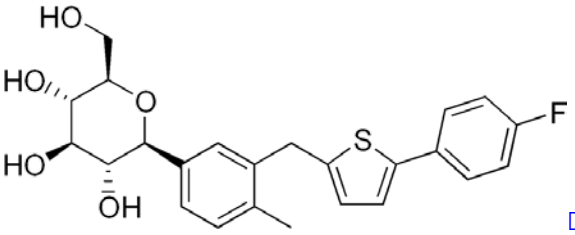
Other ingredients are: microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, iron oxide yellow (50 mg/1000 mg and 150 mg/850 mg tablets), iron oxide red (50 mg/850 mg, 50 mg/1000 mg and 150 mg/1000 mg tablets) and iron oxide black (150 mg/1000 mg and 50 mg/850 mg tablets).

The primary packaging is HDPE bottle with child-resistant closure, induction seal and desiccant.

2.2.2. Active Substances

Canagliflozin

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:



□. ½ H_2O

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 on the performance *in vivo*.

Canagliflozin (INN) 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, which is a hemihydrate, and an unstable amorphous Form II. Form I is consistently produced by the proposed commercial synthesis process.

Manufacture

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

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), assay (HPLC), impurities (HPLC, LCMS, LC), 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. Non-compendial methods have been appropriately validated in accordance with the ICH guidelines.

Stability

Stability data were provided on six commercial scale batches of active substance from the proposed manufacturer stored for 24 months under long term conditions at 25°C/60% RH 'for 9 months at 30°C /75% RH and up to 6 months under accelerated conditions at 40°C/75% RH according to the ICH guidelines in the intended container closure system representative of that intended for the market.

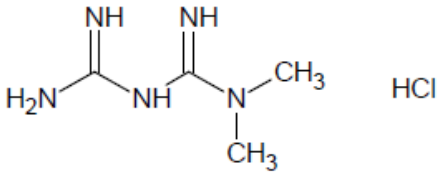
Photostability testing following the ICH guideline Q1B was performed. Results on stress conditions (including high temperature, acid, alkaline, oxidising) were also provided. The active substance is stable at high temperature and humidity and degrades moderately under basic and peroxide conditions. Canagliflozin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

Metformin hydrochloride

The chemical name of metformin hydrochloride is 1,1-Dimetylbiguanidine hydrochloride and has the following structure:



Metformin hydrochloride is a white, solid, crystalline powder. It is slighly hygroscopic, soluble in water and practically insoluble in acetone. Also metformin hydrochloride is very poorly permeable to biological membranes, this being a rate limiting step in its absorption being considered a BCS Class 3 high-solubility low-permeability drug.

Particle size does not considerably influence dissolution or bioavailability.

Metformin hydrochloride is a monographed substance in the European Pharmacopoeia. A certificate of Suitability has been granted to the manufacturer of metformin hydrochloride ensuring the manufacturing is in correspondence with the requirements of Ph. Eur

Manufacture

The steps, description of manufacturing process and in- process controls, characterisation and additional test on residual solvents, control of material, control of critical steps and intermediates, process validation and manufacturing process development are covered by the CEP.

Metformin is manufactured in one manufacturing site. The relevant information on the manufacture was assessed by the EDQM before issuing the CEP.

Specification

The active substance specification includes tests for appearance (visual examination), appearance of solution (Ph. Eur), identity (Ph. Eur.), assay (Ph. Eur.), purity (HPLC), residual solvents (GC), loss on drying (Ph. Eur), residue on ignition (Ph. Eur.) and heavy metals (Ph. Eur.).
Part of the CEP is an additional specification fixed for the determination of residual solvents. The additional GC method for determination of residual solvents is part of the CEP.The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph

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

Stability

The stability of metformin hydrochloride is fully controlled by the CEP and it shows that the active substance manufactured by the proposed supplier is sufficiently stable and the proposed retest period in the proposed container is justified.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The goal of the pharmaceutical development was to design a combination tablet of two oral antidiabetics with the minimum possible size and to be bioequivalent to commercial products containing the commercial active substances.

The canagliflozin / metformin hydrochloride film-coated tablets are capsule-shaped immediate release tablets containing a fixed dose combination of canagliflozin and metformin hydrochloride in four different strengths each containing 50 or 150 mg canagliflozin, and 850 or 1000 mg metformin hydrochloride, respectively.

Based on low solubility and low permeability, canagliflozin is classified as a BCS 4 compound and metformin hydrochloride is considered as a BCS Class 3 high-solubility low-permeability drug. The membrane permeability of metformin hydrochloride rather than dissolution is the rate-

limiting step in its absorption. Therefore, the influence of the active substances particle size distribution and granulation process conditions on the characteristics of the canagliflozin granules were extensively investigated during the pharmaceutical development and were founded to have no effect on the dissolution profile of the final pharmaceutical form.

During the pharmaceutical development different aspects of the manufacturing process were investigated. Fluid bed granulation was chosen over high shear granulation to meet the preferred wet granulation manufacturing platform due to the high drug load. Also during characterization, batches were produced at wet, dry, and target conditions to evaluate the influence of the granulation process parameters on the granules and on the final drug product. The blending process development was conducted to optimize the blending time for initial and final blending toward blend uniformity and proper tablet lubrication.

The granulation process development of canagliflozin granules and metformin hydrochloride granules was conducted to optimize the spray rate, air temperature, air flow ranges and drying end point toward appropriate granule characteristics were optimized during the pharmaceutical development in order to deliver a tablet with suitable characteristics. These process parameters were selected since they can potentially impact the critical quality attributes of the drug product.

The manufacturing principles and processing steps are the same for all the strengths of the finished product. The manufacturing steps at development and commercial scale are essentially the same. Two minor modifications were made to the commercial process, the type of equipment used for screening metformin hydrochloride (rotating impeller mill instead of vibratory sifter) and the temperature of the water used during preparation of the binder(on development scale, hypromellose is dispersed in hot water (>60 °C)) .These differences have no critical impact on the process.

A compatibility study was carried out between the proposed excipients with the drug substances in the core tablets.

Extragranular microcrystalline cellulose was included to improve the compressibility and tablet properties of the formulation like hardness and friability without affecting disintegration time.

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 quality target product profile (QTPP) was defined as an immediate release dosage form with the minimum possible size that meets compendial specifications on an oral tablet.

The critical quality attributes identified were potency, appearance, assay, chromatographic purity, uniformity of dosage units, tablet hardness, dissolution, disintegration and friability.

The formulation used during clinical studies is the same that the used for marketing

Bioequivalence study was performed showing bioequivalence between the clinical formulation and the proposed commercial formulation

The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is HDPE bottle with child-resistant closure, induction seal and desiccant.

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

No excipients derived from animal or human origin have been used.

Manufacture of the product

The finished product is manufactured using conventional wet granulation, blending, compression, and film-coating processes.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for the manufacture of an immediate release tablet.

Proven acceptable ranges (PARs) have been defined for the following steps of the medicinal product: granulation of each of the drug substances, blending, compression and film-coating. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

The dissolution methods have been proven to be discriminating.

Product specification

The finished product (release) specifications contain appropriate tests for this kind of dosage form including appearance (visual examination),dimension (calibrated caliper), identification (IR),assay (UPLC), chromatographic purity (UPLC), dissolution (HPLC) uniformity of dosage units (Ph. Eur.), water content (KF) and microbiological purity (Ph. Eur.).

Batch analysis results are provided for a number of clinical, development and production batches of all different strengths confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on three production scale batches of each tablet strength stored under long term conditions for up to 12 months at real time conditions 25 ºC / 60% RH and intermediate conditions at 30 ºC / 75% RH were presented. Six months of data under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of Vokanamet are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for content for active substances, appearance, water content impurities, dissolution and microbiological purity. The analytical procedures used are stability indicating.

In addition, the same batches were exposed to light as defined in the ICH Guideline on photostability testing of new drug substances and products and also were put under stress conditions at 50 ºC.

Based on available stability data, the shelf-life and 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.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

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.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

The assessment of the combination of canagliflozin/metformin in this report is mainly based on up to date data of canagliflozin. All responses provided during the assessment of the canagliflozin single agent were made part of the CANA/MET dossier. The assessment of metformin is based on a mix of literature and relevant studies. Metformin is regarded a well-known substance. No new studies for the combination have been provided by the Applicant.

2.3.2. Pharmacology

Canagliflozin

Canagliflozin is an inhibitor of SGLT2. SGLT2 is expressed in the proximal renal tubule predominantly in the kidney cortex, specifically in the S1 segment of the proximal tubule where it reabsorbs the majority of glucose filtered by the glomerulus. It transports sodium (Na) and glucose in a 1:1 ratio, functioning as a low–affinity high-capacity transporter. Inhibition of SGLT2 results in increased urinary glucose excretion (UGE) due to reduced glucose reabsorption. As a consequence plasma glucose levels are lowered resulting in loss of calories and anti-hyperglycaemic effects beneficial for patients with type 2 diabetes mellitus (T2DM).

Primary and secondary pharmacodynamics (PD) of canagliflozin were studied in cell-based *in vitro* assays and in several *in vivo* models of mice, rats and dogs.

Canagliflozin inhibited rat and human SGLT2 overexpressed in Chinese hamster ovary cells (CHOK1) cells as measured by inhibition of alpha-methylglycopyranoside (AMG) uptake with an IC_{50} of 3.7 nM for rSGLT2 and 4.2 nM hSGLT2, respectively. The inhibition of SGLT1 in the same cell system was more than 150-times lower, with an IC_{50} of 550 nM for rSGLT1 and 663 nM for hSGLT1, respectively. Functional activity of canagliflozin on SGLT2 and SGLT1 of other species was not determined.

Off target effects on other human glucose transporters such as SGLT3, SGLT4, SGLT6, facilative glucose transporters (GLUTs) or sodium/myo-inositol co-transporter-1 (hSMIT1) were also studied in various cell models. No relevant inhibition of these transporters by canagliflozin was detected.

Binding parameters (association and dissociation rates of canagliflozin, equilibrium constant - Kd) were determined on membranes from Madin-Darby canine kidney (MDCKII) cells overexpressing hSGLT2 in equilibrium saturation binding assays in the absence or presence of physiological levels of glucose. Canagliflozin showed relatively fast association kinetics and relatively slow dissociation kinetics with a Kd of 16.82 nM in the presence of glucose and 15.29 nM in the absence of glucose. Binding parameters on hSGLT1 and SGLT2 of other species were not determined. Washout studies demonstrated a high affinity of canagliflozin on hSGLT2 with reversibility over time.

In vivo primary PD after a single dose of canagliflozin was determined in non-diabetic and diabetic mice (*db/db* mice), non-diabetic and diabetic fatty rats (ZDF, *fa/fa* rats) and obese dogs. Primary PD parameters measured were urine glucose excretion (UGE), blood glucose during oral glucose tolerance test (OGTT), fed blood glucose and glucose renal reabsorption. The following table summarizes performed *in vivo* PD studies with canagliflozin.

Taken together, canagliflozin showed an increase in UGE, lowering in blood glucose levels after an OGTT or under fed conditions and inhibition of renal glucose reabsorption in all animal models tested. The effective dose was between 0.3 and 10 mg/kg.

Secondary PD studies in *db/db* and diet-induced obese (DIO) mice and SD and *fa/fa* 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).

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).

Metformin

The efficacy of metformin is believed to be mediated primarily *via* inhibition of hepatic glucose production.

Metformin is a well-established treatment for Type 2 diabetes and therefore, no preclinical pharmacology and safety pharmacology studies have been performed with metformin by the Applicant.

Canagliflozin / metformin

No preclinical pharmacodynamics, safety pharmacology, and pharmacodynamic drug interaction studies have been performed with the canagliflozin/metformin combination. This approach is endorsed by the CHMP. Canagliflozin and metformin act through different mechanisms of action. Adverse pharmacodynamic interactions between canagliflozin and metformin are not expected. Furthermore, there is sufficient experience from clinical trials with treatment of patients with the combination of canagliflozin/metformin.

2.3.3. Pharmacokinetics

No pharmacokinetic (PK) studies with metformin and the canagliflozin/metformin combination have been performed by the Applicant. Data on canagliflozin are based on assessment reports of canagliflozin, data on metformin are based on literature reviews.

Canagliflozin

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 (refer to section “Phototoxicity”).

Metabolism and Excretion

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 (for an overview of important canagliflozin metabolites in different species, refer to the table below). *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.

Plasma, urine and faecal metabolites after single dose administration of ^{14}C-canagliflozin in mouse (100 mg/kg, rat (3 mg/kg), dog (4 mg/kg, and human (192 mg); data from studies FK6592, FK6169, FK6183, FK6419.

	Mouse, Swiss CD-1 (FK6592)						Rat, Sprague-Dawley (FK6169)						Dog, Beagle (FK6183)			Human (FK6419)						
	Plasma 0-24h		Urine 0-48h		Feces 0-48h		Plasma 0-24h		Urine 0-48h		Feces 0-48h		Plasma 0-24h	Urine 0-48h	Feces 0-72h	Plasma					Urine 0-48h	Feces 0-48h
																1.5h	4h	8h	12h	24h		
	M	F	M	F	M	F	M	F	M	F	M	F	M	M	M	M	M	M	M	M	M	M
UD	94.2	93.9	0.25	0.2	32.5	10.1	97.7	96.5	--	0.20	3.50	5.30	96.9	0.25	11.1	62.7	47.1	45.4	65.8	98.7	--	41.5
M1	--	--	0.7	0.14	--	--	--	--	--	--	5.50	18.0	--	--	--	--	--	--	--	--	--	--
M2	--	--	0.3	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
M4	--	--	--	0.4	2.7	9.3	--	--	--	--	--	--	--	0.40	11.2	--	--	--	--	--	--	--
M5	--	--	--	0.1	0.8	2.4	--	--	--	--	--	--	--	--	--	18.6	29.6	24.1	1.89	--	13.3	--
M6	--	--	--	--	1.8	3.7	--	--	0.94	0.40	10.1	7.90	--	--	--	--	--	--	--	--	--	--
M7	2.6	1.6	1.25	1.1	6.4	14.0	--	--	--	--			--	--	7.13	16.0	18.3	24.7	28.8	--	17.2	3.2
M8	--	--	0.24	1.0	13.6	17.3	--	--	2.70	4.10	51.9	58.8	--	0.81	41.8	--	--	--	--	--	--	--
M9	1.6	2.2	2.3	3.3	27.6	29.0	--	--	0.40	0.60	17.6	2.10	--	0.51	22.5	2.42	3.70	2.58	2.83	--	--	7.0
M10	--	--	--	--	--	--	--	--	--	--	2.60	1.40	--	--	--	--	--	--	--	--	--	--

Values are expressed as % of total sample radioactivity; -- = not detected; F = Female; M = Male; UD = unchanged drug

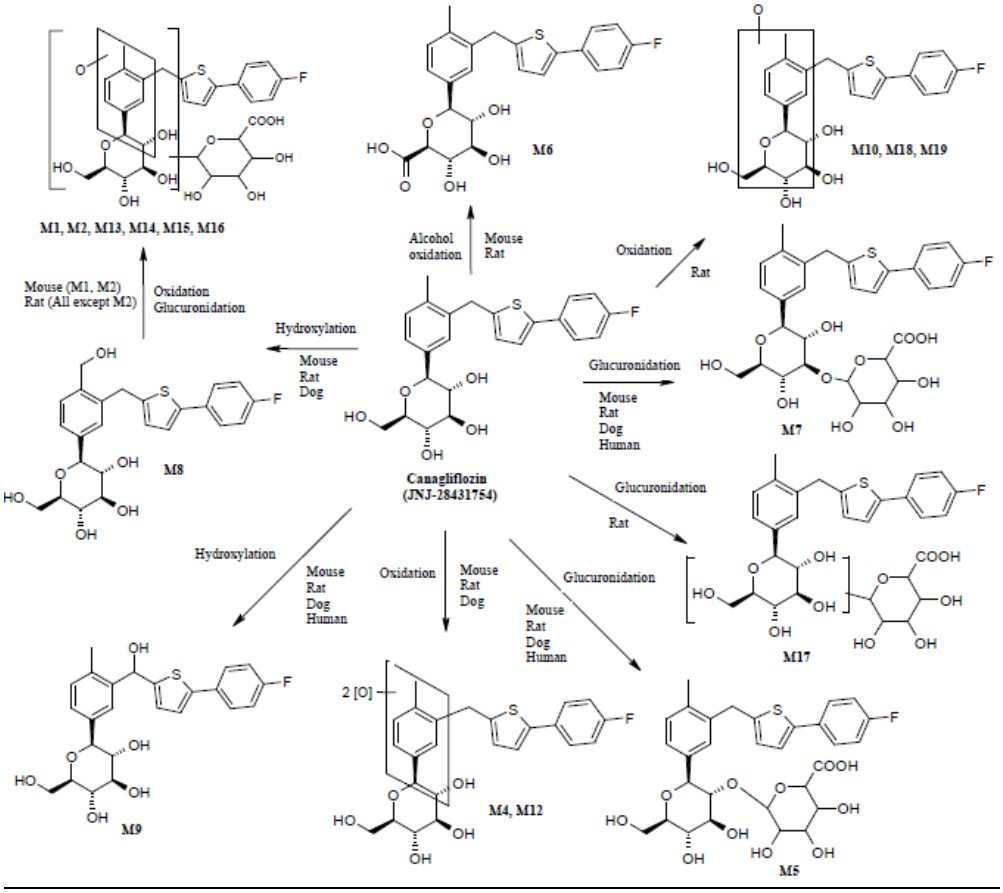
About 60% of the administered dose was excreted in human faeces and about 90% to 94% were excreted in animal (mouse, rat, and dog) faeces. About 33% of the administered dose was recovered in human urine, and in animals about 2% to 7% was recovered in urine. Biliary excretion was furthermore tested in mice and rats. The table below summarizes the routes of excretion in mice, rats, dogs and humans.

Routes of excretion of ^{14}C-canagliflozin after a single oral dose.

Species	N	Dose (mg/kg)	Sex	Urine (% dose)	Faeces (% dose)	Bile (% dose)	Recovery (% dose)	Time (h)
mice (FK6538, FK7062)	4	100	M	6	92	49 (24 h)	97.8	96
	4	100	F	6	92	NA	98.3	96
rats (FK6169, FK7526)	4	3	M	4	93	48-52 (24h)	96.9	120
	4	3	F	5	93	NA	98.4	120
dogs (FK6183)	3	4	M	2	94	NA	99.1	144
humans (FK6410)	6	192 mg	M	33	60	NA	92.9	168

Bile was collected in separate studies for 24 hours in male 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, see figure below.



Proposed *in vivo* metabolic pathways for canagliflozin in mice, rats, dogs, and humans (taken from Non-clinical overview, 2.4).

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.

Metformin

Oral and intravenous PKI in rats was dose-proportional. Oral bioavailability in rats was 29 – 34%. *In vitro* studies indicate that transepithelial transfer of metformin in the intestine is at least partly by passive permeation.

After oral administration of [^{14}C]metformin to normal and diabetic mice, the highest concentrations of radioactivity were found in the small intestine, stomach, colon, salivary gland, kidney and liver. The mean binding value of metformin to rat plasma protein was 15%. The

equilibrium plasma-to-blood cells partition ratios of metformin in rat plasma were 1.37, 1.25, and 1.33 at initial blood concentrations of 1, 5, and 20 mg/mL, respectively.

Metformin was the major radioactive component in plasma and urine from mice, rats, dogs and humans dosed with [^{14}C]metformin. A metabolite, 1-methyl biguanide, was identified in rabbit plasma and urine. Studies with various inducers and inhibitors of cytochrome P450 enzymes indicated that metformin was metabolized *via* CYP2C11, 2D1, and 3A1/2 in rats.

Metformin was excreted primarily in urine in rats and dogs. The estimated renal clearance value of metformin was considerably faster than the reported glomerular filtration rate in rats, indicating that unlike canagliflozin, metformin is subject to active renal secretion in rat renal tubules. Additionally, unlike canagliflozin metformin has been shown to be a substrate of the cationic organic transporters hOCT1 and hOCT2 and for the multidrug and toxin extrusion (MATE)-type transporter 1 (MATE1, involved in renal elimination of metformin), but not hOAT1, hOAT3 or hOCT2-A.

Canagliflozin / Metformin

No PK studies with the combination of canagliflozin/metformin have been conducted, this is agreed since toxicokinetic studies with the combination have been performed (see toxicity section for details) and sufficient clinical data are available. Interactions between canagliflozin and metformin based on cytochrome P450 metabolism are not likely since neither substance is metabolised by CYPs to a great extent nor induce or inhibit them. Furthermore, canagliflozin is secreted mainly *via* the faecal route while metformin is secreted *via* active renal secretion. Therefore, no interaction is expected following their co-administration. However, toxicokinetic results from repeat-dose and reproductive toxicity studies in rats have demonstrated increased AUC levels of metformin (up to 1.8-fold) when combined with canagliflozin at doses as low as 10 mg/kg/day (~1.5-fold the human exposure after 300 mg canagliflozin). While canagliflozin, M5 and M7 were not considered as substrates for OCT1 and OCT2, no information is provided regarding MATE1.

2.3.4. Toxicology

The combination canagliflozin and metformin has been studied in repeat-dose and developmental toxicity studies in rats. Data on canagliflozin are based on assessment reports of canagliflozin including studies on a hydroperoxide degradation product of canagliflozin, which was found during the development of the canagliflozin/metformin HCl film-coated tablet. Data on metformin are based on a review provided by the Applicant.

The following table gives an overview of studies performed with the combination of canagliflozin/metformin.

Studies with canagliflozin / metformin

Study / Study ID	Species / Study duration	Test substance	Oral Dose (mg/kg/day)	GLP
Studies with canagliflozin / metformin				
Repeat dose toxicity / TOX9582	Rat / 1 month	Canagliflozin/metformin	0, 4/300, 20/300, 100/300, 100/0, 0/300	No

Repeat dose toxicity / TOX9667	Rat / 3 month	Canagliflozin/metformin	0, 4/300, 20/300, 100/300, 100/0, 0/300	Yes
Developmental toxicity / TOX9521	Rat / GD6-17	Canagliflozin/metformin	0, 10/300, 30/300, 60/300, 60/0, 0/300	No
Developmental toxicity / TOX9590	Rat / GD6-17	Canagliflozin/metformin	0, 10/300, 30/300, 60/300, 60/0, 0/300	Yes

Single dose toxicity

Canagliflozin

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 studies were performed in mice, rats, rabbits, and dogs. The following table summarizes the findings of the performed pivotal repeat-dose toxicity studies.

Overview of pivotal repeat-dose toxicity studies with canagliflozin or the combination of canagliflozin with metformin as oral gavage in mice, rats, and dogs.

Study ID	Species/ Sex/ Number/ Group	Dose	Duration	NOAEL (mg/kg/ day)	Major findings
TOX 8262	CD-1 mice 10/sex/group	0, 30, 100, 300	3 month	100	Mortality: 300 mg/kg/day All doses/sexes: ↑food consumption beginning in Week 1 or 2 until study end; ≥30 mg/kg/day: ↑body weight gain starting from Week 1 (F) ≥100 mg/kg/day: ↑serum triglycerides (M), ↓RBC (M), ↑HGB (M), ↑HCT (M); ↑liver weight (M) 300 mg/kg/day: ↑body weight (F), soft/decreased faeces (M/F), wet urogenital region (M), abdominal distension (M/F); ↑serum UreaN (M/F), ↓total protein (M/F), ↓albumin (M/F), ↑ALT (F); ↑liver weights (F), ↑kidney weights (F); ↓heart weight (F), ↓lung weight (F), ↓brain weight (F); distended cecum (3/10 M and 5/10 F); ↑glycogen accumulation in hepatocytes (8/10 M and 9/10 F)

TOX8150	SD rats 10/sex/group plus 5/sex/group for recovery	0, 4, 20, 100	3 month + 8 week recovery	4 (M), 20 (F)	No compound-related mortalities. <u>All doses/sexes:</u> ↑food consumption; ↑urine volume, ↑specific gravity (except males at 100 mg/kg/day), ↑urinary GGT, ↑GGT/creatinine, ↑Ca excreted (mg/16h), ↑Ca/creatinine, ↑glucose, ↑glucose/creatinine; kidney weight↑; mineralization of renal interstitium; acute erosions of the glandular stomach. <u>≥4 mg/kg/day:</u> ↑serum ALT (M), AST↑(M), ↓glucose (M), ↑UreaN (M); ↑urinary ketones (M); hyperostosis in stifle (F) <u>≥20 mg/kg/day:</u> ↓body weight (F), ↓body weight gain (F); ↑serum ALT (F), ↑AST (F), ↓glucose (F), ↑UreaN (F), ↓1,25-dihydroxyvitamin D (M), ↓osteocalcin (M/F); ↑urinary P (M/F), ↑P/creatinine (M/F), ↑NAG, ↑NAG/creatinine (M), ↓urine pH (M/F), ↑total protein (F); mineralization of the renal pelvis (F), hyperostosis in stifle and sternum (M/F); ↑haematopoietic cells in the bone marrow (femur and tibia) (M) <u>100 mg/kg/day:</u> ↑serum triglycerides (M/F), ↓1,25-dihydroxyvitamin D (F), ↓25-hydroxyvitamin D, ↓PTH (M/F); ↓RBC (M), ↑RBC (F), ↑reticulocytes (M), ↑HGB (F), ↑HCT (F); ↑urinary ketones (F), ↑NAG, ↑NAG/creatinine (F), ↑total protein (M), ↓deoxypyridinoline/creatinine (M/F); increase in trabecular bone volume (M/F); ↑haematopoietic cells in the bone marrow (femur and tibia) (F/M), no recovery after 8-weeks.

TOX8574	SD rats 20/sex/group TK: 6/sex/group	0, 4, 20, 100	6 month	4	No compound-related mortalities. <u>All doses/sexes:</u> polydypsia, ↑food consumption, ↓body weight gain; ↓serum glucose, ↑UreaN, ↑ALP; ↑urine volume, ↑specific gravity, urinary Ca and Ca/creatinine↑, P and P/creatinine↑, ↑glucose, ↑glucose/creatinine; ↑kidney weight, tubular dilatation with cellular debris; trabecular hyperostosis femur/tibia, acute erosions of the glandular stomach. <u>≥4 mg/kg/day:</u> ↑serum ALT (M), ↑AST (M), ↓total billirubin (M), ↓total protein (F), ↓albumin (F), ↓Ca (F), ↓calcitonin (M), ↓osteocalcin (F); ↓urinary pH (M) <u>≥20 mg/kg/day:</u> ↓serum Cl (M), ↓Ca (M), ↓total billirubin (F), ↓creatinine (F), ↑triglycerides (F), ↓1,25-dihydroxyvitamin D (M), ↓PTH (F), ↓osteocalcin (M), ↓C-telopeptide (M); ↓RBC (F), ↓eosinophiles (M/F), ↓total white blood cells (M), ↓lymphocytes (M), ↓monocytes (M); ↓urinary ketones (M); swollen kidney (M), ↑adrenal gland weight (M), ↑liver weight (F); trabecular hyperostosis sternum (M/F); bone area↓(M) <u>100 mg/kg/day:</u> serum ↑cholesterol (M), ↑triglycerides (M), ↑albumin (M), ↓1,25-dihydroxyvitamin D (F), ↓25-hydroxyvitamin D (M/F); ↓RBC (M), ↓total white blood cells (F), ↓lymphocytes (F); ↓urinary ketones (F), ↓creatinine (M/F), ↓urinary pH (non-fasted) (M/F), ↓urinary deoxypyridinoline/creatinine (M/F); renal transitional hyperplasia (M/F), swollen kidney (F), swollen adrenal glands (M/F), ↑adrenal gland weight (F), ↑liver weight (M), ↓thymus weight (M/F), small thymus/atrophy, dilatation and distension of ureters (M/F); ↓bone area (F), ↑BMD (M), ↓extrinsic bone strength (M/F), ↑trabecular bone volume (M)

TOX9667	SD rats 10/sex/group TK: 3/sex/group	canagliflozin/metformin 0, 4/300, 20/300, 100/300, 100/0, 0/300	3 month		No compound-related mortalities. <u>All doses/sexes:</u> ↑food consumption; ↓serum glucose; ↑urinary Ca/creatinine, ↑Cl/creatinine, ↑P/creatinine, ↑Mg/creatinine, ↑glucose, ↑glucose/creatinine, ↑specific gravity; ↑kidney weight <u>≥4/300 mg/kg/day:</u> ↑serum triglycerides (F); ↓urinary pH (F); ↑urinary Na/creatinine (F), ↑K/creatinine (M), ↑Mg/creatinine (M), ↑total protein/creatinine (F); tubular dilatation (M), hyperostosis (F) <u>≥20/300 mg/kg/day:</u> ↑serum triglycerides (M), ↑UreaN (M/F), ↓ creatinine (F), ↓total billirubin (F), ↑P (M); ↓urinary pH (M), ↑urine volume (M/F), ↑urinary Na/creatinine (M), ↑K/creatinine (F), ↑Mg/creatinine (F), ↑total protein/creatinine (M), ↑ketones (M/F); ↑liver weight (M); tubular dilatation (F), hyperostosis (M) <u>100/300 mg/kg/day:</u> ↓body weight (gain), soft faeces (M); serum ↑ALP (M), ↓total protein (M); ↓PTT (M), ↑mean cell volume (M/F), ↓mean cell haemoglobin (M/F), ↑reticulocytes (M), ↓thrombocytes (M); ↑adrenal gland weight (F), not under canagliflozin alone, ↑liver weight (F); hypereosinophilia in liver (M/F)
TOX8214	Beagle dogs 3/sex/group	0, 4, 30, 200/100	3 month + 4 week recovery	30	No compound-related mortalities. Due to poor conditions, the dose of 200 mg/kg/day was reduced to 100 mg/kg/day at day 8 (F) 9 (M). <u>All doses/sexes:</u> mucoid faeces, emesis, excessive salivation <u>≥4 mg/kg/day:</u> ↓serum glucose (F); ↑urine volume (M/F), urinary ↑glucose (M/F), ↑glucose/creatinine (M/F), ↑Ca (M/F), ↑Ca/creatinine (M/F), ↑GGT (M/F), ↑GGT/creatinine (M/F), ↑NAG (M), ↑Na (F) <u>≥30 mg/kg/day:</u> ↓serum glucose (M); ↑white blood cells (F), ↑neutrophils (F), ↑fibrinogen (F); ↑urinary Cl (F), ↑P (F) <u>200/100 mg/kg/day:</u> ↓body weight (F); ↑serum AST (F), ↑UreaN (F); ↑urinary protein/creatinine (F), ↑total protein (F), ↑Na/creatinine (F), ↑Cl/creatinine (F); ↑kidney weights (M/F), tubular regeneration/degeneration, tubular dilatation (M/F) <u>200 mg/kg/day before reduction of the dose to 100 mg/kg/day at day 8 (F) 9 (M):</u> ↓activity, dehydration, haemorrhagic faeces, ↓erythema, food consumption; ↑serum ALT (M), ↑ALP (M), ↑AST (M), ↑UreaN (M), ↑total billirubin (M); ↓RBC (F), ↓HGB (F), ↓HCT (F), reticulocytes↓ (M/F), ↑white blood cells (M/F), thrombocytes↓(M); ↓serum Ca (M/F), ↑creatinine (M/F)

TOX8446	Beagle dogs 4/sex/group	0, 4, 30, 100	1 year	100	No compound-related mortalities. All doses/sexes (-week 52): emesis, abnormal stool; ↑urine volume, ↑urinary glucose, ↑Na, ↑K, ↑Cl, ↑P, ↑Ca , ↑NAG, ↑GGT, ↓deoxypyridinoline/creatinine (week 17) ≥4 mg/kg/day (-week 52): ↓body weight (M), ↓body weight gain (M); ↓serum glucose (F), 1,25-dihydroxyvitamin D↓ (F, week 17); ↑pituitary gland weight (F); ↓BMD femur (M) ≥30 mg/kg/day (-week 52): serum 1,25-dihydroxyvitamin D↓(M); ↑urinary Na/creatinine (F), 100 mg/kg/day (-week 52): ↓serum Na (M/F), ↑ALP (F), ↑triglycerides (M/F); ↑bone specific ALP (F, week 17)

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMD = bone mineral density, Ca = calcium, Cl = chloride, F = female, GGT = gamma-glutamyltransferase, HCT = haematocrit, HGB = haemoglobin, K = potassium, M = male, Na = sodium, NAG = N-acety-D-glucosamidas, P = phosphorus, PTT = prothrombin time, RBC = red blood cell count, UreaN = urea nitrogen

Mice

In the 3-month, GLP, oral mouse toxicity study canagliflozin (0, 30, 100, 300 mg/kg/day) was well tolerated up to 100 mg/kg/day. At 300 mg/kg/day increases in kidney weights and mortalities were observed, therefore the NOAEL was set at 100 mg/kg/day what is in line with the NOEL observed in the carcinogenicity study in mice (see below). Safety margins at the NOAEL of 100 mg/kg/day of 40x and 10.9x for males and 49x and 13.2x for females, were calculated towards AUC exposure levels at the clinical dose of 100 mg and 300 mg (see table below).

Rats

In the 3- and 6-month, GLP, oral rat toxicity studies (0, 4, 20, 100 mg/kg/day canagliflozin) results were consistent between studies and can mainly 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). Increased kidney weights, tubular dilatation, and mineralization were observed already at lower doses. Transitional hyperplasia of the renal pelvis was observed at 100 mg/kg/day (6-month study). The transitional hyperplasia had no atypia and was considered not to be preneoplastic. In the rat the limiting toxicity was hyperostosis which was accompanied by decreases in serum concentrations of 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D, PTH, and calcitonin. Furthermore, decreases in markers of bone resorption (serum C-telopeptide and urinary deoxypyridinoline) and bone formation (serum osteocalcin) were observed suggesting a decrease in bone turnover. To further investigate these findings various mechanistic studies were performed (see below). Based on these findings the NOAEL for the pivotal 6-month rat study was set at 4 mg/kg/day. This corresponds to safety margins of 2.0x and 0.5x for males and 3.1x and 0.8x for females, with respect to human AUC exposure levels achieved with the therapeutic 100 mg and 300 mg doses, respectively (see table below).

The combination of canagliflozin and metformin was also tested in rats. No additional toxicities were observed in the combination groups up to the high dose of 100/300 mg/kg/day as compared to single administration of both compounds at the same doses. 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. Since increases intestinal calcium absorption was also regarded as the reason for the neoplastic findings in rat, various mechanistic studies have been provided by the Applicant to verify these hypotheses:

In a study to compare oral and s.c. dosing of canagliflozin to determine the site of action (gastrointestinal tract or systemic) for canagliflozin-mediated effects on hyperostosis and increased urinary calcium excretion, both routes of administration caused decreases in mean body weights and body weight gains. Urinalysis showed that, both routes of administration resulted in similarly elevated urinary calcium and phosphorus levels as well as similar increases in urine volume and excreted glucose. The Applicant explains that the effect of s.c. dosing on urinary calcium excretion and hyperostosis might be due to biliary excretion of glucuronidated canagliflozin and cleavage by glucuronidases in the gut leading to significant canagliflozin exposure to the gut lumen and subsequent increases of calcium absorption from the intestine, this is agreed.

To further show that calcium absorption is increased after canagliflozin treatment (as a result of carbohydrate malabsorption, see section “Carcinogenicity” below) a mechanistic study was conducted. Treatment with canagliflozin increased calcium absorption by ~40% (based upon AUC_{0-24h} for ^{45}calcium) on the first day of treatment, and this increase was maintained throughout the 14-day treatment period. As a consequence, urinary calcium excretion was increased during canagliflozin treatment.

Furthermore, effects of a low calcium diet (0.02% calcium) on bone changes in rats were investigated in four short term studies (2-weeks). Canagliflozin treatment-related hyperostosis was inhibited under short-term low calcium diet conditions with or without calcium supplementation; however, interpretation of the results was not warranted by adverse effects on bone due to the low calcium diet.

Finally, the formation of hyperostosis in young and older rats was compared. Hyperostosis was only seen in younger but not in older rats and these findings correlated with histomorphometric bone findings seen only in younger rats.

Rabbits

In a 5-day dose range finding study (0, 10, 50, 500 mg/kg/day canagliflozin) in support of a pilot developmental toxicity study, no mortalities were observed and organ weights were not affected at any dose. At 10 and 50 mg/kg/day, there were no effects on clinical signs, body weight performance, food consumption, haematology, or clinical chemistry. The high dose caused reduced/absent faeces, body weight loss, and changes in clinical pathology parameters (increases in serum creatinine, slight decreases in Na, K, Ca, Cl). Urinary glucose excretion as an expected PD effect of canagliflozin was not investigated in this study.

Dogs

In a 1-year, GLP, oral dog toxicity study (0, 4, 30, 100 mg/kg/day canagliflozin) no compound-related death and effects on food consumption, ophthalmoscopy, electrocardiography, physical examination, gross pathology, or histopathology findings were observed at any dose. Increases in urinary excretion of calcium and electrolytes were generally consistent with those observed in

the 3-month, GLP, dog toxicity study. Minimal increases in excretion of GGT and NAG were not associated with renal pathology. No hyperostosis was observed at any dose, and there were no meaningful changes in bone turnover biomarkers or hormones regulating calcium metabolism. The NOAEL in this study was set at 100 mg/kg/day. Safety margins at the NOAEL of 100 mg/kg/day of 76x and 20x for males and 72x and 19x for females, were calculated towards AUC exposure levels at the clinical dose of 100 mg and 300 mg, respectively (see table below).

Several TK studies were affected by bioanalytical data manipulation by an individual. As a consequence the outcomes of these studies were not included in the non-clinical assessment by Janssen Research & Development. The conservative approach of the Applicant to invalidate the affected studies is supported, especially as sufficient data are available from the other toxicity studies or additionally performed bridging studies, which allow complete assessment of TK in all species. In general, systemic exposure to canagliflozin (AUC and C_{max}) increased in a dose-related manner in all species and no accumulation was observed. In dogs systemic exposure to canagliflozin increased less than dose proportional in both genders probably due to absorption saturation or observed emesis at the higher doses. There generally appeared to be slight gender differences in TK, with higher exposure to canagliflozin being observed in female mice and rats compared to males.

Exposure multiples of canagliflozin in toxicity studies as compared to daily clinical doses of 100 and 300 mg canagliflozin at the mean steady state AUCs (pooled from studies DIA1007 and DIA1023).

Study ID	Daily Dose (mg/kg) (NOAEL)	Animal AUC (µg*h/ml)		Animal:Human 100 (300) mg clinical dose Exposure Multiple	
Repeat-Dose		♂	♀	♂	♀
3-month mice	100	285	344	40x (10.9x)	49x (13.2x)
6-month rat	4	14	22	2.0x (0.5x)	3.1x (0.8x)
1-year dog	100	529	503	76x (20x)	72x (19x)
Carcinogenicity					
2-year mouse	100	194	353	28x (7.4x)	51x (14x)
2-year rat	30 (RTT & pheochromocytoma)	118	188	17x (4.5x)	27x (7.2x)
Fertility					
rat (FK7269)	100		508		73x (19x)
Embryo-foetal development					
rat (FK7269)	10 (maternal toxicity)		43		6.1x (1.6x)
rat (FK7269)	30 (embryo-foetal dev.)		155		22.2x (5.9x)
Rabbit	40 (maternal toxicity)		85		12x (3.3x)
Rabbit	160 (embryo-foetal dev.)		487		70x (19x)
Prenatal and Postnatal development					

rat (FK7269)	10 (maternal toxicity)	43	6.1x (1.6x)
rat (FK7269)	100 (offspring)	508	73x (19x)

Exposure levels of pregnant rats were derived from a TK bridging study (FK7269) on pregnancy Day 16.

Genotoxicity

A standard battery of genotoxicity tests was performed with canagliflozin. In conclusion, 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 (see table above).

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 (see table above).

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 were 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.

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, see above). 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 caecal 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 month 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.

Neoplasms were not observed in carcinogenicity studies with the recently approved dapagliflozin. At very high dapagliflozin doses in a mechanistic study, however, similar increase in urine calcium and hyperostosis occurred, findings that may reflect SGLT1-related carbohydrate malabsorption.

Reproduction Toxicity

The complete program on reproductive toxicology as requested by ICH S5 was performed with oral application of canagliflozin alone. An additional study on embryo-foetal development was conducted using the combination of canagliflozin and metformin. Data investigating possible effects of metformin on reproduction were presented from the public domain. Canagliflozin showed no effects on fertility and early embryonic development at exposure margins of 73x or 19x to human therapeutic exposure at a dose of 100 mg or 300 mg. Fertility of male and female rats was unaffected by metformin at doses up to 600 mg/kg/day representing an exposure of about 3x the human daily dose of 2000 mg based on body surface area. These findings are included in section 5.3 of the SmPC.

In the embryo-foetal development studies in rats, skeletal anomalies associated with the state of ossification were observed in foetuses treated with 100 mg/kg/day canagliflozin alone and in foetuses of all dose groups treated with the combination of canagliflozin and metformin starting at a dose of 10/300 mg/kg/day canagliflozin/metformin. The Applicant contributed these findings towards maternal toxicity. However, maternal toxicity did not result in a decrease of 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. Additionally, since effects of metformin plus canagliflozin were more prominent than for canagliflozin alone, the combination seems to have a negative synergistic effect on skeletal development. These findings are included in section 5.3 of the SmPC.

No effects of canagliflozin were observed on embryo-foetal development in the rabbit with a safety margin of 70x or 19x to human therapeutic exposure at a dose of 100 mg or 300 mg. No effects on fetal parameters including gross external, soft tissue, or skeletal alterations were seen in the rabbit treated with doses of up to 140 mg/kg/day metformin alone. However, metformin doses applied in the rabbit study were below human therapeutic exposures.

In the study on pre-/postnatal development, the NOAEL was established at 100 mg/kg/day canagliflozin (safety margin of 73x or 19x to human therapeutic exposure at a dose of 100 mg or 300 mg). 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.

Effects observed in the juvenile toxicity study with canagliflozin in rats were in general consistent with effects observed in adult rats. However, pelvic dilatation in male rats was only partially reversible; therefore, 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. Persistent renal findings in juvenile rats can most likely be attributed to reduced ability of the developing rat kidney to handle canagliflozin-increased urine volumes, as functional maturation of the rat kidney continues through 6 weeks of age. By comparison, human anatomic renal maturation occurs in utero during the second and third trimesters, while functional maturation continues for the first 2 years of life.

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.

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 oedema) 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).

Metformin

The Applicant provided a review on the toxicology of metformin. Metformin is a well-known substance and there is an extensive amount of clinical experience with metformin. From a preclinical point of view, this is considered adequate.

The LD_{50} values for metformin in mice, rats, rabbits, and dogs were 2400, 1770, 552, and 375 mg/kg, respectively.

Chronic toxicity studies were carried out in mice, rats, dogs, and monkeys. A 52-week oral study in mice reported no adverse effects at doses up to and including 450 mg/kg/day. This is approximately 8.8x the maximum human dose (2550 mg) on a mg/kg basis for a 50 kg individual. The highest dose of 1500 mg/kg had decreased body weight gain compared to controls, and tubular dilation was observed in the kidney in both sexes and increased tubular vacuolization was observed in males.

Studies up to 78 weeks in rats showed the non-toxic dose to be 120 mg/kg which on a mg/kg basis for a 50 kg individual is approximately 2.4x the maximum human dose (2550 mg). Higher doses in the rat resulted in decreases in weight gain and food consumption, metabolic acidosis (as reported in humans), and salivary gland toxicity.

In 6-month and 78-week oral studies in the dog, the minimal toxic dose was 50 mg/kg or about equal to the maximum top human dose (2550 mg) on a mg/kg basis. Higher doses produced mortality with symptoms of GI distress and vascular lesions and degenerative changes in the brain, heart, kidney, and skeletal muscle. In a subsequent study supporting the development of a metformin/sitagliptin combination product, mortality was observed in dogs at a dose of 50 mg/kg metformin after 5 weeks of oral dosing. Although a definitive cause of death could not be

determined, a metformin-induced lactic acidosis was postulated to underlie the morbidity/mortality observed. In a follow-up study in dogs, metformin was well tolerated at a dose of 20 mg/kg for 16 weeks. Exposure in dogs at 20 mg/kg is similar to that in humans at a 2000 mg human dose.

Rhesus monkeys tolerated 180 mg/kg or approximately 3.6x (on a mg/kg basis) the maximum human dose (2550 mg), without any noted toxic effects in a 2-year oral study. The 360 mg/kg high dose (7.2x human dose) caused 75% mortality, severe gastrointestinal distress, decreased weight gain, and cytoplasmic changes in hepatocytes and the adrenal gland.

Metformin was not mutagenic or clastogenic in the Ames bacterial mutagenicity assay, chromosomal aberration assay, cytogenetic assay, or *in vivo* micronucleus assay. No increased tumour incidence was observed in a 2-year study in mice. No tumorigenic potential was observed in rats except for an increase in benign stromal uterine polyps in females. Extensive clinical experience does not indicate an increased tumorigenic potential.

Canagliflozin / metformin

Repeat-dose toxicity / Toxicokinetics

The combination of canagliflozin and metformin was tested in repeat-dose and developmental toxicity studies in rats. No additional toxicities were observed in the combination groups up to the high dose of 100/300 mg/kg/day as compared to single administration of both compounds at the same doses. It can be concluded that that the combination of canagliflozin and metformin is well tolerated and no toxicities can be expected due to drug-drug interactions. Co-administration of both compounds did not alter exposure levels of canagliflozin as compared to single administration. Slightly increased AUC levels of metformin (1.4 to 1.8-fold) were detected when combined with canagliflozin in the mid dose (20/300 mg/kg/day, which is ~3.4-fold the human exposure after 300 mg canagliflozin) and the high dose (100/300 mg/kg/day, which is ~16.2-fold the human exposure after 300 mg canagliflozin), respectively.

Reproductive and developmental toxicology

Please refer to the respective section of canagliflozin above.

Impurities

JNJ-54526888-AAA, a hydroperoxide degradation product of canagliflozin was found during the development of the canagliflozin/metformin HCl film-coated tablet. It was found to be positive in an *in vitro* Ames in two Salmonella strains.

JNJ-54526888-AAA was within specifications but higher than the 1.5 µg/day (corresponding to 5 ppm for a 300 mg daily dose) ICH default limit for life-time clinical exposure of genotoxic impurities/degradants, the threshold of toxicological concern.

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 66 µg/d based on the proposed maximum therapeutic daily dose. The DI was considered justified by the Applicant based on occupational data (endogenous peroxide production and permissible daily exposure (PDE) calculation derived from repeated dose toxicology studies with hydrogen peroxide).

Considering that the limit for hydrogen peroxide in drinking water is 100 µg/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

The applicant provided an Environmental Risk Assessment for both active ingredients according to the current EMA Guideline (EMEA/CHMP/SWP/4447/00, June 2006) including full study reports. The environmental risk assessment for metformin hydrochloride and canagliflozin is completed.

Considering the submitted data, the active ingredients canagliflozin and metformin are not expected to pose a risk to the environment. Canagliflozin and metformin are not PBT substances. But Metformin is persistent in sediment of water-sediment systems (OECD 308) according to calculations of the assessment team. Furthermore, 4 relevant (>10%) transformation products were identified in the water-sediment system for canagliflozin.

This has been adequately reflected in the product information.

Summary of main study results on Canagliflozin

Substance (INN / Invented Name): Canagliflozin			
CAS-number (if available):928672-86-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	3.42	Potentially B study on bioaccumulation required
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.44	
	BCF	11 L/kg	not B
Persistence	DT50	38.5 d in sediment	not P
Toxicity	NOEC or CMR	NOEC = 0.56 mg/L (Daphnia, 21 d)	not T
PBT-statement :	The compound is not considered as PBT nor vPvB following the given parameters.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$	1.5 µg/l	µg/L	> 0.01 threshold Y
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	$DT_{50\ water}$: 6.4 d $DT_{50\ whole\ system}$: 39 d $DT_{50\ sediment}$: 38.5 d Mineralisation: 4.0 % Bound residues: 29.4 % Sediment shifting: 58.1% (14 days)	Results of mineralisation, bound residues, and transformation products are given after 101

		Transformation Products: 4 TP > 10%			days
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					
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC	⩾ 100	mg/kg dry weight	nominal
Bioaccumulation	OECD 305	BCF	11	L/kg	5 % lipid-normalised, no risk of bioaccumulation

Summary of main study results on Metformin

Substance (INN/Invented Name): metformin hydrochloride			
CAS-number (if available): 1115-70-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-2.7 (pH 7)	Not potentially PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-2.7	not B
	BCF	no data	Not possible
Persistence	DT50 or ready biodegradability	$DT_{50,\ water}$ = 20 d $DT_{50,\ sediment}$ = 354.8 d $DT_{50,\ whole\ system}$ = 53 d	P in Sediment
Toxicity	NOEC or CMR		not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	10	µg/L	> 0.01 threshold Phase II required
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} (sludge)= 39.2 L/kg K_{oc} (soil) = 765 - 236310 L/kg	List all values
Ready Biodegradability Test	OECD 301	Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 20 d $DT_{50,\ whole\ system}$ = 53 d % shifting to sediment = 16.6%	P

		Mineralisation = 2.2% Transformation Products < 10%			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata, 3d*	OECD 201	NOEC	99	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	100	mg/L	
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	10.3	mg/L	*Pimephales promelas, flow through conditions*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	0.1	mg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	100	mg/kg	*Chironomus riparius*

2.3.6. Discussion on non-clinical aspects

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.

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. However, M7 was the major metabolite found in rat bile, 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.

Toxicokinetic results from combination studies in rats have demonstrated increased AUC levels of metformin (up to 1.8-fold) when combined with canagliflozin at doses as low as 10 mg/kg/day (~1.5-fold the human exposure after 300 mg canagliflozin), with NOEL below human exposure. Although no apparent interaction was observed in clinical study NAP1004 at canagliflozin/metformin doses of 100/1000 mg/kg, a slight increase in metformin exposure (20%) was observed in the clinical interaction study DIA1028 at 300/2000 mg/kg. Canagliflozin, M5 and M7 are not considered as substrates for OCT1 and OCT2. No data have been provided for the renal metformin transporter MATE1. Since no clinically relevant PK interaction between canagliflozin and metformin, a main substrate of MATE1, have been observed, it is highly unlikely that any potential inhibition of MATE1 by canagliflozin would lead to clinically relevant drug-drug interactions.

No data were discussed concerning placental or milk transfer of metformin. However, human data about the use of metformin while breast-feeding can be found in the public domain.

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 (see also discussion on carcinogenicity below). 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 boner markers and calcium excretion were not observed in clinical trials, hyperostosis is not expected to occur in humans. The CHMP considered that this hypothesis is plausible.

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.

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 3 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 has provided a theoretical estimate of the local concentrations of canagliflozin in the gut, comparing rats and humans. The calculations arrive at a 12-fold higher concentration in rats at 100 mg/kg (dose which resulted in pheochromocytoma and renal tubule tumours), as compared to humans treated with 300 mg (the highest clinical dose). As pointed out by the Applicant, the actual ratio is likely to be higher, considering the differences in pharmacokinetics between rats and humans. The estimated gut concentrations of canagliflozin in both rats and humans are orders of magnitude above the in vitro IC_{50} for inhibition of SGLT1. 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, it is agreed that it is difficult to determine the exact concentration needed to significantly inhibit intestinal SGLT1. The Applicant refers to data from one clinical and one rat study, arguing that the most relevant manner to compare rats and humans is to examine results from studies in which SGLT1-dependent glucose absorption was assessed. The results of these two studies 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.

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.

In the studies on embryo-foetal development in rats, skeletal anomalies associated with the state of ossification were observed in foetuses of the high dose canagliflozin alone group and in all canagliflozin/metformin-treatment groups. Skeletal findings might be attributed to disturbances in calcium homeostasis, in particular an increase in calcium excretion in dams treated with canagliflozin. Additionally, since effects of metformin plus canagliflozin were more prominent than for canagliflozin alone, the combination might have a negative synergistic effect on skeletal development. This is adequately addressed in the SmPC. It is acknowledged that the bone structures affected by canagliflozin/metformin are similar to the structures affected by metformin alone. Due to a pharmacokinetic interaction between canagliflozin and metformin, the negative synergistic effect is most likely due to increased metformin exposure.

The NOAEL for offspring functional development and reproductive performance was at the high dose of 100 mg/kg/day canagliflozin, 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.

Effects observed in the juvenile toxicity study with canagliflozin in rats were in general consistent with effects observed in adult rats. However, pelvic dilatation in male rats was only partially reversible. Persistent renal findings in juvenile rats can most likely be attributed to reduced ability of the developing rat kidney to handle canagliflozin-increased urine volumes, as functional maturation of the rat kidney continues through 6 weeks of age. By comparison, human anatomic renal maturation occurs in utero during the second and third trimesters, while functional maturation continues for the first 2 years of life.

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

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

Based on the analyses of batches so far the Applicant proposed a specification limit of 220 ppm for the impurity canagliflozin hydroperoxide equivalent to a maximum daily intake (DI) of 66 µg/d based on the proposed maximum therapeutic daily dose. The DI was considered justified by the Applicant based on occupational data (endogenous peroxide production and permissible daily exposure (PDE) calculation derived from repeated dose toxicology studies with hydrogen peroxide). Considering that the limit for hydrogen peroxide in drinking water is 100 µg/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.

2.3.7. Conclusion on the non-clinical aspects

The PD activity of canagliflozin has sufficiently been demonstrated in *in vitro* and *in vivo* models. Metformin is a well-established substance. Small PK interactions between canagliflozin and metformin could not be excluded based on the non-clinical data, but clinical studies revealed no clinically relevant effects.

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.

Environmental Risk Assessment: Considering the submitted data, the active ingredients canagliflozin and metformin are not expected to pose a risk to the environment. Canagliflozin and metformin are not PBT substances, but Metformin is persistent in the environment. This has been adequately reflected in the product information.

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

Table 1 Phase 3 Clinical Studies Supporting the Canagliflozin/Metformin Fixed-Dose Combination (CANA/MET IR FDC) Tablet Development Program

Study ID/Type (No. Centers)	Study Design, Duration (Duration to primary endpoint/ Duration of extension phase)	HbA_{1c} Inclusion Criterion	Study Treatment Daily Dosing (once-daily)	No. Subjects per Treatment Arm (mITT)	Primary Efficacy Endpoint
ADD-ON TO METFORMIN 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 100mg	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 METFORMIN-BASED DUAL COMBINATION AHA THERAPY					
DIA3002 Add-on to metformin + SU (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}
DIA3015 Add-on to metformin + SU (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}
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}
ADD-ON TO METFORMIN AND INSULIN					
DIA3008 Cardiovascular study (369 centers) Population 3 of the insulin substudy (subjects on insulin + metformin)[b] (182 centers)	R, DB, PC, PG 18 weeks double-blind substudy (18 wks / no extension) Note: DIA3008 main study is event driven and continuing	≥7.0% to ≤10.5% (with history or high risk of CV disease)	Placebo CANA 100 mg CANA 300 mg	145 139 148	Δ BL to Wk 18 in HbA_{1c}
ADDITIONAL CANA SUPPORTIVE STUDY (WITH SUBSTANTIAL PROPORTION OF SUBJECTS ON MET)					
DIA3010[c] 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}
OTHER SUPPORTIVE STUDIES					
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}
DIA3008 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}

Table 1 Phase 3 Clinical Studies Supporting the Canagliflozin/Metformin Fixed-Dose Combination (CANA/MET IR FDC) Tablet Development Program

Study ID/Type (No. Centers)	Study Design, Duration (Duration to primary endpoint/ Duration of extension phase)	HbA_{1c} Inclusion Criterion	Study Treatment Daily Dosing (once-daily)	No. Subjects per Treatment Arm (mITT)	Primary Efficacy Endpoint
DIA3004 Moderate renal impairment (eGFR ≥30 to <50 mL/min/1.73m^2) (89 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	90 90 89	Δ BL to Wk 26 in HbA_{1c}

Key: Δ=change from, AC=active-controlled, AHA=anti-hyperglycemic agent, BL=baseline, CANA=canagliflozin, CV=cardiovascular, DB=double-blind, eGFR=estimated glomerular filtration rate, HbA_{1c}=glycosylated hemoglobin, MACE=major adverse cardiovascular events, mITT=modified intent-to-treat, No=number, PC=placebo-controlled, PG=parallel group, R=randomized, SU=sulphonylurea; wks=weeks.

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

b The primary analysis population discussed in this FDC Addendum to the ISE for the DIA3008 Insulin substudy was defined as subjects randomized who were receiving insulin ≥30 IU/day and metformin ≥2000 mg/day at study entry (Population 3).

c Slightly more than 85% (416 of 477) of canagliflozin-treated subjects in DIA3010 were taking metformin (alone or in combination with another agent, including insulin).

d The primary analysis population discussed in the CANA ISE (Module 5.3.5.3) 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).

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. These studies were also submitted to support the application for canagliflozin as monotherapy. In addition, 6 biopharmaceutic studies were conducted with CANA/MET IR FDC tablets that are summarized in the below table.

Table: 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,	40

		with end-stage renal disease, or with normal renal function	
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+459)
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.
Source: Clinical study reports

In addition, in order to support the application for CANA/MET IR FDC 6 biopharmaceutical studies were submitted. Study DIA 1037 investigated the food effect of 150/1,000-mg CANA/MET IR FDC in 24 healthy subjects. Study DIA1036 was a pilot study that evaluated the relative bioavailability of the CANA/MET IR FDC tablets (6 different dose strengths, 2 of them only developed for the US market) to single dose coadministration of Canagliflozin and Glucophage. Studies DIA1039, DIA1052, DIA1051, and DIA1038, were bioequivalence studies for the to-be-marketed CANA/MET IR FDC tablet strengths of 50/850 mg, 150/850 mg, 50/1,000 mg, and 150/1,000 mg respectively. No additional specific clinical pharmacology studies were conducted with the CANA/MET IR FDC. In addition, one study was submitted that investigated the food effect (DIA 1037).

Two PK interaction studies between canagliflozin and metformin are of relevance for this application. They were already submitted in the dossier supporting the application for the canagliflozin monotherapy (studies NAP1004 and DIA1028). No additional human pharmacology studies were provided for the coadministration of canagliflozin and metformin.

Information for metformin was provided by the Applicant based on the SmPC of Glucophage. No new PK or PD data for metformin were submitted and the well known data for metformin are not discussed in detail in this overview.

Pharmaceutical development

Canagliflozin

Absolute oral bioavailability was investigated in study DIA 1021. In vivo metabolism of 14C-canagliflozin was studied in faeces, 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 sponsored by Janssen Pharmaceutical Research and Development 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. 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 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) were transferable to the to be marketed formulation.

Cana/MET IR FDC

Bioequivalence between the FDC and canagliflozin and Glucophage, when coadministered, was demonstrated in 5 bioequivalence studies (1 pilot study with 6 different strengths and 4 pivotal bioequivalence studies). For the 50/1000, 150/850 and 150/1000 mg the bioavailability of metformin was slightly lower in the FDC tablet as compared to the combined administration of both drugs. However, the BE criteria were met in all studies for all strengths ((50/850 mg, 50/1000mg, 150/850 mg, and 150/1000 mg CANA/MET) and bioeqivalence between the FDC and the Coadministration of Canagliflozin and Glucophage can be assumed. In addition, in the pilot study investigating 6 dose strengths there were no statistically significant differences in RTG and UGE and there were no relevant differences in plasma glucose levels between the FDC treatment and the coadministered treatment in each cohort.

Pharmacokinetics

An overview over the PK parameters across studies is provided below as a summary of pooled analyses in Table 47 (single dose PK across studies) and in Table 48 (multiple dose PK across studies).

Table 47: 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 48: 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, tmax 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. However Vokanamet should be taken orally twice daily with meals to reduce the gastrointestinal undesirable effects associated with metformin. This was reflected in the SmPC.

For CANA/MET IR FDC intake of food increased AUC values for canagliflozin (upper 90% CI values below 125%, clinically not relevant) and decreased Cmax values (lower value of the 90%CI was below 80%). The effect on canagliflozin is not considered clinically relevant. A lower Cmax of metformin after food intake is in accordance with the information provided in the SPC of Glucophage. Since metformin is administered with or after food due to tolerability, and PK of canagliflozin is not influenced by food intake, overall administration of the FDC with food or after food intake is supported by the data.

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%).

Since binding of metformin to plasma proteins is negligible no interaction between Canagliflozin and metformin at the level of protein binding is expected.

Elimination

In plasma, mainly unchanged canagliflozin 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, 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 labeled dose) and M5 (13%) were found in urine, M9 (7.0%) and M7 (3.2%), but not M5 were detected in feces. 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 t1/2 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 feces 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 feces may be a possible explanation for the absence of M5 in feces. No enterohepatic pathway of clinical relevance was observed.

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. Since the individual values were within the overall observed dose range adaption in patients with known UGT1A9 and UGT2B4 alleles is not considered necessary.

Since metformin is excreted unchanged in the urine no interaction at the level of the a.m. metabolite pathways is expected.

Dose and time dependency

Cmax and AUC values of canagliflozin increased dose proportionally (50 – 300 mg 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. Steady state was reached after about 4 days of qd dosing with 50 to 300 mg canagliflozin. The exposure (AUC) was not different between qd administration proposed for canagliflozin monotherapy and and the bid administration proposed for CANA/MET IR FDC.

For metformin an inverse relationship was described between the dose ingested and the relative absorption with therapeutic doses ranging from 0.5 to 1.5 g, suggesting the involvement of an

active, saturable absorption process. Irrespectively, a bid or tid administration of metformin is established.

Variability

For canagliflozin the intra-subject coefficient of variation ranged from 15.2% to 22.1% for Cmax and from 4.8% to 9.4% for AUC. The inter-subject coefficient of variation for Cmax and AUC in healthy subjects ranged from19.1% to 27.5% in a pooled analysis following single and multiple-dose administration of 100 and 300 mg qd canagliflozin (see Table 47 and Table 48 above). For t1/2 following single-dose administration, the inter-subject coefficient of variation was between 20.1% and 25.0%. Known variability in PK of metformin does not necessarily translate to variability in PD effects.

Special populations

For canagliflozin there were no relevant differences in the PK of canagliflozin between healthy subjects and patients with T2DM. In patients with decreased renal function (CLCR<50 ml/min) exposure to canagliflozin was increased, although only <1% of canagliflozin is excreted renally. For metformin in the presence of normal renal function, there are no differences between single- or multiple-dose PK of metformin between patients with T2DM and healthy subjects, nor is there any accumulation of metformin in either group at usual clinical doses.

Patients with severe hepatic failure with a Child-Pugh-Score >9 were not investigated. These patients should be excluded from the therapy. In patients with mild to moderate hepatic failure there were only mild changes, i.e. Cmax and AUC values increased by less than 11%. Oral clearance was unchanged and the differences in volume of distribution and t1/2 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. Since the use of metformin is not recommended in patients with hepatic failure due to safety reasons, these PK considerations are of minor importance for the CANA/Met IR FDC.

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.

Since metformin is contraindicated in patients of at least moderate renal failure, the restrictions for CANA/MET in these patients are irrespective of changes in PK of canagliflozin.

In females numerically higher AUC values were observed for canagliflozin. This is not considered of clinical relevance in the absence of other factors increasing exposure. No gender specific dose adaption of Metformin is necessary based on PK.

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

However, in the elderly an increase in AUC values by about 29% could be relevant. Since in elderly subjects BP lowering effects may be more relevant for safety reasons a dose titration

starting at 50 mg bid is appropriate. Since excretion of Metformin depends on renal function, renal function in the elderly should be regularly monitored.

Pharmacokinetic interaction studies 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 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 that were partially 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 $AUC_{\tau,ss}$ 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. Such patients should be treated with 50 mg bid of the canagliflozin component and a potential increase in the dose should mainly depend on tolerability

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 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 is mentioned in the SmPC. The assumed mechanism, an inhibition at the level of P-gp, is also relevant for other digitalis glycosides.

2.4.3. Pharmacodynamics

Mechanism of action

Overall, the mechanism of action and PD effects of canagliflozin were well characterized in the clinical pharmacology program. Canagliflozin inhibits SGLT2 and, with 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. These

findings are crucial for the bridging strategy from the studies using canagliflozin qd to the bid administration of CANA/MET IR FDC.

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 (PG) 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.

Primary and Secondary pharmacology

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. Since this effect on intestinal glucose absorption is not seen with 150 mg bid there may be a difference on post prandial peak glucose plasma levels between the 300mg qd and 150 mg bid regimen. However, the inhibitory effect on SGLT1 is expected to be transient (only observable after the breakfast meal) and small and may be further reduced in the presence of metformin. Based on the estimated SGLT1-associated reduction in post-breakfast glucose obtained with canagliflozin 300 mg in Study DIA1045 (mean reduction in PG over 0-4h = 0.53 mmol/L (9.6 mg/dL), with no additional reduction expected over the 4-24h interval), the associated incremental reduction in 24-h mean PG is estimated to be 0.09 mmol/L (1.6 mg/dL). Based on relationships between mean PG (MPG) and HbA1c from Rohlfing (ΔHbA1c(%) = ΔMPG(mmol/L)/1.98) and Nathan (ΔHbA1c(%) = ΔMPG(mmol/L)/1.59), the 300 mg qd regimen is expected to provide approximately 0.05% greater reductions in HbA1c than the 150 mg bid regimen. This difference is not expected to be clinically meaningful.

A placebo-adjusted decrease in body weight by approximately 1.3 – 2.2 kg in healthy volunteers and by 1 to 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.

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

Coadministration of canagliflozin 300 mg qd with metformin 2000 mg qd in healthy volunteers 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. The lack of an additional efficacy on plasma glucose cannot be regarded as representative for patients with T2DM. No PD interactions were observed between canagliflozin and simvastatin, or warfarin. Coadministration with HCTZ was associated with a small increase in RTG and mean plasma glucose leves and slightly lower UGE. Coadministration 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.

Genetic differences in PD response

No studies investigating genetic differences in PD response have been performed.

No data were provided for PK or PD of metformin, and the Applicant refers to the information in the SmPC of Glucophage.

2.4.4. Discussion on clinical pharmacology

The development of a FDC of canagliflozin and metformin is reasonable since they have different modes of action. Whereas canagliflozin increases glucose excretion and (at single doses of 300 mg) prolongs glucose absorption, metformin activates AMP-activated protein kinase (AMPK) and thereby decreases hepatic gluconeogenesis. AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose uptake. In addition, metformin decreases intestinal absorption of glucose, improves insulin sensitivity, increases peripheral glucose uptake by phosphorylating GLUT4 enhancer factor and increases glucose utilization. Since renal glucose excretion by canagliflozin is related to plasma glucose levels it is not

expected that there is a more than additive effect when both drugs are coadministered in a FDC and it is not expected that hypoglycaemic effects of metformin are highly potentiated by canagliflozin.

The Applicant has demonstrated bioequivalence between CANA/MET and Canagliflozin + Glucophage coadministration for the following strengths: 50/850 mg, 50/1000mg, 150/850 mg, and 150/1000 mg CANA/MET. There was no relevant food effect on canagliflozin in the FDC and the reduction in metformin Cmax is consistent with the known food effect on Glucophage. Administration with or after food intake as proposed for metformin is appropriate for the CANA/MET IR FDC.

With canagliflozin RTG and UGE in healthy volunteers were independent of whether the same daily dose was administered qd or bid supporting that data from studies with qd administration can be transferred to the bid administration with the FDC. There is an effect of 300 mg qd canagliflozin on the velocity of glucose absorption which is not seen with 150 mg bid. However, this concerns only postprandial glucose absorption in the morning but not later during the day. The possible effect on Hba1c is small and is not considered clinically relevant.

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

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 may possibly be pronounced in case there is more than one factor. Patients with severe hepatic failure were excluded from the pharmacological program and these patients should be excluded from the therapy. Since metformin is not to be administered in patients with hepatic failure PK considerations for canagliflozin are not relevant for the FDC.

The increase in canagliflozin exposure in elderly subjects by 29% could be of relevance with respect to AEs associated with a decrease in BP. Therefore, a dose titration starting with 50 mg bid of canagliflozin and uptitration mainly based on tolerability considerations may be appropriate.

In patients with renal failure there was an increase in canagliflozin 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 is not eliminated by haemodialysis. Since metformin is contraindicated in patients with at least moderate renal insufficiency PK considerations for canagliflozin are not relevant for the FDC.

The interaction profile of canagliflozin has been well characterized addressing the metabolic pathways and clinically relevant co-administered drugs. The data indicate that canagliflozin has the potential for drug-drug interactions at the level of P-gp, MDR1 and MRP2. There were two interactions of clinical relevance, a decrease in canagliflozin AUC by 52% induced by rifampin and an increase of Cmax of digoxin by about 36% and AUC levels by about 20%. The latter finding is possibly related to an interaction at the level of P-gp and therefore is relevant for all of the cardiac glycosides, since all of them have a narrow therapeutic range.

Taken together, the pharmacological 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 can be sufficiently addressed by labelling in the SPC and the dose selection for canagliflozin based on tolerability.

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 time lower as compared to the estimated in vitro IC50 value of 4.2 nM. The Applicant has pointed out that possibly 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 not relevant for the FDC since metformin is not to be administered in patients with renal failure.

2.4.5. Conclusions on clinical pharmacology

The development of a FDC containing canagliflozin and metformin is reasonable since the mechanism of action is different and there is a potential for additive effects on plasma glucose levels. Bioequivalence of the FDC to the coadministration of canagliflozin and Glucophage has been demonstrated for all proposed strengths and the proposed bid dosing with or after food intake is justified based on PK and PD considerations.

Overall PK and PD of canagliflozin are well characterized.

2.5. Clinical efficacy

2.5.1. Dose response studies

The phase 2b program includes 1 dose-ranging study (451 patients) in metformin treated patients investigating CANA doses of 50 mg, 200 mg and 300 mg (DIA2001). This study has already been submitted with the CANA MAA. The CANA doses for the phase 2b study were selected based on findings from the phase 1 program (i.e. studies DIA 1015, DIA 1030, DIA 1032, NAP 1001, NAP 1008). An 18-week phase 2 study (DIA2003) investigated comparable efficacy and safety/tolerability between once daily and twice daily dosing of CANA in combination with MET. This study has been newly submitted to support the present fixed dose combination application.

Study DIA2001 was a parallel group, dose-ranging study with 7 treatment arms including an active reference arm (sitagliptin 100 mg qd). The study assessed the safety and efficacy of CANA at doses of 50 mg once daily (qd), 100 mg qd, 200 mg qd, 300 mg qd, and 300 mg twice daily

(bid) versus placebo in subjects with T2DM who had not achieved glycemic control (HbA1c levels ≥7.0% and ≤10.5%) while receiving near maximal doses of metformin (equal or greater than 1500 mg/ day). The study included a 3-4 week screening phase, a 12-week double-blind treatment phase, and a 2-week post-treatment phase. A total of 451 subjects were randomised equally to one of the following 7 treatments: CANA 50 mg (n=64), 100 mg(n=64), 200 mg(n=65), 300 mg qd (n=64), 300 mg bid (n= 64), placebo (n=65), sitagliptin 100 mg qd (n= 65).

Baseline demographic, anthropometric and disease characteristics were generally balanced across treatment groups, except for slightly more subjects with a BMI ≥30 kg/m^2 and a higher proportion of subjects with a HbA1c >8.0% in the 50 mg group. Since the treatment effect is expected to increase with increasing HbA1c values this imbalance could only have led to an increased treatment effect in this subgroup and therefore the lower boundary for an effective dose could not have been missed.

Outcomes and estimation

Primary endpoint

Changes in HbA1c (%) from baseline at week 12 compared to placebo were -0.45%, -0.51%, -0.54%, -0.71%, and -0.73% for CANA 50 mg qd, 100 mg qd, 200 mg qd, 300 mg qd, and 300 mg bid, respectively, and -0.56% for sitagliptin. All doses of CANA and sitagliptin were statistically significantly different (adjusted p<0.001 for all comparisons) from placebo.

Table 8: Analysis of Change in HbA1c (%) From Baseline to Week 12 LOCF (Study 28431754DIA2001: Intent-to-Treat Analysis Set)

	PBO (N=65)	50 qd (N=64)	100 qd (N=64)	200 qd (N=65)	300 qd (N=64)	300 bid (N=64)	Sita (N=65)
HbA1c (%)							
Value at Baseline							
N	61	62	62	62	60	62	62
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)	7.62 (0.947)
Value at Week 12 LOCF							
N	61	62	62	62	60	62	62
Mean (SD)	7.50 (0.957)	7.22 (0.881)	7.05 (0.853)	6.87 (0.676)	6.78 (0.824)	6.76 (0.723)	6.88 (0.919)
Change from Baseline							
N	61	62	62	62	60	62	62
Mean (SD)	-0.22 (0.702)	-0.79 (0.749)	-0.76 (0.992)	-0.70 (0.720)	-0.92 (0.695)	-0.95 (0.704)	-0.74 (0.615)
P-value(minus PBO)[a]		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Diff. of L-S Means (SE)		-0.45 (0.116)	-0.51 (0.116)	-0.54 (0.116)	-0.71 (0.117)	-0.73 (0.116)	-0.56 (0.116)
95% CI		(-0.747;-0.148)	(-0.804;-0.207)	(-0.841;-0.244)	(-1.006;-0.405)	(-1.029;-0.432)	(-0.862;-0.265)

KEY: PBO = placebo; qd = once-daily; bid = twice daily; CI = confidence interval; HbA1c=glycosylated hemoglobin; LOCF = last observation carried forward; L-S = least squares; N = total number of subjects per treatment group; SD = standard deviation; SE = standard error; Sita = sitagliptin.

[a] P-values and CIs were based on the pair-wise comparison of least-squares (L-S) means from an ANCOVA model including terms for treatment, baseline value and MMTT strata. For the primary analysis at Week 12 LOCF, p-values and CIs were adjusted using Dunnett's procedure.

Cross-reference: Attachments 3.1.1, 3.1.2, and 3.1.6

Main Secondary endpoints

The differences in change of FPG (mmol/L) from baseline at week 12 LOCF compared to placebo were -0.9, -1.4, -1.8, -1.8, and -1.7 for CANA 50 mg qd, 100 mg qd, 200 mg qd, 300 mg qd, and 300 mg bid, respectively, and -1.0 for sitagliptin. Responder analyses generally supported the results on HbA1c and FPG. Body weight was also reduced in a dose-dependent fashion: % changes from baseline at week 12 compared to placebo were -1.3%, -1.5%, -1.6%, -2.3%, and -2.3% for CANA 50 mg qd, 100 mg qd, 200 mg qd, 300 mg qd, and 300 mg bid, respectively, and 0.4% for sitagliptin.

In conclusion, selection of the 100 mg and 300 mg CANA dose for the phase 3 studies seems reasonable based on the study results.

In **study DIA2003** CANA was administered as 50 mg or 150 mg **bid** to provide the same total daily dose of 100 mg or 300 mg evaluated in the phase 3 CANA programme with once daily dosing. Bid dosing is in line with the dosing recommendations for MET.

DIA2003 was an 18-week, randomized, double-blind, placebo controlled, parallel-group, multicenter phase 2 study evaluating the efficacy and safety of canagliflozin bid dosing in subjects with T2DM with inadequate glycemic control (ie, HbA1c of >7.0% to <10.5%) on maximal (or near maximally) effective doses of metformin monotherapy. The study design features are consistent with those of the phase 3 studies. Rescue therapy was not an option in DIA2003.
The primary objective and key secondary objectives of this study were to demonstrate the superiority of canagliflozin 50 mg and 150 mg bid, respectively, to placebo, as measured by the change in HbA1c from baseline to Week 18. The key secondary endpoints included the change from baseline in FPG, percent change from baseline in body weight, and the proportion of subjects with HbA1c <7.0% at Week 18 last observation carried forward (LOCF); these endpoints were common to the Phase 3 studies. Additional endpoints included the proportion of subjects with HbA1c <6.5%, percent change from baseline at Week 18 in HDL-C, TGs, low-density lipoprotein-cholesterol (LDL-C), total cholesterol, LDL-C to HDL-C ratio, SBP and diastolic blood pressure (DBP).

Outcomes and estimation:

Primary endpoints

The primary efficacy results are summarised in the following table:

Table TEFF01: Primary Endpoint Analysis: Change from Baseline in HbA1c to Week 18 (mITT) - LOCF (Study 28431754-DIA2003: Modified Intent-To-Treat Analysis Set)

	Placebo (N=93)	50 mg BID (N=93)	150 mg BID (N=93)
Blood hemoglobin A1c (%)			
Value at Baseline			
N	92	90	91
Mean (SD)	7.66 (0.905)	7.63 (0.844)	7.53 (0.829)
Value at Week 18 LOCF			
N	92	90	91
Mean (SD)	7.62 (1.016)	7.16 (0.856)	6.94 (0.623)
Change from Baseline			
N	92	90	91
Mean (SD)	-0.04 (0.764)	-0.47 (0.684)	-0.58 (0.759)
LS Mean (SE)	-0.01 (0.069)	-0.45 (0.070)	-0.61 (0.069)
P-value(minus Placebo)(a)		<0.001	<0.001
Diff. of LS Means (SE)		-0.44 (0.098)	-0.60 (0.098)
95% CI (a)		(-0.637;-0.251)	(-0.792;-0.407)

(a) Pairwise comparison: p-values and CIs are based on the ANCOVA model with treatment, glycemic control (whether HbA1c value $\geq$ 8.0%), and baseline HbA1c.
Note: The table only includes subjects who had both baseline and post-baseline HbA1c.
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Main Secondary endpoints

With respect to all major secondary endpoints (ie, FPG, body weight and proportion achieving <7% HbA_{1c}) Canagliflozin was superior to placebo based on the pre-specified hierarchical testing sequence. The differences in change in FPG (mmol/L) from baseline at Week 18 LOCF compared to placebo were -1.31 and -1.33 for CANA 50 mg bid and CANA 150 mg bid, respectively. Responder analyses supported the results of both HbA_{1c} and FPG, with greater proportions of subjects achieving HbA_{1c} <7% compared to placebo (16.3% for CANA 50 mg bid and 25.6% CANA 150 mg bid). Significant reductions in percent change in body weight of 2.2% and 2.6% were also observed for CANA 50 mg bid and CANA 150 mg bid, respectively.

In conclusion, although the antihyperglycaemic response was smaller compared to the effects in the phase 3 studies, this could be (at least partly) attributed to differences in baseline HbA1c as demonstrated by an acceptable bootstrap analysis.

2.5.2. Main studies

The following tables summarise the efficacy results from the main studies supporting the present application. All studies have already been submitted in support of the CANA mono MAA.

Table 4 **HbA_{1c} (%) Change from Baseline to Primary Assessment Timepoint - LOCF: Study-by-Study Comparison (Phase 3 Studies Providing Primary Support for CANA/MET IR FDC: Modified Intent-to-Treat Analysis Set)**

	Placebo	CANA 100 mg	CANA 300 mg	Sitagliptin	Glimepiride
Dual therapy					
DIA3006 - Add-on to metformin					
N	181	365	360	354	
Baseline, mean (SD)	7.96(0.896)	7.94(0.879)	7.95(0.931)	7.92(0.875)	
Change from baseline, LS mean (SE)	-0.17(0.060)	-0.79(0.044)	-0.94(0.044)	-0.82(0.044)	
P value (minus placebo)[a]		<0.001	<0.001		
Diff of LS mean (SE) (minus placebo)		-0.62(0.071)	-0.77(0.071)	-0.66(0.071)	
95% CI[a]		(-0.758;-0.481)	(-0.914;-0.636)	(-0.795;-0.516)	
DIA3009 - Add-on to metformin					
N		478	474		473
Baseline, mean (SD)		7.78(0.787)	7.79(0.779)		7.83(0.795)
Change from baseline, LS mean (SE)		-0.82(0.039)	-0.93(0.039)		-0.81(0.039)
Diff of LS mean (SE) (minus glimepiride)		-0.01(0.050)	-0.12(0.050)		
95% CI[a]		(-0.109;0.085)	(-0.217;-0.023)		
Triple therapy					
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)	-0.13(0.075)	-0.85(0.075)	-1.06(0.076)		
P value (minus placebo)[a]		<0.001	<0.001		
Diff of LS mean (SE) (minus placebo)		-0.71(0.097)	-0.92(0.097)		
95% CI[a]		(-0.904;-0.524)	(-1.114;-0.732)		
DIA3015 – Add-on to metformin and SU					
N			374	365	
Baseline, mean (SD)			8.12 (0.910)	8.13 (0.916)	
Change from baseline, LS mean (SE)			-1.03 (0.048)	-0.66 (0.049)	
Diff of LS mean (SE) (minus sitagliptin)			-0.37 (0.064)		
95% CI[a]			(-0.500;-0.250)		
DIA3012 - Add-on to metformin and pioglitazone					
N	114	113	112		
Baseline, mean (SD)	8.00(1.010)	7.99(0.940)	7.84(0.911)		
Change from baseline, LS mean (SE)	-0.26(0.069)	-0.89(0.069)	-1.03(0.070)		
P value (minus placebo)[a]		<0.001	<0.001		
Diff of LS mean (SE) (minus placebo)		-0.62(0.095)	-0.76(0.096)		
95% CI[a]		(-0.811;-0.437)	(-0.951;-0.575)		

Table 4 **HbA_{1c} (%) Change from Baseline to Primary Assessment Timepoint - LOCF: Study-by-Study Comparison (Phase 3 Studies Providing Primary Support for CANA/MET IR FDC: Modified Intent-to-Treat Analysis Set)**

	Placebo	CANA 100 mg	CANA 300 mg	Sitagliptin	Glimepiride
DIA3008 insulin substudy - Population 3[b] (insulin + metformin)					
N	132	130	143		
Baseline, mean (SD)	8.15 (0.811)	8.20 (0.858)	8.22 (0.799)		
Change from baseline, LS mean (SE)	0.03 (0.054)	-0.64 (0.055)	-0.79 (0.052)		
P value (minus placebo)[a]		<0.001	<0.001		
Diff of LS mean (SE) (minus placebo)		-0.66 (0.077)	-0.82 (0.075)		
95% CI[a]		(-0.815;-0.513)	(-0.963;-0.668)		

[a] Pairwise comparison: p values and CIs are based on the ANCOVA model with treatment, study specific stratification factors and baseline HbA_{1c}.

[b] Subjects on insulin ≥30 IU/day and metformin ≥2,000 mg/day

Key: Cana=canagliflozin, CI = confidence interval, Diff = difference, ISE = Integrated Summary of Efficacy, LOCF = last observation carried forward, LS = least squares, N = number, SD = standard deviation, SE = standard error, SU=sulphonylurea.

Note: Predefined timepoint of primary endpoint: Week 18 LOCF (DIA3008 insulin substudy), Week 26 LOCF (DIA3002, DIA3006, and DIA3012) and Week 52 LOCF (DIA3009, DIA3015).

Source: Mod5.3.5.3\CANA ISE\Tab23; Mod5.3.5.1\DIA3008 Insulin Substudy\Tab35.

Table 5 **HbA_{1c} (%) Change From Baseline to Primary Assessment Timepoint - LOCF: Study-by-Study Comparison (Other Phase 3 Studies Supporting the CANA/MET IR FDC: Modified Intent-to-Treat Analysis Set)**

	Placebo	Cana 100 mg	Cana 300 mg
DIA3010 – Add on to AHA[a], Older adults			
N	232	239	229
Baseline, mean (SD)	7.76(0.785)	7.77(0.773)	7.69(0.779)
Change from baseline, LS mean (SE)	-0.03(0.063)	-0.60(0.063)	-0.73(0.064)
P value (minus placebo)[b]		<0.001	<0.001
Diff of LS mean (SE) (minus placebo)		-0.57(0.069)	-0.70(0.070)
95% CI[b]		(-0.708;-0.436)	(-0.841;-0.566)
DIA3005 – Monotherapy			
N	189	191	194
Baseline, mean (SD)	7.97(0.955)	8.06(0.959)	8.01(0.988)
Change from baseline, LS mean (SE)	0.14(0.065)	-0.77(0.065)	-1.03(0.064)
P value (minus placebo)[b]		<0.001	<0.001
Diff of LS mean (SE) (minus placebo)		-0.91(0.091)	-1.16(0.091)
95% CI[b]		(-1.088;-0.729)	(-1.342;-0.985)
DIA3008 substudy - Add-on to SU[c]			
N	40	40	39
Baseline, mean (SD)	8.49(1.130)	8.29(0.831)	8.28(1.005)
Change from baseline, LS mean (SE)	0.04(0.146)	-0.70(0.145)	-0.79(0.147)
P value (minus placebo)[b]		<0.001	<0.001
Diff of LS mean (SE) (minus placebo)		-0.74(0.206)	-0.83(0.207)
95% CI[b]		(-1.145;-0.329)	(-1.237;-0.415)
DIA3004 - Moderate renal impairment			
N	87	88	89
Baseline, mean (SD)	8.02(0.917)	7.89(0.898)	7.97(0.805)
Change from baseline, LS mean (SE)	-0.03(0.090)	-0.33(0.090)	-0.44(0.089)
P value (minus placebo)[b]		0.012	<0.001
Diff of LS mean (SE) (minus placebo)		-0.30(0.117)	-0.40(0.117)
95% CI[b]		(-0.529;-0.066)	(-0.635;-0.174)

[a] Slightly more than 85% (416 of 477) of canagliflozin-treated subjects in DIA3010 were taking metformin (alone or in combination with another agent, including insulin).

[b] Pairwise comparison: p values and CIs are based on the ANCOVA model with treatment, study specific stratification factors and baseline HbA_{1c}.

[c] Data for DIA3008 SU substudy presented for Population 1 (subjects on protocol-specified doses of SU monotherapy regardless of stratification)

Key: AHA = antihyperglycemic agent, Cana=canagliflozin, CI = confidence interval, Diff = difference, ISE = Integrated Summary of Efficacy, LOCF = last observation carried forward, LS = least squares, N = number, SD = standard deviation, SE = standard error, SU=sulphonylurea.

Note: Predefined timepoint of primary endpoint: Week 18 LOCF (DIA3008 SU Substudy), Week 26 LOCF (DIA3004, DIA3005, DIA3010)

Source: Mod5.3.5.3\CANA ISE\Tab23

Add-on to metformin monotherapy studies

Study DIA3006: this study aimed at investigating the add-on use of CANA in subjects with inadequate glycemic 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, -1.11mmHg 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:

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: <u>Main Study:</u> CANA 100 mg (N=195), CANA 300 mg (N=197) Placebo (N=192) <u>High Glycemic Substudy:</u> 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, mmol/L) Proportion of subjects with HbA_{1c} <7.0% Percent change in 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)	

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 glycemic 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.

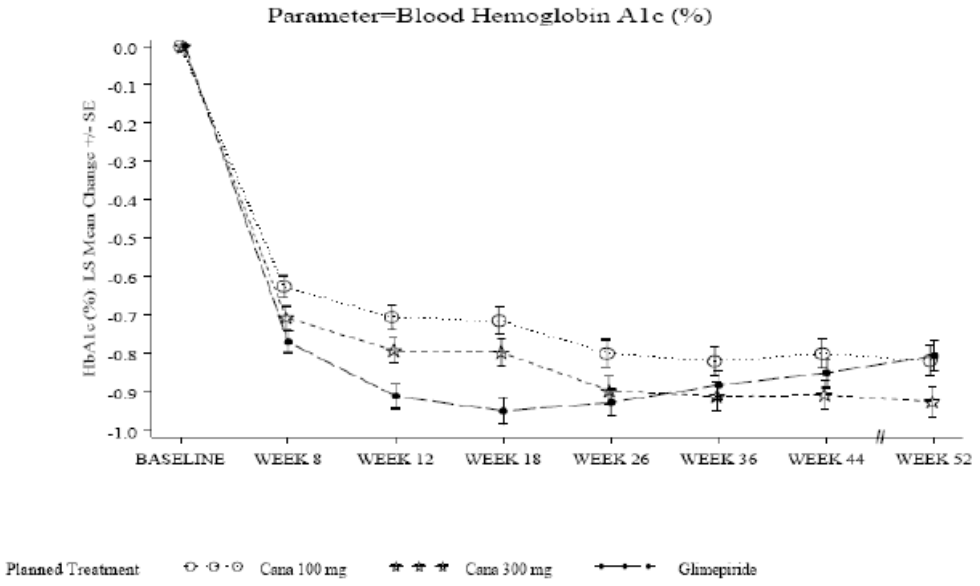
The results on the secondary glycaemic endpoints (FPG lowering, proportion of responders) generally supported those on HbA1c. Body weight decreased in the CANA groups compared to a small gain in the glimepiride group. A substudy investigating body composition showed that fat loss contributed significantly 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 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, mmol/L) Proportion of subjects with HbA_{1c} <7.0% Percent change in body weight
Database lock date	25 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. 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)	

Add-on to metformin based dual combination AHA therapy

Study DIA3002: the aim of this study was to examine the add-on use of CANA compared to placebo in subjects with inadequate glycemic 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 Glycemic 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, mmol/L) Proportion of subjects with HbA_{1c} <7.0% Percent change in 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 glycemic 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-subtracted 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 Glycemic 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:

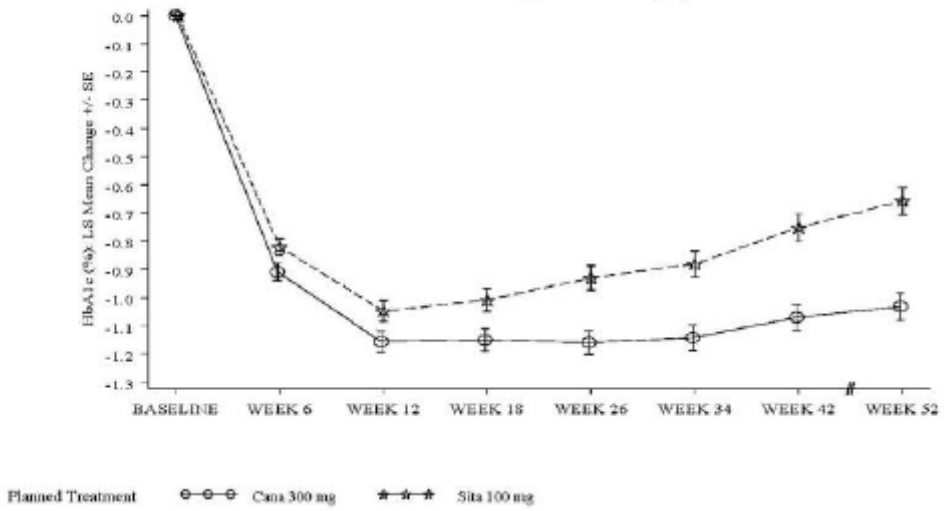
		Fasting plasma glucose (FPG, mmol/L) Proportion of subjects with HbA_{1c} <7.0% Percent change in body weight
Database lock date	19 December 2011	
Primary analysis description	Analysis of covariance (ANCOVA) model with treatment and stratification factors as fixed effects and HbA_{1c} baseline value 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 glycemic withdrawal criteria (23% vs 11% for canagliflozin). (Note: in DIA3015, subjects meeting prespecified glycemic 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 3 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 3 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 Glycemic 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, mmol/L) Proportion of subjects with HbA_{1c} <7.0% Percent change in 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)	

Add-on to metformin and insulin

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 antihyperglycemic 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 3 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 glycemic 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 glycemic 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 3 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. Glycemic 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, mmol/L) Proportion of subjects with HbA_{1c} <7.0% Percent change in 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 glycemic control in the subgroup of subjects receiving **SU monotherapy** at a protocol pre-specified dose (for details please refer to "treatments" in clinical AR). However, due to misstratification (for details please refer to "study conduct", Clinical AR) 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, mmol/L) Proportion of subjects with HbA_{1c} <7.0% Percent change in 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)	

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. It includes a high proportion (about 70%) of subjects for whom CANA was added to ongoing metformin therapy and is therefore also relevant for the FDC.

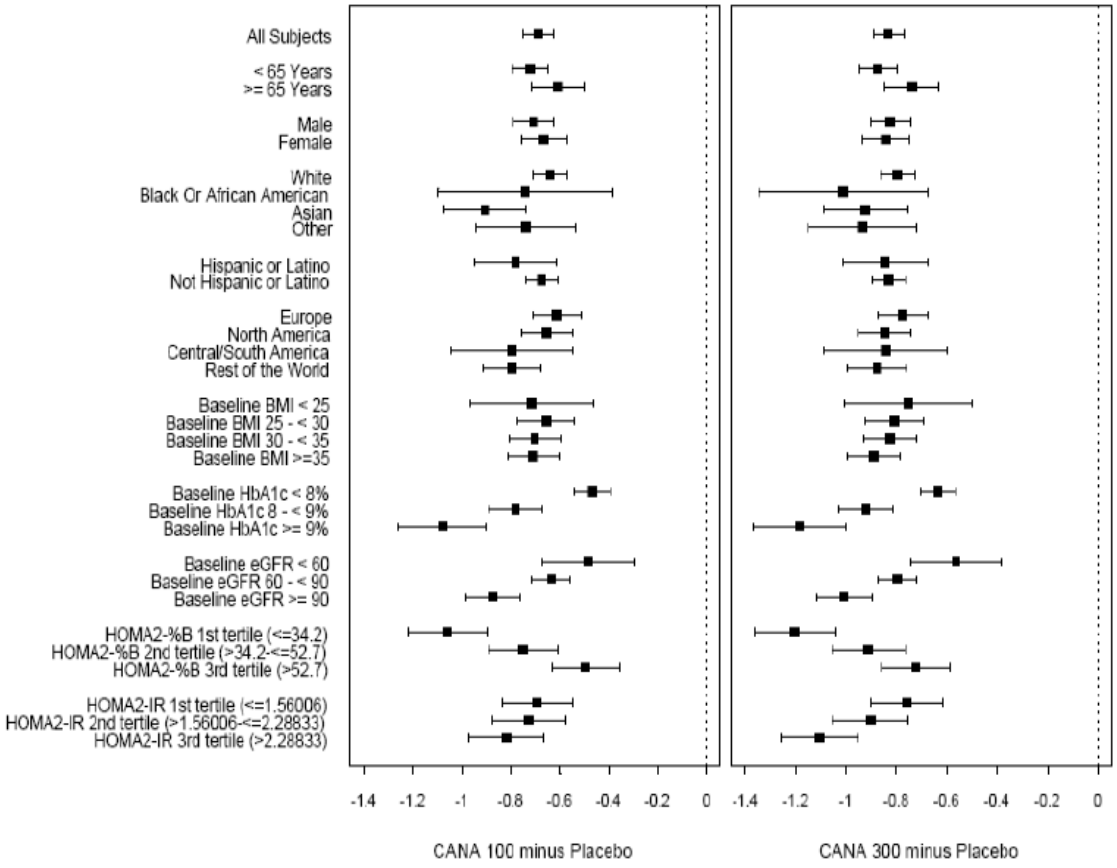
Baseline characteristics were generally similar across the pooled CANA 100 mg, CANA 300 mg group, and placebo treatment group. In each pooled treatment group, there was a slightly higher proportion of males compared with females. The median age was 60 years, a total of 1031 (25%) patients was 65-<75 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 by 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.

In the pooled dataset the mean percent change from baseline in body weight at the primary assessment time point, 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 following:

Subgroup analysis by baseline HbA1c: the most prominent effect occurred in patients with high baseline values. The effect (placebo subtracted 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.

Supportive studies

Additional CANA supportive study with substantial proportion of subjects on MET

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 3 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 3 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 3 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 that 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 3 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, mmol/L) Proportion of subjects with HbA_{1c} <7.0% Percent change in 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)	

Other supportive studies

Study DIA3005: this study evaluated the efficacy of canagliflozin 100 mg and 300 mg, administered as **monotherapy** in adults with T2DM who had **inadequate glycemic 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 glycemic 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: <u>Main Study:</u> CANA 100 mg (N=195), CANA 300 mg (N=197) Placebo (N=192) <u>High Glycemic Substudy:</u> 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, mmol/L) Proportion of subjects with HbA_{1c} <7.0% Percent change in 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);	Placebo-subtracted LS mean (SE): CANA 100 mg -0.91 (0.091);

	CANA 100 mg 8.06 (0.959); CANA 300 mg 8.01 (0.988)	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 glycemic 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 3 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.

Results of extension studies

In addition to the 52-week results for the **DIA3009** and **DIA3015** studies (see above), 26-week extension periods were conducted for the extension studies of the add-on to metformin studies (**DIA3002** and **DIA3006** to further substantiate the durability of effect on both the primary endpoint of HbA1c. Results are presented in the following table:

Table 7 **HbA_{1c} (%) Change from Baseline to Week 52 in Four Extension Studies- LOCF: Study-by-Study Comparison (Phase 3 Add-on to Metformin Studies and Additional Supportive Studies CANA/MET IR FDC: Modified Intent-to-Treat [mITT] Analysis Set)**

	Placebo	Cana 100 mg	Cana 300 mg	Sitagliptin
Add-on to Metformin Studies				
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)	
Additional Supportive Studies				
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 14; Mod5.3.5.1\DIA3004\Tab 13; Mod5.3.5.1\DIA3006\Tab 12; Mod5.3.5.1\DIA3005\Tab 12

In conclusion, durability of action over 52 weeks has been demonstrated for both doses of CANA.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The phase 3 clinical studies that provided primary support for the CANA tablets also provide support for the CANA/ MET IR FDC. A total of 5,151 subjects in the CANA phase 3 programme were treated with CANA and MET.

Additional clinical data serve to bridge the results from the phase 3 studies of once-daily administration of CANA as an add-on treatment to metformin (alone or with other AHAs) to the twice daily administration proposed for CANA/ MET IR FDC. These data stem from the following studies: four phase 1 studies that evaluated the pharmacokinetic bioequivalence of the to-be marketed formulation of the CANA/MET IR FDC tablets to the individual tablet components; one phase 1 study evaluated the effect of food on the pharmacokinetics of the to-be marketed formulation of the CANA/MET IR FDC; study DIA2003 was performed to support the CANA/ MET IR FDC, which will be dosed twice daily, consistent with the dosing of metformin IR.

The dose selection for the FDC (50/850 mg CANA/ MET, 50/1000 mg CANA/ MET, 150/850 mg CANA/MET, 150/1000 mg CANA/MET) is supported by the results of the phase 3 studies of add-on use of CANA in subjects already on metformin (alone or with another AHA). In addition, results of study DIA1032 showed that in healthy subjects the PD effects (24 hour mean renal glucose threshold) of the administration of 150 mg administered bid was not discernibly different from 300 mg administered once-daily; and, similarly, 50 mg administered bid was not meaningfully different from 100 mg administered once-daily. Doses for metformin within the FDC were in line with the dosing recommendations of the metformin originator product.

The phase 3 programme supporting the combination of CANA and MET included 6 studies (including placebo- and active-controlled studies) of add-on combination use of CANA with MET (alone or in combination with other AHAs), and a substudy (of the CV safety study [DIA3008]) assessing the add-on combination of CANA with MET plus insulin, and 2 additional studies with CANA added to ongoing current diabetes treatment in which a substantial proportion of subjects were receiving treatment with MET. Nearly 80% (8,068 of 10,285) of subjects in the phase 3 programme were on a background treatment of metformin and 5,151 subjects were treated with CANA and metformin.

HbA1c was chosen as the primary endpoint in all phase 2/3 studies, which is in line with the "Note for Guidance on the Clinical Investigation of Medicinal Products for the treatment of diabetes mellitus (CPMP/EWP/1080/00)". Further to the evaluation of CANA on glycaemic endpoints, the effects of CANA on body weight, blood pressure and lipid parameters were investigated. Pharmacodynamic endpoints assessed in selected phase 3 studies to characterise the mechanism of action included RTG and beta-cell function/ insulin secretion endpoints.

The placebo controlled phase 3 studies DIA3006, DIA3002 and DIA3012 had a core double blind period for the primary endpoint of 26 weeks. For the DIA3008 Insulin and SU sub-studies 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. Studies DIA3006 and DIA3002 had 26 week extension periods. Results of HbA1c at week 52 are submitted for these add-on to metformin studies.

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 generally not excluded. Inadequate glycaemic control was defined in most of the studies as an HbA1c level of ≥7.0 and ≤10.5%, which is appropriate.

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 re-assuring.

Study DIA2003, which was newly submitted in support of the FDC, was designed to provide clinical data with twice daily dosing of CANA did not differ in design from the phase 3 studies. The core double blind period lasted for 18 weeks.

No patients below the age of 18 were included in the development programme. A product specific waiver has been granted by the PDCO on 20 April 2011.

Of the 5151 subjects exposed to CANA and MET across the phase 3 studies, 1408 were at least 65 years of age, including 1218 who were 65 to<75 years of age, 189 who were 75 to <85 years, and 1 subject who was ≥85 years. Hence, more than 100 geriatric patients were included in the phase 3 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.

Scientific advice has been obtained from CHMP and was considered in the development plan. The clinical trials generally were considered to be well designed and conducted. During the review process, no concerns regarding GCP compliance arose.

The statistical methods used are well described and considered appropriate.

Efficacy data and additional analyses

Results from phase 3 programme

In support of the CANA/ MET IR FDC, analyses of results from the phase 3 CANA programme relevant to this FDC were evaluated. All studies have already been submitted for and assessed during the marketing authorisation procedure of CANA mono.

Across the phase 3 placebo-controlled add-on to metformin studies, the efficacy of canagliflozin in lowering HbA1c, relative to placebo (LS mean placebo subtracted difference), was generally consistent and ranged from -0.76% to -0.92% with the 300 mg dose and from 0.62% to 0.71% with the 100 mg dose. Hence, CANA given once daily add-on to metformin led to a dose dependent, clinically relevant glycaemic improvement. Durability of glycaemic control was demonstrated by the week 52 data in studies DIA3006 and DIA 3002.

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 HbA1c-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 3 studies that included a MMTT) and discontinuation rates due to rescue therapy.

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 3 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. 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 3 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 is predominantly due to loss of calories (urinary nutrient loss) and not a consequence of dehydration. The effect on body weight and composition may favourably influence CV risk in the frequently obese patients with T2DM. However, the effect size is insufficient for an anti-obesity claim (no such claim was made within this submission).

Efficacy in subgroups

Results of subgroup analyses performed in the pooled population of the placebo controlled phase 3 studies found no important differences when comparing the effect of CANA in lowering HbA1c 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 HbA1c relative to placebo were observed with CANA among subjects with higher baseline HbA1c 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.

As outlined above elderly patients were adequately represented in the phase 3 program. Of note, in study DIA3010, aiming at investigating the efficacy and safety of CANA in the elderly, the age distribution did not differ markedly from that in the other phase 3 studies with the majority of patients being below 65 years of age (55-65 years), less than 3% of patients between 65 and 75 years of age, below 1% between 75 and 85 years, and no patient 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 antihyperglycaemic effect was still 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.

Unsurprisingly, given CANA's mechanism of action with the extent of UGE being proportional to renal function, the efficacy of CANA was found to be dependent upon baseline GFR. Subgroup analyses performed across phase 3 studies showed a gradual decline in efficacy of CANA with progressive renal impairment. This is however without implications for the present MAA since the proposed labelling contraindicates the FDC in patients with moderate renal impairment in line with the existing contraindication for metformin in this patient group.

Across all phase 3 studies, clinically relevant lowering of SBP and DBP was observed, which is generally 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 in combination with metformin is expected to reduce microvascular risk and may also favourably influence CV risk in patients with T2DM.

Results from bridging studies (Summary phase 1 and in extension DIA2003)

Study DIA2003 (CANA bid + MET vs. Placebo + MET) was performed to support the CANA/ MET IR FDC, which will be dosed twice daily, consistent with the dosing of metformin IR. The study showed reductions in HbA1c, FPG, and percent body weight, and an increase in the proportion of subjects achieving the HbA1c target <7.0%. Compared with study DIA 3006 (CANA qd + MET vs. Placebo + MET), the magnitude of reduction in HbA1c as well as effects on secondary antihyperglycaemic endpoints observed in DIA2003 were smaller and for the 50 mg bid dose were of borderline clinical significance.

This may at least partly be explained by baseline differences: in study DIA2003 mean baseline HbA1c was 7.6% (5.6-10.1%) and in study DIA3006 mean baseline HbA1c was 8.0% (6.3-10.7%). Among other things, the lower baseline values were due to the fact that 22.2% of the patients included had week 2 HbA1c values below 7%. Results of the sensitivity analysis excluding these patients showed that subjects in this study with baseline HbA1c <7.0% attenuated the results from the primary efficacy analysis modestly in the 150 bid group, but not in the 50 mg bid group.

To further investigate the impact of baseline HbA1c between studies DIA2003 and DIA3006 the Applicant conducted a simulation ("bootstrap simulation") to assess the potential impact of baseline glycaemic control in studies DIA2003 and DIA3006 on the primary efficacy results. From the study DIA3006 population, 10000 simulation datasets matching the distribution of HbA1c baseline values of study DIA2003 in 6 categories were analysed by ANCOVA (similar to the primary analysis in study DIA3006). HbA1c point estimates were calculated as overall mean from the bootstrapped datasets using placebo-subtracted ANCOVA LS mean changes and 95% confidence intervals were estimated by the lower 2.5% and upper 97.5% of the bootstrap population results. The bootstrap method used is considered appropriate and acceptable to

match baseline characteristics of the two studies compared. It was found that, after compensation for differences in baseline HbA1c distribution between studies, the placebo-subtracted changes in HbA1c for both CANA doses in DIA2003 are numerically consistent with a similar subgroup of patients from DIA3006 at the same total daily dose.

Although baseline differences in HbA1c (7.6% versus 8.0%) are considered modest, these differences may partly explain the differences in efficacy (effect on HbA1c). For comparison, a subgroup analysis by baseline HbA1c has been conducted within the MAA for CANA as a monotherapy and the effect (placebo subtracted LS mean change) were -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.

Overall, as demonstrated by the bootstrap simulation, the differences in efficacy are at least partly due to differences in baseline HbA1c. Interstudy variability may also have contributed to the divergent results.

Unfortunately, the design of study DIA2003 does not allow a direct comparison between once daily and twice daily dosing. However, similar pharmacokinetic and pharmacodynamic responses (24 hour mean renal glucose threshold) were demonstrated in a phase 1 study (DIA1032) regardless of once or twice daily administration (for details please refer to pharmacology section of this AR).

Overall, efficacy of CANA combined with MET seems to be maintained when given bid at the same total daily doses.

2.5.4. Conclusions on the clinical efficacy

Efficacy of the CANA/ MET FDC has been demonstrated. The fixed combination is considered justified. Since type 2 diabetes is a chronic disease requiring long term treatment, a fixed combination provides advantages for the patient and is expected to improve compliance in this usually already heavily medicated patient group. Adequate bridging data have been provided to extrapolate efficacy from the phase 3 CANA monotherapy programme to the FDC.

2.6. Clinical safety

For all of the phase 3 studies, safety evaluations included the collection of adverse events, safety laboratory tests (including haematology, 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 as well as bone formation and bone resorption markers.

Several safety monitoring committees were commissioned for the phase 3 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.

The IDMC, which included diabetologists, cardiologists, statisticians, and a consultant oncologist, monitored unblinded analyses of serious adverse events and specific CV events at specific regular intervals across the entire clinical development program for CANA.

The phase 3 clinical studies that provided the primary support for the canagliflozin (JNJ-28431754; CANA) Marketing Authorization Application (MAA) also provide the primary support for the canagliflozin/metformin immediate release (CANA/MET IR) fixed-dose combination (FDC) MAA. The safety results are mainly from two pools of phase 3 studies created from patients with metformin background therapy:

- A pooled dataset (DS1-M) including 3 placebo-controlled Phase 3 studies (DIA3002, DIA3006, and DIA3012) in which canagliflozin was added to subjects on antihyperglycemic agent (AHA) regimens including metformin (alone or in combination with other oral AHAs).
- A pooled dataset (DS3M-LT2) including those subjects whose background diabetes therapy at baseline included metformin from 6 Phase 3 studies (DIA3002, DIA3006, DIA3008, DIA3009, DIA3010, and DIA3012), with a data cutoff date of 01 July 2012.

Data sets based only on patients receiving CANA in combination with metformin are marked by an “M” in their name. Simultaneously, the Applicant provided a further update (later data cutoff) of the broad dataset (DS3) submitted for the CANA mono MAA. This update is called DS3-LT2. DS1 is a dataset which was also already submitted with the CANA mono MAA and comprises placebo-controlled trials of shorter duration.

Most study patients, namely 73%, had metformin included in their therapy regimen (4471 out of 6177 patients received CANA). Therefore, the differences in size between the data sets of patients receiving metformin vs. all patients are not very large.

The following table lists the datasets and the trials from which they were created:

Comparison of Pooled Datasets Supporting CANA/MET FDC MAA and CANA Single Agent MAA

Dataset	Support for CANA Single Agent MAA	Support for CANA/MET FDC MAA
Placebo-controlled Studies Dataset (Core period [Week 26] cutoff)	**DS1**	**DS1-M**
	DIA3002 (Add-on to metformin + sulphonylurea) DIA3006 (Add-on to metformin)[b]	DIA3002 (Add-on to metformin + sulphonylurea) DIA3006 (Add-on to metformin)[b]
	DIA3012 (Add-on to metformin + pioglitazone) DIA3005 (Monotherapy)[a]	DIA3012 (Add-on to metformin + pioglitazone)
Broad Dataset (01 July 2012 cutoff)	**DS3-LT2**	**DS3M-LT2**

	DIA3002 (Add-on to metformin + sulphonylurea) DIA3006 (Add-on to metformin)[c]	DIA3002 (Add-on to metformin + sulphonylurea) DIA3006 (Add-on to metformin)[c]
	DIA3008 (Add-on to any diabetes therapy in subjects with or at high risk for CV disease)	DIA3008 (Add-on to any diabetes therapy in subjects with or at high risk for CV disease)[d]
	DIA3009 (Add-on to metformin)	DIA3009 (Add-on to metformin)
	DIA3010 (Add-on to any diabetes therapy in older subjects)	DIA3010 (Add-on to any diabetes therapy in older subjects)[d]
	DIA3012 (Add-on to metformin + pioglitazone)[c]	DIA3012 (Add-on to metformin + pioglitazone)[c]
	DIA3004 (Add-on to any diabetes therapy in subjects with moderate renal impairment)	
	DIA3005 (Monotherapy)[a]	

a Subjects in the sitagliptin arm are not included in DS1 or DS1-M.
b Subjects in the High Glycemic Cohort are not included in DS1.
c Subjects assigned to placebo were switched to sitagliptin during the double-blind extension period.
d Subjects not on metformin-based background AHA therapy at baseline in these studies are not included in DS3M-LT2.

There were no remarkable imbalances in the baseline characteristics of the different treatment groups (placebo, CANA 100 mg and CANA 300 mg). Overall, there were more males than females in the study program but the female population with T2DM is nevertheless adequately reflected in the clinical trial program. A large proportion of patients were white so that the study results are relevant for the European population. Diabetes duration, baseline HbA1c and BMI indicate that the population is representative for diabetic patients in daily practice. The percentage of patients with at least one vascular complication was rather low (around 20%) so that the studied diabetic population appears rather healthy. The number of elderly patients (≥75 years) was below 100 in each dose group of the CANA-metformin pool, which is lower than in the CANA mono program and can be explained by the exclusion of patients for whom metformin is contraindicated. However, relevant conclusions on this age group can also be drawn from data on CANA in general (irrespective of combination with metformin).

Patient exposure

The following table summarises the patient exposure in the phase 3 programme, stratified for treatment duration.

Overall Exposure in Subjects on Metformin at Baseline in all Phase 3 Studies through 01 July 2012

	Cana 100 mg	Cana 300 mg	Cana Total	Non-Cana
Total Number of Subjects with Metformin at Baseline in Phase 3 Program	2392	2759	5151	2917
6-month Exposure	2172	2428	4600	2539
12-month Exposure	2009	2193	4202	2201
18-month Exposure	1158	1126	2284	1072
24-month Exposure	346	333	679	307

Note: The cutoff for studies DIA3002, DIA3006, DIA3012, and DIA3015 is end of the study. The cutoff of the rest of the phase 3 studies (DIA3004, DIA3008, DIA3009, and DIA3010) is July 1, 2012.

Note: 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.
Note: The summary is based on modified intent-to-treat set which included all randomized subjects that took at least one dose of study treatment.

Thus, up to 24 months the number of exposed patients is considered high enough to allow meaningful conclusions.

Adverse events

The following table (Table 17) summarises the incidence of adverse events (AEs) in the broadest CANA-metformin data set DS3M-LT2. For comparison the corresponding evaluation for all patients on CANA (not only in combination with metformin) is tabulated below.

Overall Summary of Adverse Events - Regardless of Use of Rescue Medication:
Dataset DS3M-LT2

Number (%) of Subjects with at least one TEAE of following Types	All Non-Cana (N=2538) n (%)	Cana 100 mg (N=2391) n (%)	Cana 300 mg (N=2380) n (%)
Any adverse events	**1909 (75.2)**	**1826 (76.4)**	**1824 (76.6)**
Adverse events leading to discontinuation	123 (4.8)	126 (5.3)	176 (7.4)
Adverse events related to study drug[a]	563 (22.2)	699 (29.2)	804 (33.8)
Adverse events related to study drug[a] and leading to discontinuation	49 (1.9)	80 (3.3)	116 (4.9)
Serious adverse events	**303 (11.9)**	**284 (11.9)**	**292 (12.3)**
Serious adverse events leading to discontinuation	50 (2.0)	45 (1.9)	34 (1.4)
Serious adverse events related to study drug[a]	14 (0.6)	21 (0.9)	22 (0.9)
Serious adverse events related to study drug[a] and leading to discontinuation	4 (0.2)	11 (0.5)	8 (0.3)
Deaths	16 (0.6)	12 (0.5)	15 (0.6)

Dataset DS3-LT2

Number (%) of Subjects with at least one TEAE of following Types	All Non-Cana (N=3262) n (%)	Cana 100 mg (N=3092) n (%)	Cana 300 mg (N=3085) n (%)
Any adverse events	**2473 (75.8)**	**2369 (76.6)**	**2375 (77.0)**
Adverse events leading to discontinuation	164 (5.0)	173 (5.6)	224 (7.3)
Adverse events related to study drug[a]	711 (21.8)	910 (29.4)	1037 (33.6)
Adverse events related to study drug[a] and leading to discontinuation	70 (2.1)	110 (3.6)	142 (4.6)
Serious adverse events	**445 (13.6)**	**417 (13.5)**	**406 (13.2)**
Serious adverse events leading to discontinuation	71 (2.2)	63 (2.0)	52 (1.7)
Serious adverse events related to study drug[a]	27 (0.8)	35 (1.1)	33 (1.1)
Serious adverse events related to study drug[a] and leading to discontinuation	10 (0.3)	17 (0.5)	14 (0.5)
Deaths	37 (1.1)	25 (0.8)	24 (0.8)

Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of rescue medication.

[a] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.

The overall rate of AEs and serious AEs is fairly balanced between the treatment groups in both data sets, DS3M-LT2 and DS3-LT2. In both data sets there is also a slight increase in the incidence of AEs related to study drug and AEs leading to discontinuation in the CANA groups compared to the non-CANA group. In DS3M-LT2, the incidence of SAEs was slightly lower in all treatment groups (including Non-CANA) than in DS3-LT2. This is probably due to the fact that patients with more severe background disease are often not eligible for metformin treatment due to contraindications.

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

The most frequent AEs, sorted by organ system, in patients receiving the CANA-metformin combination are tabulated below. Salient differences between CANA and comparator are marked in **bold**.

Adverse Events in At Least 2% of Subjects in Any Treatment Group by Body System and Preferred Term - Prior to Use of Rescue Medication: DS3M-LT2 Dataset

	All Non-Cana	Cana 100 mg	Cana 300 mg
Body System Or Organ Class	(N=2538)	(N=2391)	(N=2380)
Dictionary-Derived Term			
Total no. subjects with the AEs	1845 (72.7)	1807 (75.6)	1811 (76.1)
Ear and Labyrinth Disorders	103 (4.1)	82 (3.4)	80 (3.4)
Vertigo	55 (2.2)	44 (1.8)	45 (1.9)
Gastrointestinal Disorders	534 (21.0)	554 (23.2)	567 (23.8)
Constipation	44 (1.7)	70 (2.9)	66 (2.8)
Diarrhoea	159 (6.3)	126 (5.3)	177 (7.4)
Nausea	67 (2.6)	65 (2.7)	86 (3.6)
Toothache	31 (1.2)	51 (2.1)	37 (1.6)
General Disorders and Administration Site Conditions	275 (10.8)	286 (12.0)	321 (13.5)
Fatigue	51 (2.0)	60 (2.5)	66 (2.8)
Oedema Peripheral	72 (2.8)	34 (1.4)	34 (1.4)
Pyrexia	42 (1.7)	40 (1.7)	52 (2.2)
Thirst	**0**	30 (**1.3**)	55 (**2.3**)
Infections and Infestations	952 (37.5)	1013 (42.4)	1022 (42.9)
Bronchitis	92 (3.6)	86 (3.6)	78 (3.3)
Gastroenteritis	58 (2.3)	42 (1.8)	60 (2.5)
Influenza	88 (3.5)	98 (4.1)	95 (4.0)
Nasopharyngitis	233 (9.2)	239 (10.0)	235 (9.9)
Sinusitis	58 (2.3)	58 (2.4)	65 (2.7)
Upper Respiratory Tract Infection	203 (8.0)	170 (7.1)	168 (7.1)
Urinary Tract Infection	134 (5.3)	165 (6.9)	157 (6.6)
Vulvovaginal Mycotic Infection	17 (**0.7**)	57 (**2.4**)	63 (**2.6**)
Investigations	232 (9.1)	198 (8.3)	219 (9.2)
Blood Creatine Phosphokinase Increased	55 (2.2)	20 (0.8)	15 (0.6)
Metabolism and Nutrition Disorders	391 (15.4)	309 (12.9)	336 (14.1)
Hyperglycaemia	72 (2.8)	39 (1.6)	33 (1.4)
Hypoglycaemia	210 (8.3)	157 (6.6)	185 (7.8)
Musculoskeletal and Connective Tissue Disorders	521 (20.5)	539 (22.5)	525 (22.1)

Arthralgia	114 (4.5)	119 (5.0)	89 (3.7)
Back Pain	117 (4.6)	134 (5.6)	148 (6.2)
Musculoskeletal Pain	56 (2.2)	56 (2.3)	59 (2.5)
Osteoarthritis	40 (1.6)	47 (2.0)	45 (1.9)
Pain in Extremity	83 (3.3)	78 (3.3)	64 (2.7)
Nervous System Disorders	344 (13.6)	342 (14.3)	378 (15.9)
Dizziness	31 (1.2)	28 (1.2)	48 (2.0)
Headache	140 (5.5)	94 (3.9)	123 (5.2)
Renal and Urinary Disorders	146 (**5.8**)	254 (**10.6**)	259 (**10.9**)
Pollakiuria	21 (**0.8**)	87 (**3.6**)	102 (**4.3**)
Reproductive System and Breast Disorders	97 (**3.8**)	210 (**8.8**)	262 (**11.0**)
Balanitis	10 (**0.4**)	59 (**2.5**)	53 (**2.2**)
Balanoposthitis	4 (**0.2**)	26 (**1.1**)	48 (**2.0**)
Vulvovaginal Pruritus	5 (**0.2**)	35 (**1.5**)	55 (**2.3**)
Respiratory, Thoracic and Mediastinal			
Disorders	287 (11.3)	257 (10.7)	254 (10.7)
Cough	102 (4.0)	92 (3.8)	84 (3.5)
Oropharyngeal Pain	50 (2.0)	40 (1.7)	40 (1.7)
Vascular Disorders	180 (7.1)	156 (6.5)	153 (6.4)
Hypertension	107 (**4.2**)	65 (**2.7**)	52 (**2.2**)

Note: Percentages calculated with the number of subjects in each group as denominator. incidence is based on the number of subjects experiencing at least one adverse event, not the number of events, prior to use of rescue medication

Most of the imbalances displayed in the table above reflect the known physiological actions of CANA or known side effects resulting from them. These comprise e.g. thirst, pollakiuria and all signs of urogenital infection. Vice versa, the incidence of hypertension was reduced with CANA. All other imbalances listed in the table above are not considered meaningful, either because of being too small or because the absolute number of patients affected is very low.

There were no meaningful differences between DS3M-LT2 and DS3-LT2.

AEs of special interest:

It is known that certain antidiabetics may aggravate **hypoglycaemia** when combined with hypoglycaemic agents although they do not cause hypoglycaemia when administered alone. Therefore the Applicant provided an evaluation of hypoglycaemic events separated for studies with vs. without background therapy with hypoglycaemic agents (suphonylureas, insulin).

In the phase 3 studies the Applicant defined documented hypoglycaemias as follows:

- Biochemically documented hypoglycaemic episode: a hypoglycaemic episode with a concurrent reported fingerstick glucose of ≤70 mg/dL (3.9 mmol/L) (regardless of the presence of symptoms).
- Severe hypoglycaemic episode: when the answer “Yes” was recorded to any of the following 3 questions on the hypoglycaemia eCRF: “Did the subject require the assistance of others to treat?”, “Did the subject lose consciousness during the episode?”, or “Did the subject have a seizure during the episode?”

The following tables reveal that CANA itself does not induce hypoglycaemia to a relevant extent. Also, when CANA is administered along with a non-hypoglycaemic agent including metformin the

incidence of hypoglycaemias essentially remains at placebo level. The following table provides the results in placebo-controlled studies **without** hypoglycaemic background therapy:

Documented Hypoglycaemia - Prior to Use of Rescue Medication (ISS Phase 3 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 hypoglycaemia	11(2.2)	26(3.8)	29(4.3)
Biochemically documented hypoglycaemia	11(2.2)	26(3.8)	28(4.1)
Severe hypoglycaemia	0	1(0.1)	1(0.1)
Total number of episodes	20	69	57
Subjects with numbers of documented hypoglycaemia	11(2.2)	26(3.8)	29(4.3)
1 episode	8(1.6)	15(2.2)	15(2.2)
2 episodes	2(0.4)	3(0.4)	7(1.0)
≥3 episodes	1(0.2)	8(1.2)	7(1.0)
Event rate per subject-year exposure	0.10	0.22	0.18
Subjects with any biochemically documented hypoglycaemia	11(2.2)	26(3.8)	28(4.1)
≤70 mg/dL (3.9 mmol/L)	11(2.2)	26(3.8)	28(4.1)
<63 mg/dL (3.5 mmol/L)	7(1.4)	14(2.1)	16(2.4)
<56 mg/dL (3.1 mmol/L)	2(0.4)	5(0.7)	4(0.6)
<36 mg/dL (2.0 mmol/L)	2(0.4)	1(0.1)	0

Note: Count (%) is based on number of subjects, not number of events, prior to use of rescue medication.
Note: Documented hypoglycaemia includes episodes with concurrent glucose measurement <70 mg/dL (3.9 mmol/L) and/or meeting criteria for severe hypoglycaemia. Biochemically documented hypoglycaemia includes episodes with concurrent glucose measurement ≤70 mg/dL (3.9 mmol/L)
Note: Exposure adjusted incidence rate is calculated as the total number of subjects with at least one event divided by the total drug exposure in person years. Exposure adjusted event rate is calculated as the total number of events divided by the total drug exposure in person years.

For comparison, the table below shows the incidence of hypoglycaemia in placebo-controlled studies with background therapy **including** hypoglycaemic agents.

Treatment-Emergent Documented Hypoglycaemia (Biochemically Documented and/or Severe) - Prior to Rescue Medication (Studies 28431754-DIA3002: 28431754-DIA3008; 28431754-DIA3015 Safety Analysis Sets)

	Placebo	**CANA 100 mg**	**CANA 300 mg**	**Comparator**
DIA3002 (background: met+SU)	(N=156)	(N=157)	(N=156)	NA
Subjects with any documented hypoglycaemia	24(15.4)	43(27.4)	47(30.1)	NA
Biochemically documented hypoglycaemia[a]	24(15.4)	42(26.8)	47(30.1)	NA
Severe hypoglycaemia	1(0.6)	1(0.6)	0	NA
Total number of episodes	69	184	239	NA
Event rate per subject-year exposure	***1.04***	***2.58***	***3.38***	NA
DIA3008 Insulin Substudy	(N=565)	(N=566)	(N=587)	NA

Subjects with any documented hypoglycaemia	208(36.8)	279(49.3)	285(48.6)	NA
Biochemically documented hypoglycaemia[a]	208(36.8)	279(49.3)	283(48.2)	NA
Severe hypoglycaemia	14(2.5)	10(1.8)	16(2.7)	NA
Total number of episodes	945	1355	1629	NA
Event rate per subject-year exposure	5.26	7.21	8.44	NA
DIA3008 Sulphonylurea Substudy	(N=69)	(N=74)	(N=72)	NA
Subjects with any documented hypoglycaemia	4(5.8)	3(4.1)	9(12.5)	NA
Biochemically documented hypoglycaemia[a]	4(5.8)	3(4.1)	9(12.5)	NA
Severe hypoglycaemia	0	0	0	NA
Total number of episodes	8	14	14	NA
Event rate per subject-year exposure	0.37	0.58	0.59	NA
DIA3015 (comparator sitagliptin, background met+SU)	NA	NA	(N=377)	Sita (N=378)
Subjects with any documented hypoglycaemia	NA	NA	163(43.2)	154(40.7)
Biochemically documented hypoglycaemia[a]	NA	NA	162(43.0)	152(40.2)
Severe hypoglycaemia	NA	NA	15(4.0)	13(3.4)
Total number of episodes	NA	NA	1277	1143
Event rate per subject-year exposure	NA	NA	4.14	3.81

a Subjects with any treatment-emergent biochemically documented hypoglycaemia episodes (symptomatic and asymptomatic)
NA = Not Applicable

The combination CANA + metformin does not appear to induce clinically relevant hypoglycaemia when given alone. However, addition of CANA to agents with high hypoglycaemic propensity (SU or insulin here) leads to a higher rate of hypoglycaemias than SU or insulin alone. This is also known for other glucose-lowering agents that are not associated with hypoglycaemia themselves. In two of these studies metformin was part of the background therapy but the combination CANA + metformin was not measured against placebo. Hence the exact role of metformin cannot be delineated, but most likely metformin does not influence hypoglycaemia rate to a large extent. Increased hypoglycaemia in combination with SU or insulin is adequately labelled in the SmPC and listed as identified risk in the RMP.

SGLT2 inhibitors lead to the steady presence of glucose in urine which may favour proliferation of microorganisms in the urogenital tract. The following two tables provide the frequency of **urinary tract infections** (UTI) in patients treated with CANA +metformin.

Overall Summary of Urinary Tract Infection Adverse Events - Regardless of Use of Rescue Medication: DS3M-LT2 Dataset

	All Non-Cana (N=2538)	Cana 100 mg (N=2391)	Cana 300 mg (N=2380)
Number (%) of Subjects with at least one AE of following Types	n (%)	n (%)	n (%)
Any UTI[a]	160 (6.3)	199 (8.3)	191 (8.0)
UTI[a] leading to discontinuation	2 (0.1)	8 (0.3)	5 (0.2)
UTI[a] related to study drug[b]	73 (2.9)	123 (5.1)	117 (4.9)
Serious adverse events of UTI[a]	7 (0.3)	13 (0.5)	7 (0.3)

Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication.

[a] Urinary Tract Infection Adverse Events based upon a prespecified subset of preferred terms from a MedDRA query listed in the SAP

[b] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.

Urinary Tract Infection Adverse Events by Preferred Term - Regardless of Use of Rescue Medication: DS3M-LT2 Dataset

Dictionary-Derived Term	All Non-Cana (N=2538) n (%)	Cana 100 mg (N=2391) n (%)	Cana 300 mg (N=2380) n (%)
Total no. subjects WITH ANY UTIs	160 (6.3)	199 (8.3)	191 (8.0)
Incidence Rate Per 1000 Person-Years Exposure	50.56	62.19	61.46
Cystitis	14 (0.6)	21 (0.9)	27 (1.1)
Escherichia Urinary Tract Infection	0	0	1 (<0.1)
Kidney Infection	1 (<0.1)	2 (0.1)	2 (0.1)
Pyelonephritis	0	7 (0.3)	0
Pyelonephritis Acute	4 (0.2)	0	1 (<0.1)
Pyelonephritis Chronic	0	3 (0.1)	2 (0.1)
Streptococcal Urinary Tract Infection	0	0	1 (<0.1)
Urinary Tract Infection	144 (5.7)	170 (7.1)	160 (6.7)
Urinary Tract Infection Bacterial	1 (<0.1)	0	0
Urinary Tract Infection Enterococcal	1 (<0.1)	0	0
Urinary Tract Infection Fungal	1 (<0.1)	1 (<0.1)	1 (<0.1)
Urosepsis	1 (<0.1)	4 (0.2)	1 (<0.1)

The incidence of UTI overall was only slightly higher with CANA than with placebo. Few events led to discontinuation and few events were serious. There was a numerically higher incidence of serious AEs including urosepsis in patients treated with 100 mg but not in patients treated with 300 mg CANA. Due to the small event numbers the relevance of this finding is not clear. The prescriber should be aware of UTI as a possible side effect of CANA. This is adequately reflected in the SmPC and listed as identified risk in the RMP.

Genital infections are also known side effects of SGLT2 inhibitors. In **females** the following event rates were reported in the broad data set (DS3-LT2):

Overall Summary of Mycotic Vulvovaginitis and Vulvovaginitis NOS Adverse Events - Regardless of Use of Rescue Medication: DS3M-LT2 Dataset

	All Non-Cana (N=1041)	Cana 100 mg (N=991)	Cana 300 mg (N=1023)
Number (%) of Subjects with at least one AE of following Types	n (%)	n (%)	n (%)
Any vulvovaginitis[a]	32 (3.1)	154 (15.5)	153 (15.0)
Vulvovaginitis[a] leading to discontinuation	0	9 (0.9)	16 (1.6)
Vulvovaginitis[a] related to study drug[b]	21 (2.0)	123 (12.4)	126 (12.3)
Serious adverse events of vulvovaginitis[a]	0	0	0

Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication

[a] Mycotic vulvovaginitis and vulvovaginitis NOS based upon a prespecified subset of preferred terms from a MedDRA query listed in the SAP.

[b] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.

There was a clearly and highly increased incidence of genital infections, mostly mycotic vulvovaginitis, in both CANA/metformin dose groups. 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. Genital infections are appropriately labelled in the SmPC and listed as identified risk in the RMP.

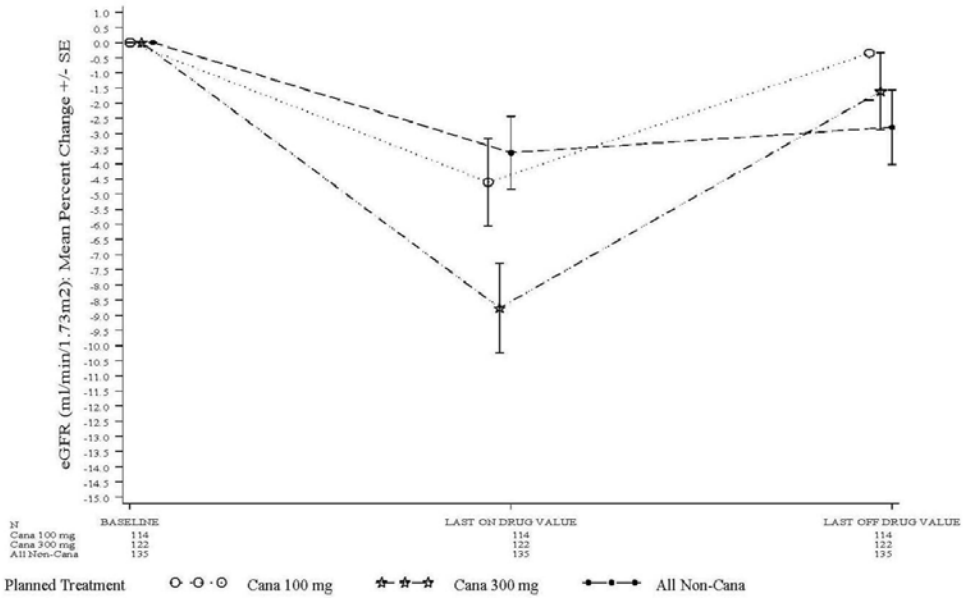
The following table gives a short overview of genital infections in **males**.

Overall Summary of Male Genital Infection Adverse Events - Regardless of Rescue Medication: DS1-M Dataset

	Placebo (N=246)	Cana 100 mg (N=327)	Cana 300 mg (N=315)
Number (%) of Subjects with at least one AE of following Types	n (%)	n (%)	n (%)
Any male genital infections	2 (0.8)	15 (4.6)	10 (3.2)
Male genital infections leading to discontinuation	0	2 (0.6)	1 (0.3)
Male genital infections related to study drug	2 (0.8)	11 (3.4)	8 (2.5)
Serious adverse events of male genital infection	0	0	0

The table above reveals that also in males the rate of genital infections is strongly increased with CANA/metformin. However, the absolute numbers are much lower than in females, reflecting the fact that males are much less predisposed to genital infection than females. Again, no serious events of genital infection were observed.

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 3 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).

The osmotic diuresis induced by SGLT2 inhibition can result in changes associated with volume depletion Thus, signs of **volume depletion** and AEs linked to volume depletion can be expected with CANA therapy. The following tables list the incidence of AEs related to dehydration in general as well as the most frequent individual events. Results from DS3M-LT2 are shown.

Overall Summary of Reduced Intravascular Volume-related Adverse Events - Regardless of Use of Rescue Medication: DS3M-LT2 Dataset

	All Non-Cana	Cana 100 mg	Cana 300 mg
	(N=2538)	(N=2391)	(N=2380)
Number (%) of Subjects with at least one AE of following Types	n (%)	n (%)	n (%)
Any volume depletion adverse event	60 (2.4)	63 (2.6)	94 (3.9)
Volume depletion leading to discontinuation	3 (0.1)	1 (<0.1)	2 (0.1)
Volume depletion related to study drug	12 (0.5)	17 (0.7)	36 (1.5)
Serious adverse events of volume depletion	6 (0.2)	9 (0.4)	5 (0.2)

Reduced Intravascular Volume-related Adverse Events - Regardless of Use of Rescue Medication: DS3M-LT2 Dataset

Dictionary-Derived Term	All Non-Cana (N=2538) n (%)	Cana 100 mg (N=2391) n (%)	Cana 300 mg (N=2380) n (%)
Total no. subjects With adverse events[a]	60 (2.4)	63 (2.6)	94 (3.9)
Incidence Rate Per 1000 Person-Years Exposure	18.96	19.69	30.25

Blood Pressure Decreased	1 (<0.1)	2 (0.1)	2 (0.1)
Dehydration	10 (0.4)	2 (0.1)	8 (0.3)
Dizziness Postural	18 (0.7)	19 (0.8)	24 (1.0)
Hypotension	15 (0.6)	30 (1.3)	36 (1.5)
Orthostatic Hypotension	4 (0.2)	7 (0.3)	18 (0.8)
Orthostatic Intolerance	1 (<0.1)	1 (<0.1)	0
Presyncope	7 (0.3)	2 (0.1)	1 (<0.1)
Syncope	10 (0.4)	7 (0.3)	14 (0.6)
Urine Output Decreased	1 (<0.1)	0	0

CANA clearly increased the incidence in volume depletion related events in a dose-dependent manner, most pronounced for hypotension; (pre)syncopal events were uncommon and did not clearly differ between treatment groups. The effect was smaller in DS3M-LT2 as compared to DS3-LT2. This is probably due to the fact that patients with higher degrees of renal impairment or other more severe background disease have a higher risk for CANA-dependent volume depletion but are less likely to be eligible for metformin treatment and hence less frequently represented in DS3M-LT2.

Reassuringly, serious AEs were not increased in the 300 mg CANA group; the slight increase in the 100 mg CANA group in DS3M-LT2 is probably a chance finding. Hypotension could be a problem in 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. Care should be taken when using CANA/metformin in these patients. This is reflected in the SmPC and dehydration-related events are included as identified risk in the RMP. The influence of concomitant therapy with diuretics and antihypertensive drugs is presented in the section on interactions below.

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 2 and 3 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 and it did not include both 100 and 300mg dosage strengths of canagliflozin.

In the meta-analysis performed, the CV events are fairly balanced between the treatment groups in both evaluations. It is reassuring that the event rate for MACE was nearly identical between

the All CANA and the comparator group and that 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; see table below for details.

MACE Events (All Phase 2/3 Studies: mITT Analysis Set)

	Non-Cana[a]	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)[b]
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)	

MACE = CV death, nonfatal myocardial infarction (MI), and nonfatal stroke.

a Placebo and/or active comparator therapy.

b Hazard ratio (HR) of pooled canagliflozin subjects versus control subjects with events is from Cox proportional hazards model including term for strata (CANVAS vs. other Phase 2/3 studies).

c Includes events that occur between the first dose of study drug and up to 30 days after discontinuation of study drug. The analysis excludes subjects in DIA3005's high glycaemic cohort.

d Subjects with multiple event types are included in the event category that occurred earliest.

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 need to be further followed post-marketing in the CV outcome study CANVAS and in the PSURs; the evaluation of the MACE-Plus endpoint gave similar results.

The following tables summarise the main results for MACE and MACE-Plus events, stratified for patients with high vs. low CV risk; high CV risk was defined as meeting the inclusion criteria for the CV outcome trial CANVAS.

MACE Events for CANVAS Subjects and Selected Non-CANVAS Subjects (mITT)

	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)

MACE-Plus Events for CANVAS Subjects and Selected Non-CANVAS Subjects (mITT)

	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.

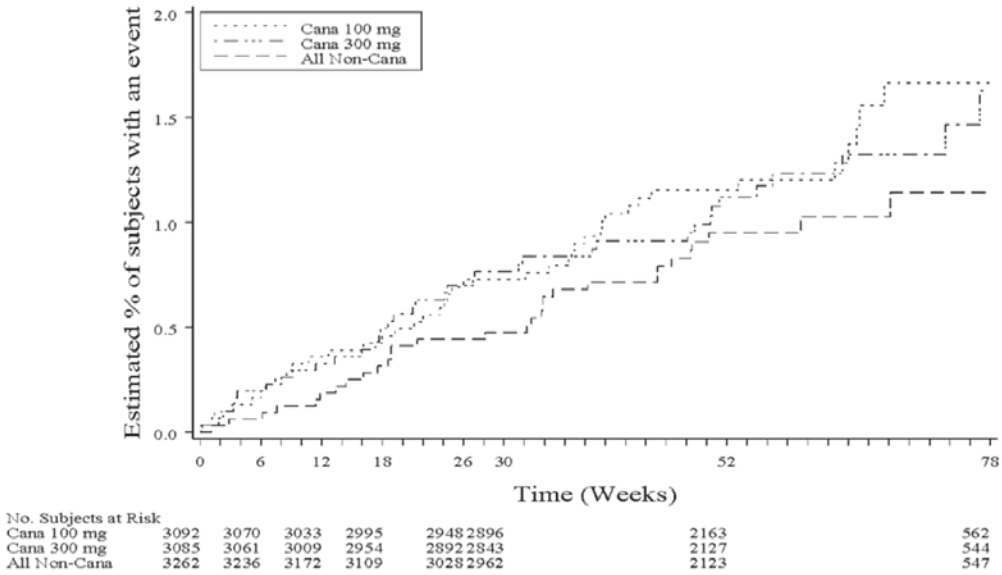
According to the results tabulated above, patients with high CV risk have a higher HR for CANA-related CV events than patients with low CV risk. However, even in the high risk (CANVAS and CANVAS-like) patients the HR is close to 1, and the upper limit of the 95% CI is acceptable (around 1.4 for MACE and MACE-plus). Further results will become available from the ongoing CANVAS study.

The Applicant also summarised the incidence of AEs related to **congestive heart failure**. In the Non-CANA group of the broad dataset, **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.

Metformin is known not to increase the incidence of CV events so that focussing on CANA + metformin patients only is not expected to change the picture; in fact most of the study patients received a co-treatment with metformin.

The following table shows the incidence of **bone fractures** (all and low-trauma) in the broad dataset, 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 3 Longer term Exposure Broad Dataset: Safety Analysis Set)

A slight imbalance between CANA and comparator is obvious. This was driven by a more pronounced imbalance in the CV outcome study CANVAS. The Applicant provided an analysis of fracture events in the CANVAS study (data cut-off 31 May 2013), see table below.

Post Randomization Adjudicated Fracture Adverse Events - CANVAS

	Cana 100 mg (N=1,445)	Cana 300 mg (N=1,441)	All Cana (N=2,886)	All Non-cana (N=1,441)
Subjects with any event	57 (3.9)	57 (4.0)	114 (4.0)	37 (2.6)
Incidence rate (/1,000 subject-years)[a]	16.3	16.4	16.3	10.8
HR (vs all non-cana)[b]	1.52(1, 2.3)	1.50(0.99, 2.27)	1.51(1.04, 2.19)	N/A

Key: cana=canagliflozin, HR=hazard ratio, N=number.

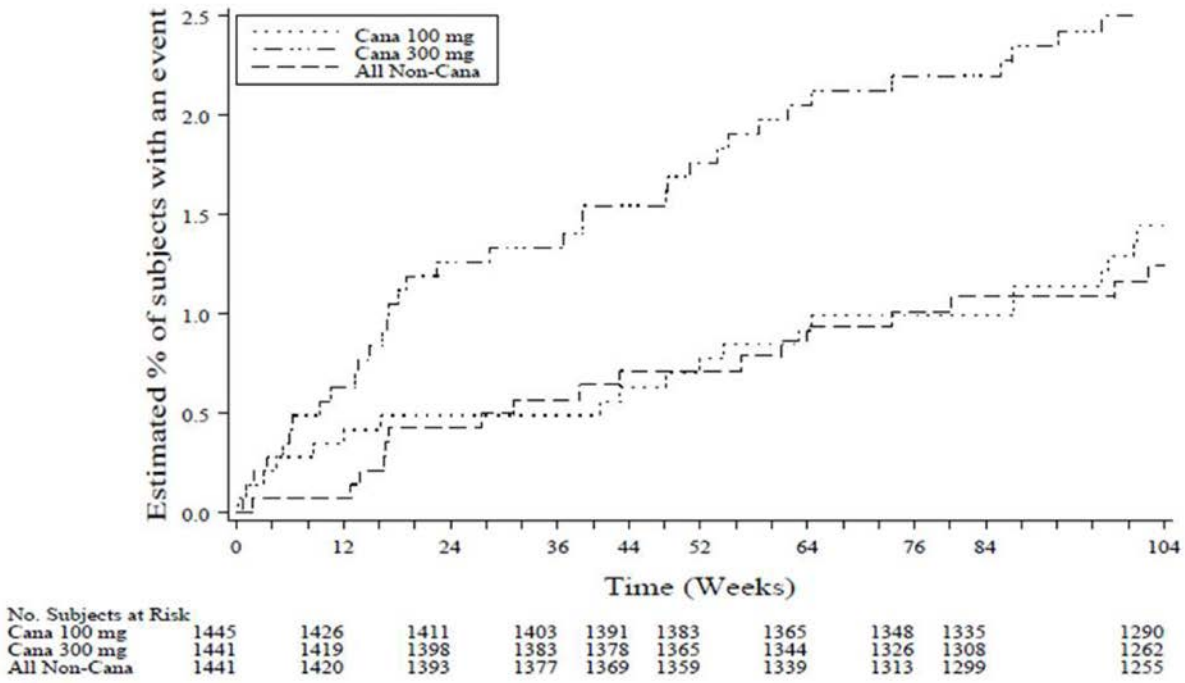
a Incidence is based on the number of subjects with at least one fracture and not number of events. Incidence rates are per 1,000 subject-years, where a subject's follow-up time (subject-year) is calculated from the first dose date to the first fracture event date.

b HR is from the Cox proportional hazards model, stratified by study ID.

In contrast to the fracture imbalance in the CANVAS study, an examination of adjudicated fractures in the pooled non-CANVAS studies of the Phase 3 program (N=5,867) through Week 52 revealed a slightly higher incidence rate in the Non-CANA group. The incidences were **10.8**, **12.0**, and **14.1** events per 1,000 patient-years for CANA 100 mg, CANA 300 mg and Non-CANA, respectively.

The Kaplan-Meier plot indicates that the difference between CANA and comparator became obvious very early in treatment (after around 6 weeks). Usually bone changes (e.g. noticeable decrease in bone density) need more time to develop. On the other hand, the increase in fractures may be due to increased falls related to CANA-induced dizziness or hypotension. Most fractures that occurred 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. The CANVAS study included patients with high CV risk, i.e. a

population which may be particularly sensitive to CANA-induced haemodynamic changes. In fact, an increased rate of **falls** were observed in the CANA 300 mg group of the CANVAS trial with the majority of the excess cases occurring within the first 16-24 weeks of treatment initiation; the 100 mg dose behaved similar to comparator, see Kaplan-Meier plot below.



Kaplan-Meier Plot of Time to First Post-Randomization Adverse Event Associated With Fall – CANVAS

Bone mineral density (BMD) was measured by DXA up to 104 weeks in study DIA3010.The results were as follows:

DIA3010: DXA BMD Placebo-subtracted Percent Change in DXA BMD from Baseline at Week 26, 52 and 104

	Week 26		Week 52		Week 104	
Location	Cana 100 LS Mean Diff (SE) [95%CI]	Cana 300 LS Mean Diff (SE) [95%CI]	Cana 100 LS Mean Diff (SE) [95%CI]	Cana 300 LS Mean Diff (SE) [95%CI]	Cana 100 LS Mean Diff (SE) [95%CI]	Cana 300 LS Mean Diff (SE) [95%CI]
Lumbar Spine	0.2 (0.3) [-0.4,0.8]	−0.3 (0.3) [-0.9, 0.3]	−0.4 (0.3) [-1.0, 0.3]	−0.7 (0.3) [-1.4, -0.1]	−0.3 (0.4) [-1.1, 0.5]	−0.7 (0.4) [-1.5, 0.1]
Total Hip	−0.4 (0.2) [-0.8, -0.0]	−0.5 (0.2) [-0.9, -0.1]	−0.4 (0.3) [-1.0, 0.1]	−0.7 (0.3) [-1.3, -0.2]	−0.9 (0.4) [-1.5, -0.2]	−1.2 (0.4) [-1.9, -0.6]
Femoral Neck	0.3 (0.3) [-.03, 1.0]	0.4 (0.3) [-.03, 1.1]	0.1 (0.4) [-0.6, 0.8]	0.6 (0.4) [-0.1, 1.4]	−0.1 (0.4) [-1.0, 0.8]	−0.1 (0.4) [-0.9, 0.8]
Distal Forearm	−0.3 (0.3) [-0.9, 0.4]	−0.4 (0.3) [-1.0, 0.3]	0.5 (0.3) [-0.1. 1.2]	0.1 (0.3) [-0.6. 0.7]	0.0 (0.4) [-0.8, 0.9]	−0.4 (0.4) [-1.3, 0.4]

Key: BMD=bone mineral density, cana=canagliflozin, Diff = difference, DXA=dual-energy X-ray absorptiometry, CI=confidence interval, SE=standard error.

These data reveal only small (<1% in most cases) changes in both directions in BMD in the bone regions tested.

Nonclinical studies and phase 1/2 trials demonstrated that CANA has **phototoxic potential**, although only at high light intensity which is considered clinically irrelevant. In phase 3 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 reassuringly the number of events was low.

Photosensitivity Skin Adverse Events - Regardless of Use of Rescue Medication (ISS Phase 3 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 1 and phase 2 studies. There was a marked increase in the incidence of skin ulcer in the broad dataset. 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.

The Applicant provided an updated analysis of **bladder cancer** cases (cut-off date 31 Dec 2013).

Bladder tumour adverse events occurred at a low and similar incidence across treatment groups, see table below. The 95% confidence intervals around the difference between each canagliflozin treatment group (including All Cana) and the pooled control group ("All Non-cana"), included zero. All bladder tumour adverse events occurring in the non-canagliflozin group were in subjects on placebo.

Table: Incidence of Post-randomization Bladder Tumor Adverse Events in the Canagliflozin Phase 3 Program (data as of 31 December 2013)

	Cana 100 mg	Cana 300 mg	All Cana	All Non-cana	Cana 100 mg Minus All Non-cana	Cana 300 mg Minus All Non-cana	All Cana Minus All Non-cana
	N=3,139	N=3,506	N=6,645	N=3,640			
	n (%)	n (%)	n (%)	n (%)	(95%CI)[a]	(95%CI)[a]	(95%CI)[a]
Number of subjects with bladder tumour	5 (0.16)	7 (0.20)	12 (0.18)	5 (0.14)	0.02 (-0.18; 0.23)	0.06 (-0.16; 0.28)	0.04 (-0.14; 0.22)

The total exposure through 31 December 2013 is estimated at 5,824, 6,038, and 5,921 subject-years for the canagliflozin 100 mg, canagliflozin 300 mg and non-canagliflozin groups, respectively. From this, it can be calculated that there were **0.86**, **1.16** and **0.84** cases per 1000 subject years in the CANA 100, CANA 300 and Non-CANA group, respectively.

Serious adverse events and deaths

There was no increase in overall death rate in the CANA groups as compared to control, see section on Adverse Events above. 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.

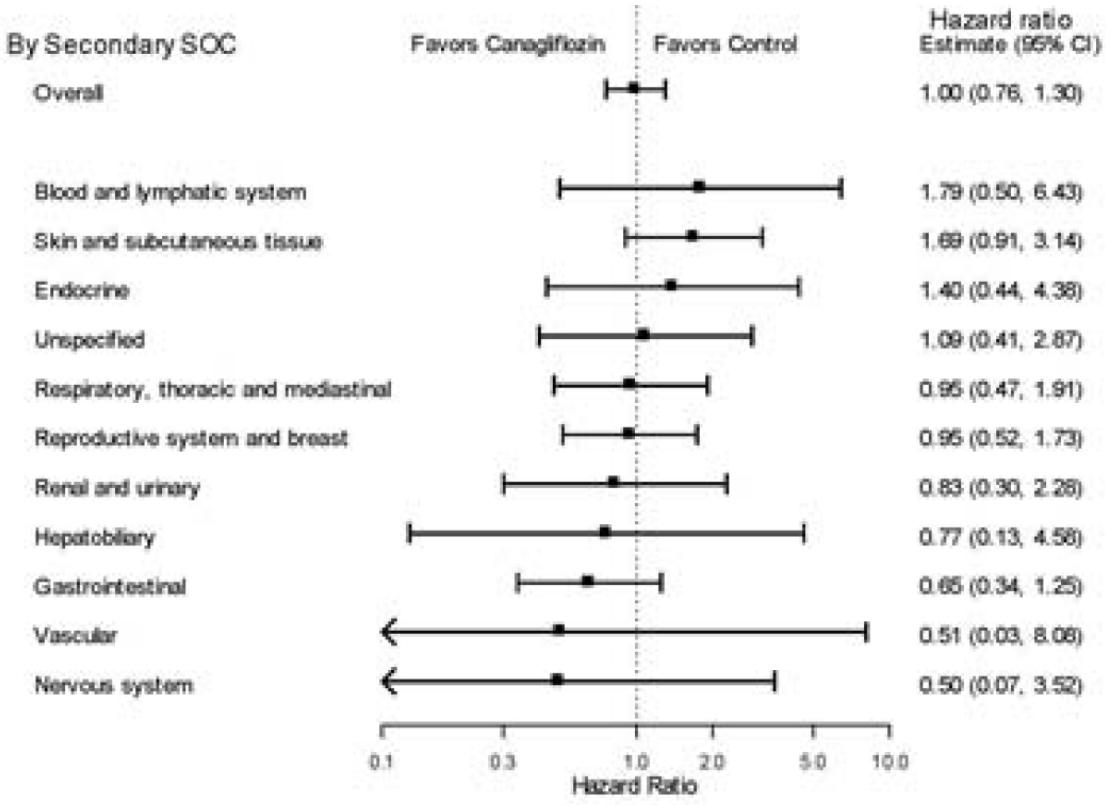
In the non-clinical 2-year rat carcinogenesis study (see Non-Clinical AR for details) three types of **neoplasms** became obvious which were apparently related to CANA administration. These were phaeochromocytomas, Leydig cell tumours of the testis and renal tumours. Far the most of the phaeochromocytomas 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 conclusion 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 1 trial DIA2001.

In the DS3 data set (shorter observation time than DS3-LT2), 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 DS3-LT1 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 imbalance 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 this 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, probably due to haemoconcentration.

The following table displays the incidence of marked in **blood pressure** changes from baseline to week 26. Blood pressure increase was less frequent and decrease was more frequent with

CANA/met. The BP lowering effect of CANA is most likely related to its diuretic action. The mean arterial blood pressure decreased with CANA vs. placebo by around 5 mm Hg (systolic) and around 3 mm Hg (diastolic) in the broad data set.

Number of Subjects with Vital Signs Outside Pre-Defined Limits - Regardless of Use of Rescue Medication - Up to 2 Days After Last Study Medication: DS3M-LT2

	All Non-Cana n (%)	Cana 100 mg n (%)	Cana 300 mg n (%)
Any post-baseline value	2457	2339	2303
Systolic blood pressure (mmHg)			
Average SBP decrease from baseline ≥20 mmHg and ≤90 mmHg	9 (0.4)	17 (0.7)	24 (1.0)
Average SBP increase from baseline ≥20 mmHg and ≥160 mmHg	162 (6.6)	91 (3.9)	67 (2.9)
Diastolic blood pressure (mmHg)			
Average DBP decrease from baseline ≥15 mmHg and ≤50 mmHg	7 (0.3)	6 (0.3)	28 (1.2)
Average DBP increase from baseline ≥15 mmHg and ≥100 mmHg	42 (1.7)	25 (1.1)	18 (0.8)

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.

Safety in special populations

In the **older population** (over 75 years) the incidence of AEs was rather high in all groups (CANA and Non-CANA), probably because of background disease. AEs considered related to study drug were clearly increased in all CANA groups vs. the Non-CANA group. It is, however, reassuring that serious AEs and AEs leading to discontinuation were not increased with CANA as compared to control. Nevertheless, due to the low number of subjects the numbers shown above have to be interpreted with caution.

It can be assumed that most diabetic patients over 75 years of age will have some degree of renal impairment. The Applicant worked out that the increase in AE incidence (any AE) is much more pronounced in patients ≥75 if moderate renal insufficiency is present. In patients of this age group with better renal function (no or mild renal impairment) the AE incidence (any AE) is

hardly different from placebo. Hence, the decreased tolerability of CANA may to a large extent depend on accompanying disease and not on age *per se*. Thus, there are no hints for special risks of CANA/MET in patients ≥75 years with eGFR ≥60. For patients with lower eGFR CANA/MET is not intended anyway because of the MET component.

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. The incidence and nature of hypersensitivity reactions meets the expectations for a drug substance. There a no hints for a particularly high allergenic potential of CANA.

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. Thus, use of CANA/MET should not be recommended in patients taking loop diuretics.

Number of Subjects with Volume Depletion Adverse Events by Selected Baseline Characteristics - Regardless of Use of Rescue Medication (ISS Phase 3 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)

Discontinuation due to AEs

There was some imbalance in the incidence of AEs leading to discontinuation between CANA and control, most pronounced in the high-dose CANA group (5.0%, 5.6% and 7.3% for Non-CANA, CANA 100 mg and CANA 300 mg in combination with metformin, respectively). This imbalance was largely due to sequelae of increased diuresis or to urinary tract and genital infections.

2.6.1. Discussion on clinical safety

The safety information of the drug combination CANA + MET is based on the phase 2 and phase 3 studies that were conducted with CANA. From these studies patients who concomitantly received metformin were selected and combined to safety data sets comparing CANA + metformin treated patients with patients receiving metformin + placebo or active comparator. In addition to metformin, other antidiabetic background therapy was used in some studies. Due to the design of the studies, adverse events due to metformin itself will not be detected. This is acceptable since the safety profile of metformin is well established. For comparison, data sets were also built from all patients treated with CANA (vs. comparator), irrespective of co-treatment. Around 70% of the study patients in the whole phase 2/3 development program received CANA in combination with metformin.

The safety profile of CANA largely met the expectations for an SGLT2 inhibitor. It was not relevantly changed by co-treatment with metformin. Overall, the tolerability of CANA/metformin appeared to be slightly better than with CANA alone, but this is most likely due to the fact that patients on CANA + MET had less severe background disease (e.g. renal insufficiency) since metformin is not given to these patients. Thus, the discussion below, mainly focussing on the safety of CANA, is also valid for the combination CANA/MET.

CANA-dependent increased glucose excretion via urine leads to osmotic diuresis and thereby water loss. Simultaneously, since SGLT2 is also a sodium carrier (sodium-glucose co-transporter), there is also sodium loss. In consequence, haemoconcentration may occur, which manifests itself not primarily as hypernatraemia (although serum sodium becomes slightly increased within the normal range) but usually as increased haematocrit and haemoglobin. In fact, haemoglobin regularly increases during CANA therapy to some extent (mean increase from 140 g/L to 148 g/L after 52 weeks). Water and sodium loss may lead to dehydration with all its sequelae including hypotension and syncope in vulnerable patients. The frequency of dehydration-related adverse events was dose-dependently increased with CANA therapy. Accordingly, the mean arterial blood pressure decreased with CANA by around 5 mm Hg (systolic) and around 3 mm Hg (diastolic) in the broad data set. Principally, the blood pressure lowering effect is a desirable effect in the frequently hypertensive, overweight patient with type 2 diabetes but needs to be appropriately labelled because such an effect is not usually expected for a glucose-lowering agent. Caution should be exercised in patients for whom a dapagliflozin 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. The starting dose for CANA is 50 mg bid. This is expected to minimise the risk of relevant AEs shortly after treatment initiation.

Glucose in urine favours urogenital infections. As with other SGLT2 inhibitors, the most pronounced increase was observed in 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. This is addressed in the SmPC. Therefore, these events are not regarded as a major safety concern.

CANA was phototoxic in non-clinical tests. Dedicated phase 1 and phase 2 clinical trials revealed that acute or delayed photosensitivity reactions are unlikely at the light intensities of normal sunlight. 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. Metformin is not phototoxic and is not expected to enhance CANA effects in this respect.

Bone fractures, in particular low-trauma fractures were slightly increased with CANA. However, this difference manifested itself already a few weeks after onset of treatment so that CANA-dependent changes in bone structure or density are an unlikely reason. In fact, DXA measurements up to 104 weeks of therapy did not reveal a relevant effect of CANA on BMD. In addition, serum markers of bone turnover and PTH levels did not change relevantly (the latter actually slightly decreased with CANA use compared to comparator in patients with renal impairment). These results do not indicate a CANA-induced urinary calcium loss or otherwise negative effect on bone. On the other hand, it turned out that the fracture imbalance resulted from the CV outcome study CANVAS. In this study there was a clearly increased incidence of falls after initiation of treatment with 300 mg/d CANA; for the 100mg/d dose the fall incidence remained similar to comparator. CANVAS included patients with high CV risk that may be more vulnerable to sequelae of CANA-induced water loss, in particular in the 300 mg/d group (see above). The risk of falls and thereby bone fractures will be minimised by the reduced starting dose of 50 mg bid. Appropriate warnings for cautionary measures in patients with known CV disease are included in the SmPC.

Antidiabetic agents may lead to hypoglycaemia, depending on their mechanism of action. With CANA, the amount of excreted glucose is lower with lower blood glucose levels so that the hypoglycaemic action of CANA should be limited. Nevertheless, CANA slightly increased the incidence of documented low blood glucose levels (≤ 70 mg/dL [3.9 mmol/L]) in the absence of a hypoglycaemic background therapy, but clinically more relevant hypoglycaemia (blood glucose below 56 mg/dL [3.1 mmol/L]) was rare and balanced under these circumstances. As observed with other antidiabetic agents with a low propensity to cause hypoglycaemia when given alone, CANA markedly increased the incidence of hypoglycaemia vs. placebo if the background therapy included insulin or sulphonylureas. Thus, care should be taken when CANA/MET is added to insulin or sulphonylureas and dose reduction of the latter medications may be considered. Reassuringly, the incidence of severe hypoglycaemias was not increased with CANA.

The kidney is the primary target organ for CANA. Therefore, CANA may behave differently in patients with relevant (at least moderate) renal impairment not only from an efficacy (see efficacy section) but also from a safety perspective. However, due to the metformin component, the combination CANA/MET is not intended for use in these patients so that a discussion of safety of CANA in this population is not required.

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 unstable angina). 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), reasonably excluding a relevant increase in CV risk of CANA. Remarkably, there was a rather pronounced numerical difference in HR of MACE and MACE-plus between patients with high CV risk (CANVAS criteria) and patients not meeting the CANVAS inclusion criteria (lower CV risk). Nevertheless, even in the patients with high CV risk, the HR with CANA did not exceed 1 with an acceptable upper limit of the 95% CI of around 1.4 for MACE and MACE-plus. 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 incidence of 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 with CANA revealed neoplastic findings in rats but not in mice. Benign and malignant tumours of the renal cortex and the adrenal medulla (phaechromocytomas) were observed as well as benign Leydig cell tumours of the testes. For the renal tumours the Applicant provided a reasonable explanation. 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. The combination CANA/MET was not tested in carcinogenicity studies. This is acceptable since there is no hint that metformin induces neoplasms or promotes tumour development.

For further assurance the Applicant provided an analysis of the broadest data set (irrespective of combination with metformin) with a late data cut-off (31 Dec 2012) and calculated hazard ratios (HRs) for overall tumours and 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.

For another SGLT2 inhibitor, dapagliflozin, a numerical increase in bladder cancer cases was initially observed. Therefore, the Applicant followed these events for CANA and provided an updated analysis (cut-off date 31 Dec 2013). The incidence of bladder cancer in the CANA trials was low and within the expected range; there was no meaningful difference in incidence or cases per subject years between the CANA and comparator groups. The Applicant plans to follow bladder cancer further in ongoing and future studies. This is considered appropriate.

There was an increase in serum LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C). The LDL-C/HDL-C ratio, however, 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.

Metformin is a well-established substance with a well-known safety profile. The most common side effects are headache and gastrointestinal symptoms. Approximately 10-25% of patients starting metformin report nausea, indigestion, abdominal cramps, bloating, diarrhea, or some combination of these. Metformin has direct effects on gastrointestinal function including glucose and bile salt absorption. Metformin has been associated with serious lactic acidosis. The estimated incidence of lactic acidosis attributable to metformin use is 3-6 per 100,000 patient-years of treatment.

The mechanism of action of metformin is highly different from that of CANA so that no relevant interactions in regard to safety are expected. The data presented by the Applicant in patients simultaneously treated with CANA and metformin gives no hint for worse tolerability of CANA or metformin when administered in combination.

2.6.2. Conclusions on the clinical safety

The safety profile of the CANA/MET IR FDC is acceptable for the following reasons. Metformin did not decrease the safety and tolerability of CANA. The safety profile of metformin and the resulting precautionary measures are well known.

CANA revealed the expected safety profile 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. However, the prescriber and patient should be aware of these effects because they are unexpected for a diabetes drug and care should be taken in potentially vulnerable patients. This is reflected in sections 4.4 and 4.8 of the product information.

Based on currently available data, CV safety of CANA is reasonably well demonstrated. The imbalance in strokes not favouring CANA is of concern but based on a limited number of cases and needs ongoing monitoring. 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. The latter was mainly observed upon initiation of treatment. This effect will be blunted by the lower starting dose of 50 mg bid.

Non-clinical data indicate phototoxicity of CANA but clinical data indicate that this would play only a role at artificially high light intensities. Phase 3 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 notable imbalance in the incidence of neoplasms in the CANA vs. comparator group in the latest safety evaluation.

Taken together, the combination CANA/metformin is considered approvable from a safety point of view with appropriate labelling and post-marketing measures.

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 4, the PRAC considered by consensus that the risk management system for Canagliflozin/Metformin hydrochloride (fixed-dose combination) (Vokanamet) indicated in adults aged 18 years and older with T2DM could be acceptable provided an updated risk management plan and satisfactory responses to the List of Outstanding issues are submitted (i.e. to include bladder cancer as important potential risk in the RMP).

The CHMP endorsed this advice with changes.

These changes concerned the following elements of the Risk Management Plan:

The CHMP did not agree to the PRAC request that “Bladder cancer should be included as an important potential risk”. The CHMP requested that long term safety data on bladder cancer should be considered as missing information.

The CHMP justified these changes as follows:

The CHMP, having viewed the non-clinical and clinical data submitted in this application concluded that there was no signal for bladder cancer and thus bladder cancer could not be considered as an important potential risk of CANA. However, taking into account the numerical imbalances in bladder cancer found in the dapagliflozin studies, the CHMP was of the view that bladder cancer should be further investigated post-marketing also for CANA and therefore the Committee recommended that the lack of long-term safety data on bladder cancer be included in the RMP as missing information.

The CHMP agreed to version 5 of the Risk Management Plan, which included the following:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

SUMMARY OF SAFETY CONCERNS – CANAGLIFLOZIN

Important identified risks	
	Vulvovaginal candidiasis
	Balanitis or balanoposthitis
	Urinary tract infections
	Hypoglycaemia in combination with insulin or glucose-independent insulin secretagogues
	Volume depletion
	Bone fractures
Important potential risks	
	Renal impairment/Renal failure
	Clinical consequences of increased haematocrit
	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
	Long-term safety data for bladder cancer
	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 <30 mL/min/1.73m^2)

ADDITIONAL SAFETY CONCERNS – CANAGLIFLOZIN/METFORMIN HCL FDC

Important identified risks	Lactic acidosis

- **Pharmacovigilance plan**

Table 2.2: Ongoing and planned studies in the PhV development plan

Trial/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)
DIA3008 Category 3	To evaluate the effects of canagliflozin on major cardiovascular events (MACE)[d] in adult subjects with T2DM	Cardiovascular safety Renal impairment/Renal failure Clinical consequences of increased haematocrit Bone fractures Photosensitivity Bladder cancer	16 Nov 2009	IDMC Status Reports: Twice annually until study completion.[a] Final report: 2Q 2018[b]
DIA4003 Category 3	To assess the effects of canagliflozin on renal endpoints in adult subjects with T2DM and an elevated risk of CV events	Cardiovascular safety Bladder cancer		Final report: 2Q 2018
Cardiovascular meta-analysis (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[c]
Primary bladder cancer meta-analysis (including DIA3008 and DIA4003) Category 3	To evaluate the incidence of bladder cancer in the canagliflozin group compared to the placebo group.	Bladder cancer		Final report: 4Q 2017[e]
DNE3001 Category 3	To evaluate the effects of canagliflozin on renal and	Bladder cancer		IDMC Status Reports: Twice annually

Trial/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)
	cardiovascular outcomes in subjects with T2DM and diabetic nephropathy			until study completion.[a] Final report: 3Q 2019
Secondary bladder cancer meta-analysis, if indicated following results of primary meta-analysis (including DIA3008, DIA4003, and DNE3001) Category 3	To evaluate the incidence of bladder cancer in the canagliflozin group compared to the placebo group.	Bladder cancer		Final report: 3Q 2019[f]
DIA1055 Category 3	To evaluate the single- and multiple-dose 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	Safety and tolerability in paediatric patients	1Q 2015	4Q 2018

[a] After each IDMC review, the IDMC's recommendation will be provided to the EMA and CHMP. Should a safety concern be communicated to the sponsor in one of these official IDMC memos, the official memo and all subsequent formal communications on the specific safety concern raised by the IDMC to the sponsor will be shared with the EMA and CHMP. These documents will be available upon request to other Health Authorities.

[b] This report will include efficacy and non-CV safety data from trial DIA3008.

[c] This report will include results of the meta-analysis of cardiovascular outcomes data from trial DIA3008 and the planned DIA4003 trial.

[d] MACE = CV death, nonfatal myocardial infarction [MI], and nonfatal stroke

[e] This report will include results of the meta-analysis of bladder cancer adverse events data from trials DIA3008 and DIA4003.

[f] This report will include results of the meta-analysis of bladder cancer adverse events data from trials DIA3008, DIA4003, and DNE3001.

Trial/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)

Note: IDMC= Independent Data Monitoring Committee

The CHMP, 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.

The CHMP also considered that the studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

- **Risk minimisation measures**

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks:		
Lactic acidosis	**SmPC:** Contraindications (Section 4.3) to metformin due to increased risk of lactic acidosis include: moderate and severe renal impairment; acute conditions with potential to alter renal function; acute or chronic disease which may cause tissue hypoxia; hepatic impairment, acute alcohol intoxication, alcoholism. Special warnings and precautions for use (Section 4.4) describes risk factors and at risk subpopulations, diagnosis and management of lactic acidosis. Interaction with other medicinal products and other forms of interaction (Section 4.5) describes increased risk of lactic acidosis in acute alcohol intoxication and with cationic drugs that are eliminated by renal tubular secretion eg, cimetidine. It also states intravascular administration of iodinated contrast agents in radiological studies may lead to renal failure, resulting in metformin accumulation and risk of lactic acidosis. Therefore, canagliflozin/metformin HCl FDC must be discontinued prior to or at the time of the test, not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal. Undesirable effects (Section 4.8) lists lactic acidosis as adverse drug reaction. Overdose (Section 4.9) states high overdose of metformin or concomitant risks may lead to lactic acidosis. The most effective method to remove lactate and metformin is haemodialysis.	None
Vulvovaginal candidiasis	**SmPC :** Special warnings and precautions for use (Section 4.4): describes increased risk in patients with a history of genital mycotic infections. Undesirable effects (Section 4.8) lists vulvovaginal candidiasis as adverse drug reaction and states this occurred most frequently within the first 4 months of	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	treatment.	
Balanitis or balanoposthitis	**SmPC:** Special warnings and precautions for use (Section 4.4) describes increased risk in uncircumcised patients and patients with a history of genital mycotic infections and informs of phimosis as rare complication, which may require circumcision. Undesirable effects (Section 4.8) lists balanitis or balanoposthitis as adverse drug reaction.	None
Urinary tract infections	**SmPC:** Undesirable effects (Section 4.8) lists urinary tract infections as adverse drug reaction.	None
Hypoglycaemia in combination with insulin or glucose-independent insulin secretagogues	**SmPC:** Posology and method of administration (Section 4.2) and Interaction with other medicinal products and other forms of interaction (Section 4.5) indicates a reduction in the dose of insulin or glucose-independent insulin secretagogue may be required to reduce the risk of hypoglycaemia, when canagliflozin/metformin HCl FDC is used as add-on to either of these agents. Undesirable effects (Section 4.8) lists hypoglycaemia in combination with insulin or SU as adverse drug reaction.	None
Volume depletion	**SmPC:** Posology and method of administration (Section 4.2) states, for patients not adequately controlled on metformin, the recommended starting dose of canagliflozin/metformin HCl FDC should provide canagliflozin dosed at 50 mg twice daily plus the dose of metformin already being taken or the nearest therapeutically appropriate dose. For patients who are tolerating a canagliflozin/metformin HCl FDC dose containing canagliflozin 50 mg who need tighter glycaemic control, the dose can be increased to canagliflozin/metformin HCl FDC containing 150 mg canagliflozin twice daily. Care should be taken when increasing the dose in patients for whom the initial canagliflozin induced diuresis poses a risk, eg, patients ≥75 years of age, patients with known	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	cardiovascular disease. If there is evidence of volume depletion, this should be corrected prior to initiating canagliflozin/metformin HCl FDC. For patients switching from separate tablets of canagliflozin and metformin, dose titration with canagliflozin (added to the optimal dose of metformin) should be considered before the patient is switched to canagliflozin/metformin HCl FDC. Special warnings and precautions for use (Section 4.4) states adverse reactions related to volume depletion were seen more commonly with the 300 mg dose and occurred most frequently within the first 3 months of treatment. 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, patients on diuretics, or elderly patients (≥65 years of age). Patients should be counselled to report symptoms of volume depletion and, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status is recommended. Temporary interruption of treatment may be considered for patients who develop volume depletion, until the condition is corrected. Canagliflozin is not recommended for use in patients on loop diuretics or who are volume depleted, eg, due to acute illness (such as gastrointestinal illness). Undesirable effects (Section 4.8) lists postural dizziness, orthostatic hypotension, hypotension, dehydration, and syncope as adverse drug reactions related to volume depletion.	
Bone fractures	**SmPC:** Undesirable effects (Section 4.8) lists bone fracture in tabulated summary of adverse drug reactions. The incidence rates of bone fracture in subjects with known or at high risk for cardiovascular disease are provided.	None
Important potential risks:		
Renal impairment/ Renal failure	**SmPC:** Contraindications (Section 4.3) states canagliflozin/metformin HCl FDC is contraindicated	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	in patients with moderate and severe renal impairment. Special warnings and precautions for use (Section 4.4) states that in patients ≥75 years of age, greater decreases in eGFR were reported with canagliflozin therapy. As metformin is excreted by the kidney, eGFR or CrCl should be determined before initiating treatment and regularly thereafter: At least annually in patients with normal renal function. At least 2 to 4 times a year in patients with eGFR at the lower limit of normal and in elderly patients. Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired; for example, when initiating antihypertensive or diuretic therapy and when starting treatment with a nonsteroidal anti-inflammatory drug. Undesirable effects (Section 4.8) lists Blood creatinine increased and Blood urea increased as adverse drug reactions.	
Clinical consequences of increased haematocrit	Special warnings and precautions for use (Section 4.4) states that haematocrit increase was observed with canagliflozin treatment; therefore, caution in patients with already elevated haematocrit is warranted. Undesirable effects (Section 4.8) lists Haematocrit increased as an adverse drug reaction.	None
Photosensitivity	None proposed.	None
Hypoglycaemia in the absence of insulin or glucose-independent insulin secretagogues	**SmPC:** Undesirable effects (Section 4.8) provides incidence of hypoglycaemia when canagliflozin is used as monotherapy or as add-on therapy to metformin and the increased incidence of hypoglycaemia when canagliflozin is used as add-on therapy to insulin or glucose-independent insulin secretagogues.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Off-label use for weight loss	**SmPC:** Therapeutic indications (Section 4.1) clearly states canagliflozin/metformin HCl FDC is indicated in adults aged 18 years and older with T2DM as an adjunct to diet and exercise to improve glycaemic control.	None
Missing information		
Long-term cardiovascular safety in patients	**SmPC:** None proposed.	None
Long-term safety data for bladder cancer	**SmPC:** None proposed.	None
Use in patients with congestive heart failure defined as New York Heart Association (NYHA) class IV	**SmPC:** Contraindication (SmPC Section 4.3) states canagliflozin/metformin HCl FDC is contraindicated in patients with acute or chronic disease which may cause tissue hypoxia such as cardiac failure. Special warnings and precautions for use (Section 4.4) describes that there is no experience in clinical trials with canagliflozin in NYHA class IV.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Use in paediatric patients between 10 and 18 years of age	**SmPC:** Posology and method of administration (Section 4.2) indicates the safety and efficacy of canagliflozin/metformin HCl FDC in children under 18 years of age have not been established.	None
Use in pregnancy	**SmPC:** Fertility, pregnancy and lactation (Section 4.6) states there are no data to support the use of canagliflozin alone or canagliflozin/metformin HCl FDC in pregnant women. Studies in animals with canagliflozin have shown reproductive toxicity. A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition, or postnatal development. Canagliflozin/metformin HCl FDC should not be used during pregnancy. When pregnancy is detected, treatment with canagliflozin/metformin HCl FDC should be discontinued.	None
Use in nursing mothers	**SmPC:** Fertility, pregnancy and lactation (Section 4.6) states no studies in lactating animals have been conducted with the combined active substances of canagliflozin/metformin HCl FDC. It is unknown whether canagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of canagliflozin/metabolites in milk, as well as pharmacologically mediated effects in breast-feeding offspring and juvenile rats exposed to canagliflozin. Metformin is excreted into human breast milk in small amounts. A risk to newborns/infants cannot be excluded. canagliflozin/metformin HCl FDC should not be used during breast-feeding.	None
Use in very elderly patients (≥85 years)	**SmPC:** Posology and method of administration (Section 4.2) states for patients who are tolerating a canagliflozin/metformin HCl FDC dose containing	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	canagliflozin 50 mg who need tighter glycaemic control, the dose can be increased to canagliflozin/metformin HCl FDC containing 150 mg canagliflozin twice daily. Care should be taken when increasing the dose of canagliflozin/metformin HCl FDC in patients ≥75 years of age. For patients switching from separate tablets of canagliflozin and metformin, dose titration with canagliflozin (added to the optimal dose of metformin) should be considered before the patient is switched to canagliflozin/metformin HCl FDC. Because metformin is eliminated in part by the kidney and elderly patients are more likely to have decreased renal function, canagliflozin/metformin HCl FDC should be used with caution as age increases. Regular assessment of renal function is necessary to aid in prevention of metformin-associated lactic acidosis. The risk of volume depletion associated with canagliflozin should be taken into account. Special warnings and precautions for use (Section 4.4) describes a higher incidence of adverse reactions associated with volume depletion (eg, postural dizziness, orthostatic hypotension, hypotension) and greater decreases in eGFR reported in patients ≥75 years of age. Undesirable effects (Section 4.8) provides the incidence of adverse reactions related to volume depletion and decreases in eGFR in the elderly (≥75 years) with both doses of canagliflozin.	
Use in patients with severe hepatic impairment	**SmPC:** Contraindications (Section 4.3) states canagliflozin/metformin HCl FDC is contraindicated in patients with hepatic impairment.	None
Use in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2)	**SmPC:** Contraindications (Section 4.3) states canagliflozin/metformin HCl FDC is contraindicated in patients with moderate and severe renal impairment.	None

The CHMP, 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.

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

Beneficial effects

Adequate bridging data have been submitted which allow for extrapolating the results of the CANA phase 3 programme, which used a qd dosing regimen of CANA, to the bid dosed FDC applied for.

In the phase 3 programme, about 70% of patients were on a metformin-based background regimen relevant to the current application. The monotherapy study (DIA3005) and the add-on to SU-substudy (DIA 3008) provide additional support for the efficacy of CANA.

CANA 100 mg and 300 mg per day, compared to placebo, provided consistent, statistically significant and clinically relevant improvements in glycaemic control when given as monotherapy in patients intolerant 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.

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 kg and 5.7 kg 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 nutrient loss via urinary glucose excretion. Fluid loss appears to play only a minor role.

Across all phase 3 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. However, caution should be exercised in vulnerable patients who may experience adverse

reactions due to a CANA-induced drop in blood pressure or volume depletion. 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 groups, respectively).

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

Durability of antihyperglycaemic efficacy was maintained in several 52 week extension studies.

Efficacy of the metformin component is considered well established.

Since type II diabetes is a chronic disease requiring long term treatment a fixed combination is expected to provide advantages for the patients as regards convenience and compliance.

Uncertainty in the knowledge about the beneficial effects

A transient post dose delay of intestinal glucose absorption has been observed with 300 mg qd administration but not with lower doses, e.g. 150 mg qd. A dose related inhibition of intestinal SGLT1 has been discussed as a possible explanation. However, the magnitude of the effect is small and considered to be without clinical relevance in patients switching from a qd regimen (e.g. coadministration of CANA and metformin) to a bid regimen with the FDC CANA/MET.

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 potential adverse events 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. However, due to its metformin component, the FDC CANA/MET is not intended for use in patients with moderate renal impairment.

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. The starting dose of 50 mg bid appears appropriate for these 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 are rare and of similar frequency as observed with placebo.

The unfavourable effects of metformin are well established; most frequent are headache, nausea/vomiting, flatulence and diarrhoea. Lactic acidosis is rare.

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 2/3 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 both MACE and MACE-plus, which is reassuring.

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. Any such effect is expected to be blunted by the recommended starting dose of 100 mg/day.

For another SGLT2 inhibitor, dapagliflozin, a numerical increase in bladder cancer cases was observed in the pre-licensing studies. Therefore, and despite the absence of a non-clinical signal, bladder cancer has been included as potential risk in the RMP of dapagliflozin. Although the clinical safety data for CANA do not indicate a notable imbalance in incidence or cases per subject years between the CANA and comparator groups, the lack of long-term safety data on bladder cancer should be included as missing information in the RMP of CANA/MET. The Applicant plans to follow bladder cancer further in ongoing and future studies, which was considered appropriate by the CHMP.

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. The antihyperglycaemic efficacy of metformin is well-established. CANA added to metformin has been shown to confer an additional clinically relevant improvement in glycaemic control, thus justifying the combination of these substances. The effect of CANA appears to be maintained in the long-term based on the available data (up to week 52).

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. 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 hypertensive patients as it may 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.

The fixed combination product may enhance patient convenience and compliance in an often already heavily medicated patient population.

Unfavourable effects

The most important risk of CANA is drop in blood pressure and dehydration and its sequelae in vulnerable patients. Since such effects are usually not expected for a glucose-lowering agent, these have been appropriately labelled to increase awareness among physicians and patients.

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 and related falls cannot be excluded.

Genital infections were usually not serious and are considered manageable. Thus, genital infections, although frequent and unpleasant, are no important risk. The frequencies of urinary tract infections were nearly balanced between CANA and comparator and thus are not considered a major concern.

The safety profile of metformin is well known; frequent adverse events include headache and gastrointestinal symptoms which usually do not pose a relevant risk. A rare but severe side effect of metformin is lactic acidosis, but its occurrence can be largely avoided by adhering to the known contraindications.

Benefit-risk balance

The benefit-risk ratio of CANA/MET is considered favourable.

The antihyperglycaemic efficacy of metformin is well-established and CANA, as add-on to metformin, confers additional clinically relevant improvement in glycaemic control, thus justifying the combination of these substances. The safety profile of the combination CANA and MET is acceptable and the risks are considered manageable in clinical practice and are appropriately labelled.

Discussion on the benefit-risk balance

The fixed dose combination of CANA and MET could clearly be a valuable asset to the already existing treatment options for T2DM. Both active substances contribute to the overall treatment effect of this FDC. The effect is clearly clinically relevant and can be achieved with the fixed combination alone 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 and hence do not preclude the granting of the Marketing Authorisation. Metformin has a positive benefit-risk balance which is not changed by the addition of CANA.

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 Vokanamet in the treatment of

adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- *in patients not adequately controlled on their maximally tolerated doses of metformin alone*
- *in patients on their maximally tolerated doses of metformin along with other glucose-lowering medicinal products including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5, and 5.1 for available data on different add-on therapies)*
- *in patients already being treated with the combination of canagliflozin and metformin as separate tablets.*

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 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.

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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the review of the data the CHMP considered that the active substance canagliflozin contained in the medicinal product Vokanamet was to be qualified as a new active substance at the time of submission of this application. On 15 November 2013 a marketing authorisation valid throughout the European Union for Invokana was issued, containing canagliflozin.