Johnson & Johnson Private Limited

Clinical Protocol

Protocol Title

A prospective, multi-centric, open-label, single-arm, phase 4 study to evaluate the safety and efficacy of canagliflozin + metformin hydrochloride IR fixed-dose combination as an adjunct to diet and exercise to improve glycemic control in Indian adult patients with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate

Short Title

A study to evaluate the safety and efficacy of canagliflozin + metformin hydrochloride IR fixed-dose combination in Indian adults with type 2 diabetes

Protocol 28431754DIA4032; Phase 4
AMENDMENT 1
Protocol Version 2.0

JNJ-28431754 (canagliflozin)

Status: Approved
Date: 4 February 2021
Prepared by: Johnson & Johnson Private Limited
EDMS number: EDMS-ERI-181652461, 5.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document	Date
Amendment 1	4-Feb-2021
Original Protocol	31-Oct-2018

Amendment 1 (4 February 2021)

Overall Rationale for the Amendment: Incorporating changes in the treatment for overdose part and certain important one's in exclusion criteria & SoA

Section Number and Name	Description of Change	Brief Rationale
1.1 Dose Regimens	"Local Prescribing Information" instead of "Prescribing Information"	More Specific
1.3 Schedule of Activities (SoA)	Added a window period of 7 days after 28 days	To ensure more maximum follow up completion
1.3 Schedule of Activities (SoA)	Added Serum beta HCG test for eligible females at screening	To rule out pregnancy at screening
1.3. Schedule of Activities (SoA)	"Urine Pregnancy Test" instead of "Pregnancy Test'	More Specific
1.3 Schedule of Activities (SoA)	Removed UPT for females at screening	Since Serum beta HCG is done at screening
1.3 Schedule of Activities (SoA)	Added a row "Patient Diary Dispensing & Review"	For efficient recording of adverse events, if any
4.2 Scientific Rationale for Study Design	"To be dispensed" instead of "selected"	More Specific
4.2. Scientific Rationale for Study Design	"Local Prescribing Information" instead of "Prescribing Information"	More Specific
4.2 Scientific Rationale for Study Design	Added "For dispensing details please refer to section 6.1"	For detailed information
4.3. Justification for Dose	"Local Prescribing Information" instead of "Prescribing Information"	More Specific
4.3. Justification for Dose	Added "and available commercialized strengths in India"	More Specific
4.4 End of study definition	Removed "Study completion" Added "Wk 24 of the Treatment Phase"	More Specific
4.4 End of study definition	Added "early withdrawal evaluation visit/ EOT Visit"	More Specific
5.1. Inclusion Criteria (3)	Added "Willing to Adhere" Instead of "adhering"	More Specific
5.1. Inclusion Criteria (7)	Corrected typo from 2 to 6	Correction
5.1. Inclusion Criteria (7)	Removed "urine" & added "serum beta HCG test at screening	Correction
5.1. Inclusion Criteria (7)	Added "negative UPT" at baseline	Correction

Section Number and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria	"Local Prescribing Information" instead of "Prescribing Information"	More Specific
	Added canagliflozin & metformin separately along with canagliflozin+metformin	For more detailed exclusion criteria for hypersensitivity reactions
	Deleted individual SGLT2i names (dapagliflozin and empagliflozin)	To avoid future update if any new drug is approved
6.1. Study Interventions Administered	"Local Prescribing Information" instead of "Prescribing Information"	More Specific
6.6. Study Interventions Administered	"Local Prescribing Information" instead of "Prescribing Information"	More Specific
6.6. Study Interventions Administered	"Local Prescribing Information" instead of "Prescribing Information"	More Specific
7.2. Participant Discontinuation/ Withdrawal From the Study	Added 24 weeks for non compliance duration	Additional information
8. STUDY ASSESSMENTS AND PROCEDURES	Specified about urine pregnancy test and removed serum	To maintain consistency
8.1 Efficacy Assessments	Deleted 26 weeks & replaced with 24 weeks	Correction
8.2.1 Vital Signs	Extra steps deleted	To facilitate ease of measurement
8.4. Treatment of Overdose	Provided detailed plan for management of accidental overdose	Provided as per prescribing information
	Removed the clause of PK analysis	As per recommendation in prescribing information
10.3 Appendix 3: Clinical Laboratory Tests	Other Screening Tests: Deleted Urine Pregnancy & added serum beta HCG test	More Specific
10.11 Appendix 11: Protocol Amendment History	Instead of "original", protocol with amendment 1	
Unlisted (Unexpected) Adverse Event/Reference Safety Information	Removed the term "investigators brochure"	To maintain consistency
Sponsor's Responsible Medical Officer	PPD	Change of personal (Administrative change)

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1. PROTOCOL SUMMARY

1.1. Synopsis

A prospective, multi-centric, open-label, single-arm, phase 4 study to evaluate the safety and efficacy of canagliflozin + metformin hydrochloride IR fixed-dose combination as an adjunct to diet and exercise to improve glycemic control in Indian adult patients with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate

Canagliflozin + metformin hydrochloride IR is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and biguanide combination product which combines two oral antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RTG), and thereby increases urinary glucose excretion (UGE). Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization (Fleming JW 2015).

OBJECTIVES AND ENDPOINTS

Objectives

Primary Objective

In adult Indian patients with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate:

The primary objective is to assess safety of canagliflozin + metformin hydrochloride IR fixed-dose combination

Secondary Objective

In adult Indian patients with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate:

The secondary objective is to assess efficacy of canagliflozin + metformin hydrochloride IR fixed-dose combination.

Tertiary/Exploratory Objectives

In adult Indian patients with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate:

The tertiary/exploratory objectives are to assess other efficacy parameters like FPG, PPG, body weight, waist circumference, BP, and proportion of patients achieving HbA1c goal of below 7%.

Endpoints

Primary Endpoint

The percentage (%) of adverse events (AEs), serious adverse events (SAEs), unexpected adverse events or adverse drug reactions [Time Frame: 24 weeks].

Secondary Endpoint

Change from baseline in Glycosylated Haemoglobin (HbA1c) % [Time Frame: 12 and 24 weeks]

Tertiary/Exploratory Endpoints

Change from baseline in fasting plasma glucose (FPG) in mg/dL [Time Frame: 12 and 24 weeks]

Change from baseline in 2-hr post-prandial plasma glucose (PPG) in mg/dL [Time Frame: 12 and 24 weeks]

Proportion of patients achieving HbA1c goal of below 7% [Time Frame: 12 and 24 weeks]

Change from baseline in blood pressure (BP) in mmHg [Time Frame: 12 and 24 weeks]

Change from baseline in body weight in Kg [Time Frame: 12 and 24 weeks]

Change from baseline in waist circumference in cm [Time Frame: 12 and 24 weeks].

Hypothesis

The study will be descriptive in nature to assess safety and efficacy of canagliflozin + metformin hydrochloride IR fixed-dose in Indian patients with type 2 diabetes mellitus.

OVERALL DESIGN

This is a prospective, multi-center, open-label, single-arm, phase 4 study in Indian adult patients with type 2 diabetes mellitus to evaluate the safety and efficacy of canagliflozin + metformin hydrochloride IR fixed-dose combination as an adjunct to diet and exercise to improve glycemic control when treatment with both canagliflozin and metformin is appropriate.

The study will be conducted in 3 phases: a 7-day screening phase, a 24 weeks treatment phase extending from Day 1 (baseline) to completing at the Week 24 visit (or the end-of-treatment [EOT] visit for subjects discontinuing study treatment early), and a 28 days post-treatment phase- Telephone follow-up contact (or optional study visit, at the discretion of the investigator) approximately 28 days after the last dose of study drug. The duration of individual participation will be approximately 29 weeks.

Key safety assessments include adverse events (AEs), serious adverse events (SAEs), unexpected adverse events or adverse drug reactions. Key efficacy assessments include HbA1C, FPG, PPG, blood pressure, body weight, and waist circumference.

NUMBER OF PARTICIPANTS

A total of 276 participants will be enrolled in this study.

INTERVENTION GROUPS AND DURATION

Study phases:

- Pretreatment phase
    - Screening period
        - ♦ Screening visit (week -1)
- Treatment phase
    - Starting at the baseline (Day 1) visit and completing at the Week 24 visit (or the end-of-treatment [EOT] visit for subjects discontinuing study treatment early)
- Posttreatment phase (28 days follow-up contact)
    - Telephonic follow-up contact (or optional study visit, at the discretion of the investigator) approximately 28 days after the last dose of study drug

Study duration:

Screening period will be of 1 week, during which study participants will be evaluated for eligibility criteria. Study participants will be followed up for study duration period of 24 weeks. The total duration of the study, including the 1-week screening period, the 24-week treatment phase and the 4-week post-treatment phase is approximately 29 weeks for each subject.

Dose Regimens:

Study participants will receive canagliflozin + metformin hydrochloride IR fixed-dose combination tablets at a dose determined by the investigator. Study participants will be asked to take one tablet orally twice daily with meals throughout the study period. Dosing can be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin 2000 mg and canagliflozin 300 mg in patients with an eGFR of 60 mL/min/1.73 m^2 or greater. Dose initiation and dose adjustment will be done as per local prescribing information of canagliflozin + metformin hydrochloride IR, as determined by the investigator.

SAFETY EVALUATIONS

Safety evaluations, according to the time points provided in the Time and Events Schedule, will include the collection of adverse events, safety laboratory tests (including chemistry, fasting lipid profile, hematology, and urinalysis), vital signs (blood pressures and pulse rates), body weight, physical examinations, SMBG, and collection of potential hypoglycemic episodes (eg, from the subject diary provided to subjects).

EFFICACY EVALUATIONS

The primary measure of efficacy is change HbA1c(%) from baseline. Secondary measures of efficacy include changes from baseline in parameters like FPG, PPG, body weight, waist circumference and blood pressure.

STATISTICAL METHODS

Sample size: 276

Approximately 276 patients will be enrolled to obtain data of at least 251 patients, considering 10% dropout rate. Based on existing data available and considering treatment emergent adverse event rate to be 20.6% and margin of error 5%, a sample size of 251 will be required to yield a power of 80% and 5% level of significance. (Janssen Research & Development 2014)

Sample size is derived based on the formula: n = [(Z(1-alpha/2))^2 x p x (1- p)] / d^2

Where in, n is calculated sample size, Z is degree of confidence (ie, 95% which yields 1.96), d is maximum tolerated error or upper bound for the margin of error (0.05), p is proportion (0.206 considering rate of treatment emergent adverse events to be 20.6%).

Dropout rate of 10% is considered for sample size calculation.

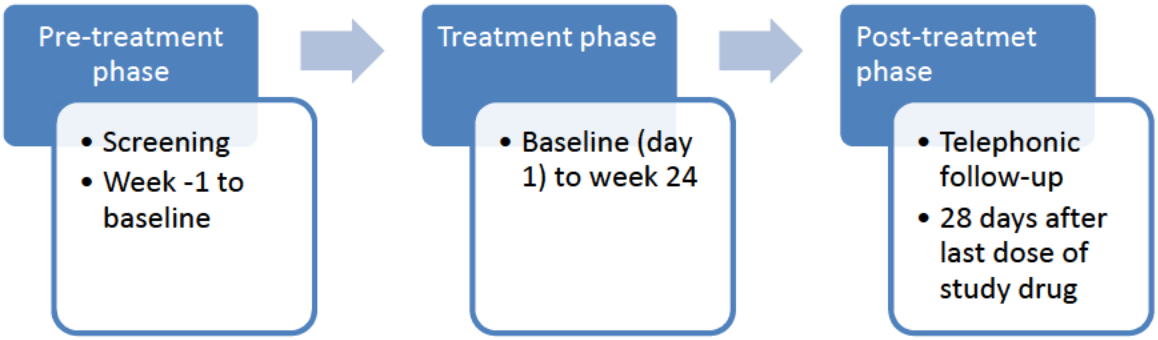
Safety parameters to be evaluated at 24 weeks is: the percentage (%) of adverse events (AEs), serious adverse events (SAEs), unexpected adverse events or adverse drug reactions. The statistical evaluation will be performed using SAS®, version 9.4 or later. Data will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables, and using frequency and percentage (i.e., number and proportion of subjects – n, %) for discrete/categorical variables, unless specified otherwise.

Secondary parameters to be evaluated at week 12 and week 24 is: change from baseline in Glycosylated Haemoglobin (HbA1c) %. Other exploratory endpoints include change from baseline in parameters like FPG, PPG, body weight, waist circumference, blood pressure and proportion of patients achieving HbA1c

goal of below 7%. Change from baseline values for HbA1c, FPG, PPG, BP, body weight will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum).

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities (SoA)

Phase	Pretreatment		Treatment				Posttreatment	
Period	Screening visit[a]	Baseline[b]					Telephone follow-up contact	
Week	Week -1	Day 1 Visit	Week 6 Visit / Up-titration	Week 12	Week 18	Week 24/EOT/Early withdrawal[c]	4 weeks +7 days after last dose of study drug	Notes
Screening/Administrative								
Informed consent (ICF)[d]	X							Must be signed before first study-related activity.
Demographics	X	X	X	X	X	X		
Review medical history requirements	X	X	X	X	X	X		
Inclusion/exclusion criteria	X	X						
Pre-study therapy[e]	X	X						
Preplanned surgery/procedure(s)	X							
Serum Beta HCG	X							
Urine Pregnancy test		X						
Study Intervention Administration								
Dispense/administer study intervention		X	X	X	X			
Study intervention accountability		X	X	X	X	X		
Clinical Procedures								
Physical examination[f]	X	X				X		
Body weight[g]	X	X	X	X	X	X		
Height	X							
Vital Signs[h]	X	X	X	X	X	X		
12-lead electrocardiogram[i]	X							
Laboratory Assessments								
HbA1c[j]	X	X		X		X		
Fasting plasma glucose[k]	X	X	X	X	X	X		
Serum Chemistry Panel[j]	X	X		X		X		
Hematology	X					X		
Fasting serum lipid profile[l]		X		X		X		
Urine analysis		X		X		X		

First morning void urine for albumin/creatinine ratio		X		X		X		
Safety Assessments								
Record adverse events[m]	X	X	X	X	X	X	X	
Record hypoglycemic episodes[n]	X	X	X	X	X	X	X	
Ongoing Participant Review								
Concomitant therapy[o]	X	X	X	X	X	X	X	
Patient Diary Dispensing & Review	X	X	X	X	X	X		

Footnotes:

Must be signed before first study-related activity.

[a] The period between the screening visit and the baseline visit may be extended up to 4 weeks if adjustment of blood-pressure medications or lipid-altering medications is necessary (subjects should be on a stable regimen of blood pressure and lipid-altering medications for at least 4 weeks before Day 1)

[b] All visits will be scheduled based on the date of baseline visit (Day 1). The study visits should generally occur within a 7-day recommended window (i.e. ±7 days) around the protocol-specified visit schedule during the treatment phase.

[c] End-of-treatment/early withdrawal evaluations will be performed at the end of the treatment phase or at the time the subject is withdrawn from the study. The early withdrawal evaluations should be performed as soon as possible after stopping the study drug.

[d] The informed consent form must be signed at the screening visit before any study procedures are performed.

[e] Record any medications taken from up to 30 days before screening (and up to 6 months before screening for antihyperglycemic agents) until the first dose of study drug on Day 1 (Baseline) as prestudy therapy in the corresponding page of the CRF.

[f] Physical examinations will include a full review of body systems (head and neck, eyes, chest and lungs, cardiovascular (CV), extremities and back, abdomen, and neurological examination). Breast and pelvic/genitourinary system examinations (i.e. prostate, rectal, and gynecologic examinations) should be performed if considered clinically appropriate by the investigator.

[g] Body weight will be measured as per routine practice of the particular study center..

[h] Vital signs will consist of pulse and blood pressure measurements and will be obtained after the subject has been in a seated position for 5 minutes and before blood sample collection for laboratory tests. Pulse rate will be measured once at each clinic visit. BP recording will be done as per standard practice at the study center.

[I] Electrocardiograms will be conducted at the investigator site or affiliated facility.

[j] HbA1c and serum chemistry are performed at the screening visit and should not be repeated at baseline, unless the screening visit was performed more than 3 weeks before the baseline visit). FSH may be done in some cases to check eligibility as per inclusion criteria.

[k] Subjects must fast for at least 8 hours before blood sample collection.

[l] Subjects must fast for at least 8 hours before blood sample collection. Subjects may be instructed at screening visit about 8 hours fasting at baseline visit. If not fasting at the time of the screening visit, the subject should return to the sites within 72 hours to have a fasting lipid profile drawn.

[m] Adverse events will be monitored throughout the study from the time of signing the informed consent form until the end of the study.

[n] Hypoglycemic episodes should be recorded on the hypoglycemia CRF and also on the adverse event CRF if considered as an adverse event by the investigator. Patient diary will be dispensed to assess hypoglycemic episodes.

[o] Concomitant therapy includes all medications since the first dose of study drug on Day 1.

For fasting laboratory assessments, if the participant has not fasted before the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to provide the necessary sample(s) for the assessment.

Any testing that is not considered standard of care (e.g. ECG, lipid panels, etc) will be covered by Sponsor. There will be no expenses for the patients for protocol required tests.

2. INTRODUCTION

Canagliflozin is an orally active inhibitor of SGLT2. It lowers RTG and leads to increase in urinary glucose excretion (UGE), thereby lowering plasma glucose in patients with type 2 diabetes mellitus. Metformin decreases hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Fixed dose-combination of canagliflozin and metformin IR is approved by USFDA in August 2014. Bioequivalence of this FDC is shown in clinical trials. Efficacy and safety of canagliflozin + metformin IR is supported by multiple clinical trials. FDC is advantageous for patients in simplifying the treatment regimens. This can also improve treatment adherence (Fleming JW 2015).

The term “study intervention” throughout the protocol, refers to Canagliflozin + metformin hydrochloride IR FDC.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

2.1. Study Rationale

Marketing authorization in India is granted by DCGI (drug controller general of India) in form-45 dated 27th March 2018 for six dosage strengths of FDC: canagliflozin + metformin hydrochloride IR (50 mg + 500 mg, 150 mg + 500 mg, 50 mg + 850 mg, 150 mg + 850 mg, 50 mg + 1000 mg, 150 mg + 1000 mg). As a condition for approval, marketing authorization holder has been asked to conduct a phase 4 clinical trial. The protocol of phase 4 needs to be submitted for review by the subject expert committee of DCGI; before launching the product in the market. ((India) 2018) (Central Drug Standard Control Organization)

This study will provide data on safety, and efficacy of this combination in Indian population and fulfill the premarketing regulatory commitment in India.

2.2. Background

Efficacy/Safety Studies

Pivotal supporting data for the CANA/MET IR FDC efficacy include**:**

- Phase 3 clinical studies of canagliflozin as add-on therapy in subjects on metformin (alone or in combination with other oral agents or insulin)
- One Phase 2 clinical study (28431754DIA2003 [DIA2003]) evaluating canagliflozin bid as add on therapy to metformin, conducted specifically to support canagliflozin bid dosing
- Four of the 7 Phase 1 studies that support the CANA/MET IR FDC evaluated the pharmacokinetic (PK) bioequivalence of the to-be-marketed formulation of the CANA/MET IR FDC tablets to the individual tablet components (DIA1039, DIA1052, DIA1051, and DIA1038)
- One Phase 1 study evaluated the effect of food on the PK of the to-be-marketed formulation of the CANA/MET IR FDC (DIA1037)

- One Phase 1 study evaluated the PK and Pharmacodynamics (PD) (including the RTG: the plasma glucose concentration above which tubular reabsorption of glucose cannot increase further, and glucose is excreted into the urine in direct proportion to the glucose concentration above this threshold) of canagliflozin once-daily dosing versus bid dosing (DIA1032)
- One Phase 1 study evaluated the relative bioavailability of the CANA/MET IR FDC tablets (6 different dose strengths), serving as a pilot for the Phase 1 bioequivalence studies (DIA1036)

Safety results supporting CANA/MET IR FDC include:

- A pooled dataset 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) (DS1-M).
- A pooled dataset 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 (DS3M-LT2).
- A Phase 2 study (DIA2003) that examined twice-daily dosing of canagliflozin (50 mg and 150 mg bid).
- Four Phase 1 studies that demonstrated the bioequivalence of the to-be-marketed CANA/MET IR FDC to the individual components (for the tablet strengths of 50/850 mg, 150/850 mg, 50/1,000 mg, and 150/1,000 mg [studies DIA1039, DIA1052, DIA1051, and DIA1038, respectively]) (refer to Module 2.7.1 for detail).
- Study DIA1037 evaluating the to-be-marketed CANA/MET IR FDC that showed that food did not affect canagliflozin bioavailability following single-dose administration of the 150/1,000 mg CANA/MET IR FDC tablet (refer to Module 2.7.1 for detail).
- A relative bioavailability study (DIA1036) that served as a pilot for the 4 Phase 1 bioequivalence studies.

Table 1: Subjects from India in Efficacy Analysis

(Modified Intent-to-Treat Analysis Set)

Study Identifier	Cana 100 mg	Cana 300 mg	All Cana	Placebo/ Glimepiride	All Subjects from India	All Subjects in the Study
28431754DIA3009	55	55	110	56	166	1450
28431754DIA3008 DIA3008M	185	178	363	172	535	3158

Key: Cana=canagliflozin.

Summary of Efficacy Findings

Both the 300 mg and the 100 mg canagliflozin doses provided clinically relevant - reductions in HbA1c, FPG, and body weight in subjects on the background of metformin alone or in combination with other oral AHA. The improvement in these efficacy parameters was similar in subjects from India relative to the overall population (Janssen Research & Development 2014).

Table 2: Subjects from India in Safety Analysis (ISS Phase 3 Broad Dataset 3)

(Analysis Set: Safety Analysis Set)

Study Identifier	Cana 100 mg	Cana 300 mg	All Cana	All Non-Cana	All Subjects from India	All Subjects in the Study
DS3M-LT2					(N= 839)	(N= 7309)
28431754DIA3002	0	0	0	0	0	469
28431754DIA3006	28	31	59	35	94	1284
28431754DIA3008M	185	178	353	172	535	3158
28431754DIA3009	55	55	110	56	166	1448
28431754DIA3010M	3	10	13	6	19	608
28431754DIA3012	10	5	15	10	25	342

Key: Cana=canagliflozin.

Summary of Safety Findings

In summary, the overall safety profile, including the overall incidence of adverse events, specific adverse events, serious adverse events, death, and adverse events leading to discontinuation, are generally similar between the total population and the Indian subgroup in the DS3M-LT2 dataset. No notable differences in the pattern of adverse events were seen between the total population and the Indian subgroup (Janssen Research & Development 2014).

2.3. Benefit/Risk Assessment

In support of the CANA/MET IR FDC, analyses of results from the canagliflozin Phase 3 program relevant to this FDC were evaluated. To assess efficacy in add-on use with metformin (alone or with another AHA), 6 Phase 3 studies were examined as the primary efficacy assessment, including add-on to metformin, to metformin and a SU agent, to metformin and pioglitazone, and to metformin and insulin. The results demonstrated efficacy with reductions in HbA1c, FPG, and body weight, comparable to that demonstrated in the broader canagliflozin program.

To assess safety in add-on use with metformin, a pooled dataset 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) (DS1M) and 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) were assessed. For subjects on metformin at baseline in the Phase 3 studies, a total of 4,202 had approximately a year or more exposure, and 2,284 had approximately 1.5 years or more exposure. The safety assessment in these subjects demonstrated a safety profile comparable to that identified for canagliflozin.

The efficacy data of subjects from India in selected individual studies showed that canagliflozin 100 mg and 300 mg on the background of metformin alone or in combination with other oral AHA, provided clinically relevant reductions in HbA1c, FPG, and body weight. The improvement in these efficacy parameters was similar in subjects from India relative to the overall population.

The overall safety profile of canagliflozin in subjects from India on metformin alone or metformin in combination with another AHA (including the overall incidence of adverse events, specific adverse events [including ADRs], serious adverse events, death, and adverse events leading to discontinuation] was generally similar between the total population and the Indian subgroup in the DS3M-LT2 dataset. No notable differences in the pattern of adverse events were seen between the total population and the Indian subgroup.

In conclusion, both doses of canagliflozin on the background of metformin provide glycemic improvement and body weight reduction, and were well tolerated in subjects from India. A favorable benefit and risk profile of canagliflozin 100 mg and 300 mg in combination with metformin was seen in the Indian population, consistent with the benefit and risk profile in the overall population in the global development program. (Janssen Research & Development 2014)

More detailed information about the known and expected benefits and risks of Canagliflozin + metformin hydrochloride IR FDC may be found in the document canagliflozin/metformin FDC SAR (subgroup analysis report) for India (Janssen Research & Development 2014).

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES

Primary Objective

In adult Indian patients with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate:

The primary objective is to assess safety of canagliflozin + metformin hydrochloride IR fixed-dose combination

Secondary Objective

In adult Indian patients with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate:

The secondary is to assess efficacy of canagliflozin + metformin hydrochloride IR fixed-dose combination

Tertiary/Exploratory Objectives

In adult Indian patients with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate:

The tertiary/exploratory objectives are to assess other efficacy parameters like FPG, PPG, body weight, waist circumference, BP, and proportion of patients achieving HbA1c goal of below 7%

ENDPOINTS

Primary Endpoint

The percentage (%) of adverse events (AEs), serious adverse events (SAEs), unexpected adverse events or adverse drug reactions [Time Frame: 24 weeks]

Secondary Endpoint

Change from baseline in Glycosylated Haemoglobin (HbA1c) % [Time Frame: 12 and 24 weeks]

Tertiary/Exploratory Endpoints

Change from baseline in fasting plasma glucose (FPG) in mg/dL [Time Frame: 12 and 24 weeks]

Change from baseline in 2-hr post-prandial plasma glucose (PPG) in mg/dL [Time Frame: 12 and 24 weeks]

Proportion of patients achieving HbA1c goal of below 7% [Time Frame: 12 and 24 weeks]

Change from baseline in blood pressure (BP) in mmHg [Time Frame: 12 and 24 weeks]

Change from baseline in body weight in Kg [Time Frame: 12 and 24 weeks]

Change from baseline in waist circumference in cm [Time Frame: 12 and 24 weeks].

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The study will be descriptive in nature to assess safety and efficacy of canagliflozin + metformin hydrochloride IR fixed-dose in Indian patients with type 2 diabetes mellitus.

4. STUDY DESIGN

4.1. Overall Design

This is a prospective, multi-center, open-label, single-arm, phase 4 study in Indian adults with type 2 diabetes mellitus to evaluate the safety and efficacy of canagliflozin + metformin hydrochloride IR fixed-dose combination as an adjunct to diet and exercise to improve glycemic control when treatment with both canagliflozin and metformin is appropriate.

The study will be conducted in 3 phases: a 7-day screening phase, a 24 weeks treatment phase extending from Day 1 (baseline) to completing at the Week 24 visit (or the end-of-treatment [EOT] visit for subjects discontinuing study treatment early), and a 28 days post-treatment phase-Telephone follow-up contact (or optional study visit, at the discretion of the investigator) approximately 28 days after the last dose of study drug. The duration of individual participation will be approximately 29 weeks.

Key safety assessments include adverse events (AEs), serious adverse events (SAEs), unexpected adverse events or adverse drug reactions. Key efficacy assessments include HbA1C, FPG, PPG, blood pressure, body weight, and waist circumference.

A total of 276 participants will be enrolled in this study.

4.2. Scientific Rationale for Study Design

Prospective, Multi-Center, Single Arm, Open Label

Single arm design will be used to assess safety and efficacy parameters. Because of single arm study there is no risk of potential bias during data collection and analysis, so blinding is not required.

Safety & Tolerability Assessment, Secondary Efficacy Endpoints

As this FDC of canagliflozin + metformin HCL IR, per se, will be first time used in Indian patients, analysis of safety as a primary endpoint is chosen considering regulatory requirement of conducting phase 4 studies in India. Inclusion of secondary efficacy endpoints will provide more data on potential benefits of study intervention in Indian population.

Dosing Forms, Strengths, Schedule, Route of Administration

Two dosage strengths of canagliflozin + metformin HCl IR (50 mg + 500 mg; 50 mg + 1000 mg) will be utilized. These are to be dispensed as per local prescribing information of the study intervention. For dispensing details please refer to Section 6.1.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The primary ethical concern is NOT APPLICABLE

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American red cross (Blood Needs & Blood Supply, Facts & Statistics, Red Cross 2018).

4.3. Justification for Dose

Two dosage strengths of canagliflozin + metformin HCl IR (50 mg + 500 mg; 50 mg + 1000 mg) will be utilized. Dose of study intervention canagliflozin + metformin HCL IR FDC is selected as per approved local prescribing information of the product and available commercialized strengths in India.

4.4. End of Study Definition

A participant will be considered to have completed the study if he or she has completed post treatment telephonic assessments visit.

For subjects discontinuing study drug before, Wk 24 of the Treatment Phase, an early withdrawal evaluation visit / EOT Visit, should be performed as soon as possible after stopping the study drug. A telephonic follow-up should also be done 28 days after study drug discontinuation.

5. STUDY POPULATION

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Male or female

2. 18 to 65 years of age, inclusive.

3. Subject willing to adhere to diet and exercise regimen as recommended by the investigator

4. T2DM with inadequate glycemic control on diet and exercise, who in Investigator's opinion are eligible to receive study drug as per prescribing information along with standard care for management of T2DM

5. Subject/ LAR must have signed an informed consent form (ICF) indicating that they understand the purpose of, and procedures required for, the study and are willing to participate in the study.

6. Women must be:
   - Postmenopausal, defined as
     - >45 years of age with amenorrhea for at least 18 months, or
     - >45 years of age with amenorrhea for at least 6 months and <18 months and a serum follicle stimulating hormone (FSH) level >40 IU/L, or
   - surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal occlusion), or otherwise be incapable of pregnancy, or
   - sexually active and practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, tubal ligation, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, and consistent with local regulations regarding use

of birth control methods for subjects participating in clinical studies, for the duration of their participation in the study, or
– not sexually active.

Note: subjects who are not sexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study

7. Women of childbearing potential (ie, those subjects who do not meet the postmenopausal definition above in Inclusion Criterion 6, regardless of age must have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening and negative UPT at baseline (predose, Day 1).

8. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

9. Treatment naïve patients or patients on stable AHA therapy (for at least 12 weeks before screening) and have a screening visit HbA1c of ≥7.0% and ≤10.0%.

10. In the opinion of the Investigator, the subject is capable of understanding and complying with protocol requirements.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. history of liver or renal insufficiency (estimated creatinine clearance below 45 mL/min); significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances.

2. Contraindication or limitation for administration of study drug according to local Prescribing Information; Metabolic acidosis)

3. Known allergies, hypersensitivity, or intolerance to Canagliflozin, Metformin or Canagliflozin + metformin hydrochloride IR FDC or its excipients (refer to local prescribing information)

4. Use of any other SGLT2 inhibitor () within 12 weeks before the screening visit

5. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 30 days after last dose of study medication; or intending to donate ova during such time period

6. Received an investigational intervention or used an invasive investigational medical device within 30 days before the planned first dose of study intervention

7. History of hereditary glucose-galactose malabsorption or primary renal glucosuria

8. History of diabetic ketoacidosis, type 1 diabetes mellitus (T1DM), pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy

9. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are noted in Appendix 4, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.5, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

Dose of study drug is given with meals, twice a day.

Diet and exercise instructions are advised to participants as per standard of care.

5.4. Screen Failures

At the Screening Visit, the results of the following laboratory tests performed at the laboratory must be within the limits specified below (or in the inclusion criteria).

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and date of birth (as allowed by local regulations). In cases where the participant is not enrolled into the study, the date seen and date of birth (as allowed by local regulations) will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

The study intervention (canagliflozin + metformin hydrochloride IR fixed-dose combination), 50 mg + 500 mg or 50 mg + 1000 mg, will be provided as tablets for oral administration. Participants will be instructed to take their assigned dose of the study intervention orally twice daily each day. The study intervention is to be taken with approximately 240 mL (8 ounces) of water. The tablets should be swallowed intact and participants should not attempt to dissolve them in water. Each dose should be taken with meal, at approximately the same time each day. Dosing can be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin 2000 mg and canagliflozin 300 mg in patients with an eGFR of 60 mL/min/1.73 m^2 or greater. Dose initiation and dose adjustment will be done as per local prescribing information of canagliflozin + metformin hydrochloride IR, as determined by the investigator.

Study intervention administration must be captured in the source documents and the CRF.

Canagliflozin + metformin hydrochloride IR FDC will be manufactured and provided under the responsibility of the sponsor.

6.2. Preparation/Handling/Storage/Accountability

All study intervention must be stored as per label.

The dispensing of study intervention to the participant, and the return of study intervention from the participant (if applicable), must be documented on the intervention accountability form. Participants, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study intervention.

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant except if mentioned in IP procedure manual. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable

6.4. Study Intervention Compliance

The number of study intervention dispensed will be recorded and compared with the number returned.

6.5. Concomitant Therapy

Prestudy therapies administered up to 12 weeks before first dose of study intervention must be recorded at screening.

Concomitant therapies (all medications since the first dose of study drug on Day 1) must be recorded throughout the study beginning with start of the first dose of study intervention to 28 days after the last dose of study intervention.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study intervention must be recorded in the CRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication.

6.5.1. Rescue Medication

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

The sponsor will not supply insulin or other rescue medication that will be obtained locally

6.6. Dose Modification

Any dose/dosage adjustment should be overseen by medically-qualified study-site personnel (principal or subinvestigator unless an immediate safety risk appears to be present).

The study intervention JNJ-28431754 (canagliflozin + metformin hydrochloride IR fixed-dose combination), will be provided as tablets for oral administration. Participants will be instructed to take their assigned dose of the study intervention orally twice daily each day. Dosing can be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended

daily dose of metformin 2000 mg and canagliflozin 300 mg in patients with an eGFR of 60 mL/min/1.73 m^2 or greater. Dose initiation and dose adjustment will be done as per local prescribing information of canagliflozin + metformin hydrochloride IR, as determined by the investigator.

The decision to proceed to the next dose level of Canagliflozin + metformin hydrochloride IR FDC (either an increase or a decrease) will be made by the investigator based on safety, tolerability, and as per local prescribing information of the study drug.

6.7. Intervention After the End of the Study

Telephone contact (or optional study visit, at the discretion of the investigator) will be made to determine any serious adverse events 4 weeks after the last dose of study intervention, unless the participant has died, is lost to follow-up, or has withdrawn consent. If the information on any serious adverse events is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the participant has died, the date and cause of death will be collected and documented on the CRF.

Participants will be instructed that study intervention will not be made available to them after they have completed/discontinued study intervention and that they should return to their primary physician to determine standard of care.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the participant to discontinue study intervention
- The participant becomes pregnant

If a participant discontinues study intervention for any reason before the end of the treatment phase, assessments should be obtained and follow-up telephonic call should be done 28 days after last dose of study drug. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be automatically withdrawn from the study if they have to discontinue study intervention before the end of the intervention regimen.

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent

- Death
- Noncompliance defined as participant failed to take ≥80% of study intervention over 24 weeks.
- Discontinuation of study intervention for any reason. A participant's study intervention will be automatically discontinued if:
  - The investigator or sponsor believes (eg, that for safety or tolerability reasons (eg, adverse event) it is in the best interest of the participant to discontinue study intervention
  - The participant becomes pregnant

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study intervention assigned to the withdrawn participant may not be assigned to another participant. Additional participants will be entered to ensure the protocol-specified number of participants complete the study. If a participant discontinues study intervention and withdraws from the study before the end of the treatment phase, assessments should be obtained and follow-up telephonic call should be done 28 days after last dose of study drug. If the reason for withdrawal from the study is withdrawal on consent then no additional assessments are allowed.

7.3. Lost to Follow-up

If a participant is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the participant and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented. Refer to Section 7.2, Participant Discontinuation/Withdrawal From the Study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of efficacy and safety measurements applicable to this study.

Additional urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

For each participant, the maximum amount of blood drawn from each participant in this study will not exceed 100 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form.

Refer to the Schedule of Activities for the timing and frequency of all sample collections.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Package Insert for Canagliflozin + Metformin HCl IR FDC

8.1. Efficacy Assessments

The primary measure of efficacy is HbA1c. Secondary measures of efficacy include FPG, 2hr PPG, body weight, and blood pressure.

Efficacy endpoints (ie, criteria for evaluation of efficacy measures) include the following:

The secondary efficacy endpoint will be the change in HbA1c from baseline to Week 12 and week 24; only subjects who have both baseline and at least 1 post-baseline measurement will be included.

Key exploratory efficacy endpoints will include the change from baseline to Week 12 and week 24 in FPG, 2 hr PPG, body weight, waist circumference, blood pressure.

The proportion of subjects with HbA1c <7.0% at Week 24 will also be a key exploratory endpoint.

8.2. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Appendix 5, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities:

The primary safety endpoint is the percentage (%) of adverse events (AEs), serious adverse events (SAEs), unexpected adverse events or adverse drug reactions occurring over a study period of 24 weeks from the first day of study intervention.

Safety evaluations, according to the time points provided in the Time and Events Schedule, will include the collection of adverse events, hypoglycemic episodes, safety laboratory tests (including chemistry, hematology, and urinalysis), vital signs, body weight, height, physical examinations.

8.2.1. Vital Signs

Pulse/heart rate, blood pressure will be assessed.

Pulse and blood pressure measurements and will be obtained after the subject has been in a seated position for 5 minutes and before blood sample collection for laboratory tests.

blood pressure should preferably be measured by the same individual, using the same equipment, at each clinic visit to reduce variability.

Blood pressure and pulse/heart rate measurements should be assessed with a automated device. Manual techniques may be used only if an automated device is not available.

8.2.2. Electrocardiogram (ECG)

Electrocardiograms will be conducted at the investigator site or affiliated facility

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

8.2.3. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and first morning void urine for urinalysis will be collected as noted in Appendix 3, Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

8.2.4. Hypoglycemia Episodes

Subjects will be asked for any symptoms like dizziness, sweating, etc. during the study period. Laboratory parameters would also be recorded during hypoglycemic episodes. Dosage of study drug may be adjusted, or rescue therapy may be provided as per assessment by investigator.

8.3. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Anticipated events will be recorded and reported as described in Appendix 2.

For further details on adverse events and serious adverse events (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Appendix 5, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. In this study, 28-day telephonic follow-up will be done after last dose of study drug to assess adverse events.

Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 28 days after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the participant is not specifically questioned.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 5, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the intervention caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the institute where required). The sponsor assumes responsibility for appropriate reporting of anticipated events to the regulatory authorities according to requirements of the countries in which the studies are conducted. The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, still birth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.

Follow up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Disease-Related Events and Disease-Related Outcomes not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

8.4. Treatment of Overdose

For this study, any dose of Canagliflozin + metformin hydrochloride IR FDC greater than 300 mg + 2000 mg within a 24-hour time period will be considered an overdose. The sponsor does not recommend specific intervention for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until Canagliflozin + metformin hydrochloride IR FDC can no longer be detected systemically (at least 7 days).
- In the event of an overdose, it is reasonable to employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. The most effective method to remove lactate and metformin is hemodialysis. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Not applicable.

8.7. Genetics

Not applicable.

8.8. Biomarkers

Not applicable.

8.9. [Health Economics] [Medical Resource Utilization and Health Economics]

Not applicable.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

9.1. Statistical Hypotheses

No formal hypothesis testing will be conducted.

9.2. Sample Size Determination

As described in synopsis.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Safety	All randomized participants who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.

9.4. Statistical Analyses

Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, coefficient of variation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate.

9.4.1. Safety Analyses

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Intervention-emergent adverse events are adverse events with onset during the intervention phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in pre- versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

Vital Signs

Descriptive statistics of pulse and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

Physical Examination

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

Physical examination findings (including body weight and waist circumference) will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

9.5. Interim Analysis

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

ADR	adverse drug reaction
AE	adverse event
BP	Blood Pressure
CANA	Canagliflozin
CANA/MET IR FDC	canagliflozin + metformin HCL IR FDC
CRF	case report form(s) (paper or electronic)
ECG	Electrocardiogram
EGFR	estimated glomerular filtration rate
EOT	End of treatment
FDC	Fixed Dose combination
FPG	fasting plasma glucose
HbA1C	glycosylated hemoglobin
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IR	Immediate release
IRB	Institutional Review Board
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPG	post-prandial plasma glucose
RTG	Renal threshold of glucose
SAE	Serious adverse event
SGLT2I	sodium Glucose cotransporter 2 inhibitor
SoA	Schedule of Activities
T2DM	Type 2 Diabetes mellitus
UGE	Urinary glucose excretion
WOCBP	Woman of Childbearing Potential

10.2. Appendix 2: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

- Urinary tract infection
- Genital mycotic infection
- Polyuria/Pollakiuria
- Volume depletion adverse events

Reporting of Anticipated Events

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described under All Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described under Serious Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

10.3. Appendix 3: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the local laboratory

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	RBC Indices: MCV MCH	White Blood Cell (CBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Sodium Potassium Blood urea nitrogen (BUN) Creatinine Glucose Fasting and 2hr PPG Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic	Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein Fasting serum lipid profile (triglycerides, LDL-C, HDL-C, total cholesterol)	
Routine Urinalysis	Dipstick Protein		
	First morning void urine for albumin/creatinine ratio		
Other Screening Tests	• HbA1c • Serum beta HCG Testing [for women of childbearing potential only]		

10.4. Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- Local Prescribing Information of the study drug

- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) and contracts for details on financial disclosure.

INFORMED CONSENT PROCESS

Each participant (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed

that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease]. [Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations.

The participant or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the participant's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

If the participant or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant or legally acceptable representative is obtained.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding Canagliflozin + metformin hydrochloride IR FDC or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of Canagliflozin + metformin hydrochloride IR FDC, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information.

For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after their return to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. The data will be entered into the study database and verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in printed or electronic format. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

For paper CRF use: All printed forms must be filled out legibly in black ballpoint pen or typed. The appropriate pages of the CRF must be signed and dated by the investigator.

For electronic CRF use: The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

For paper CRF: Corrections to paper CRF must be made in such a way that the original entry is not obscured. Correction fluid or tape must NOT be used. The correct data must be inserted, dated, and initialed. If multi-part pressure-sensitive CRF are used, the separated parts of the CRF left at the study site must not be written on once the original has been sent to the sponsor. Completed CRF will be continuously submitted according to the sponsor's instructions and reviewed by the sponsor to determine their acceptability. If corrections to a CRF are needed after removal of the original CRF copy from the study site, Data Correction/Clarification Forms (DCF) will be generated and transmitted to the study site. The CRF must be adjusted (if applicable) and a response provided to the query (complete, sign, and date the DCF).

For electronic CRF use: If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the CRF and will be considered source data:

- Race
- Age
- Disease History
- Medical History and medication history
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF.

MONITORING

The sponsor will use a combination of monitoring techniques remote and/or on-site monitoring to monitor this study

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. At these visits, the monitor will compare data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be

respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

For paper CRF use: For CRF completed on pressure-sensitive paper, a copy is to be retained in the archives of the sponsor. A second copy must be archived by the investigator.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE CLOSURE

Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.5. Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or noninvestigational-) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or noninvestigational) product, whether or not related to that medicinal (investigational or -noninvestigational) product. (Definition per International Conference on Harmonisation- [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Canagliflozin + metformin hydrochloride IR FDC, the expectedness of an adverse event will be determined by whether or not it is listed in the local prescribing information.

Adverse Event Associated With the Use of the Intervention

An adverse event is considered associated with the use of the intervention if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

An adverse event that is not related to the use of the intervention.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant treatment(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the intervention. An alternative explanation, eg, concomitant treatment(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the intervention. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant treatment(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant treatment(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention

- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error involving a sponsor product (with or without participant/patient exposure to the sponsor study intervention, eg, name confusion)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

PROCEDURES

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes

- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF).

The cause of death of a participant in a study within 28 days of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered a serious adverse event.

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse

Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.6. Appendix 6: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 5 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of ⩽1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner

(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of >1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.7. Appendix 7: Genetics

Not applicable.

10.8. Appendix 8: Liver Safety: Suggested Actions and Follow-up Assessments

Not applicable.

10.9. Appendix 9: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable.

10.10. Appendix 10:

Not applicable.

10.11. Appendix 11: Protocol Amendment History

This is protocol with amendment 1.

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INVESTIGATOR AGREEMENT

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I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Johnson & Johnson Private Limited

Signature: PPD Date: 25.03.2021
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Johnson & Johnson Private Limited

Clinical Protocol

COVID-19 Appendix

A prospective, multi-centric, open-label, single-arm, phase 4 study to evaluate the safety and efficacy of canagliflozin + metformin hydrochloride IR fixed-dose combination as an adjunct to diet and exercise to improve glycemic control in Indian adult patients with type2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate

A study to evaluate the safety and efficacy of canagliflozin + metformin hydrochloride IR fixed-dose combination in Indian adults with type 2 diabetes

Protocol 28431754DIA4032; Phase [4]

JNJ-28431754) Canagliflozin

Status: Approved
Date: 31 May 2021
Prepared by: **Johnson & Johnson Private Limited**
EDMS number: EDMS-RIM-453560, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

- MISSED ASSESSMENTS WILL BE CAPTURED IN THE CLINICAL TRIAL MANAGEMENT SYSTEM FOR PROTOCOL DEVIATIONS, WITH THE ACTUAL VISIT DATE DOCUMENTED OR REASON FOR WITHDRAWALS SPECIFIED; DISCONTINUATIONS OF STUDY INTERVENTIONS AND WITHDRAWAL FROM THE STUDY WILL BE CAPTURED WITH THE PREFIX "COVID-19-RELATED" IN THE CRF.
- IF SITE VISITS ARE NOT POSSIBLE, TEMPORARY DIRECT-TO-PATIENT SHIPMENT OF STUDY DRUG FROM THE SITE MAY BE CONSIDERED FOR ONGOING PATIENTS. SITE STAFF NEED TO OBTAIN PERMISSION FROM THE SUBJECT AND RECORD THIS IN THE SUBJECT SOURCE RECORD. DOCUMENTATION REQUIREMENTS WILL BE COMMUNICATED BY THE SPONSOR TO THE SITE.
- ALTERNATIVES TO STUDY INTERVENTION DISPENSING, ADMINISTRATION, AND CLINICAL SAFETY LABORATORY ASSESSMENTS (INCLUDING HOME HEALTH NURSING) COULD BE CONSIDERED TO ALLOW CONTINUED STUDY PARTICIPATION FOR SUBJECTS PARTICIPATING IN THIS STUDY.

STUDY CONDUCT RELATED TO COVID-19 VACCINE DEPLOYMENT FOR NONCOVID-19 CLINICAL TRIALS

- RECORD COVID-19 VACCINE AS A CONCOMITANT THERAPY.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
JNJ-28431754) Canagliflozin Clinical Protocol 28431754DIA4032

INVESTIGATOR AGREEMENT

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(Day Month Year)

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_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD _____

Institution: **Johnson & Johnson Private Limited** _____

Signature: _____ PPD _____ Date: _____ PPD _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.