Johnson & Johnson Private Limited

Statistical Analysis Plan

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

Protocol 28431754DIA4032; Phase 4

JNJ-28431754 (canagliflozin)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

Not applicable

ABBREVIATIONS

AE	Adverse event
ATC	Anatomic and therapeutic Class
BMI	Body mass index
BP	Blood Pressure
CI	Confidence Interval
CM	Concomitant Medication
COVID-19	Coronavirus-2019
CRF	Case report form
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
EOT	End of Treatment
EW	Early withdrawal
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
HbA1c	Glycosylated Hemoglobin
IR	Immediate release
MedDRA	Medical Dictionary for Regulatory Activities
PPG	Post-prandial Plasma Glucose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This study is designed to evaluate 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.

This statistical analysis plan (SAP) for the 28431754DIA4032 describes the statistical analysis for participant information, safety, and efficacy data.

1.1. Trial Objectives

Primary Objective

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

Secondary Objective

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

Tertiary/Exploratory Objectives

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

1.2. Trial 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.

A total of 276 participants consisting of male and female between 18 to 65 years of age will be enrolled in this study. 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.

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 participants discontinuing study treatment early whichever occurs earlier), 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 treatment. The duration of individual participation will be approximately 29 weeks.

1.3. Statistical Hypotheses for Trial Objectives

The study will be descriptive in nature, no formal hypothesis testing will be conducted.

1.4. Sample Size Justification

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:

$$n = \frac{\left[Z\left(1-\frac{\alpha}{2}\right)\right]^2 p(1-p)}{d^2}$$

Where in, n is calculated sample size, Z is degree of confidence (i.e. 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%).

1.5. Randomization and Blinding

This is an open label and single arm study, randomization and blinding procedures are not applicable.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Analysis Sets

2.1.1. All Enrolled Analysis Set

All enrolled analysis set is defined as those participants who have signed the informed consent and are enrolled in the study.

2.1.2. Safety Analysis Set

All participants who had taken at least 1 dose of study treatment will be included in the safety analysis set. Participants will be analyzed according to the treatment they actually received.

2.1.3. Efficacy Analysis Set

The efficacy analysis set will include all participants who have taken at least 1 dose of study treatment and have both baseline and at least 1 post-baseline efficacy assessment.

2.2. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study treatment administration. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥date of Day 1
- Visit date - Date of Day 1, if visit date <date of Day 1

There is no 'Day 0'.

End of treatment (EOT) will be defined as assessments done at Week 24 and in case of early withdrawal it will be the last available assessment present in the data.

End of study (EOS) will be defined as Week 24 plus 28 days for participants who had completed the treatment period (24 Weeks) and post treatment visit (i.e. 28 days after the last dose of study treatment). In case of early withdrawal it will be withdrawal date plus 28 days.

2.3. Baseline

Baseline is defined as the last observation prior to the start of the first study treatment administration.

2.4. General Analysis Rules

The below mentioned general principles will be followed throughout the study.

- Continuous data will be summarized by descriptive statistics, including number of non-missing participants (N), mean, standard deviation (SD), 95% confidence interval (CI), median, and range (minimum; maximum) and for categorical variables the frequencies and percentages of participants will be presented.
- The minimum and maximum will be presented to the same number of decimal places as the original data. The mean, median and 95% CI will be rounded to one additional decimal place than the original data, while SD will be approximated to two additional decimal places.
- The percentages (%) in tables will be presented to 1 decimal place unless the sample sizes for the percentages are small enough to warrant presenting as integers.
- If a count is 0, the percentage (0%) should not be displayed. The 0 count will be displayed, but the corresponding percentage should be omitted.
- All study data will be included in study data listings. In general, all data will be listed by time point within participant.
- The change from baseline is defined as the post-baseline value minus the baseline value.
- The analysis visits will be labelled as “Screening”, “Baseline (Day 1)”, “Week 6”, “Week 12”, “Week 18”, “Week 24” and EOT/Early Withdrawal (EW) At each analysis visit, the number of participants with available data for a particular parameter will be displayed in the outputs.
- SAS® version 9.4 will be used for all analyses.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

There is neither interim analysis nor data monitoring committee (DMC) review planned for this study.

4. PARTICIPANT INFORMATION

4.1. Demographics and Baseline Characteristics

Table 1 presents a list of the demographic variables and baseline characteristics that will be summarized for all enrolled analysis set.

Table 1: Demographic Variables and Baseline Characteristics

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m2)	
Waist circumference (cm)	
Glycosylated Hemoglobin (HbA1c) %	
Fasting Plasma Glucose (FPG) (mg/dL)	
Post-prandial Plasma Glucose (PPG) (mg/dL)	
Systolic Blood Pressure (mm/Hg)	
Diastolic Blood Pressure (mm/Hg)	
Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.73m2)	
Categorical Variables	
Sex (male, female)	Frequency distribution with the number and percentage of participants in each category.
Race[a] (Indian, Non-Indian)	
eGFR categories (<60, 60 - <90, >=90) (mL/min/1.73m2)	
Age categories (<35, 35 - <65, >=65) (years)	
BMI categories (<30, 30-<35, >=35) (kg/m2)	
HbA1c (below 7%, above 7%)	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

The last non missing record before dosing will be considered as baseline for weight and height. Body mass index (BMI) will be calculated using baseline height and weight.

The demographics and baseline characteristics will be listed for all participants.

4.2. Disposition Information

The summary of analysis datasets and study disposition will be summarized for using the following categories based on all screened subjects:

- Number of participants screened
- Number of participants screened but not enrolled
- Number of participants enrolled (in the All Enrolled Analysis Set)
- Number of participants enrolled but not receiving the study treatment
- Number of participants in the Safety Analysis Set
- Number of participants in the Efficacy Analysis Set

Below disposition summaries will be presented based on Safety analysis set.

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

The summary for the treatment disposition will be as follows:

- Number of participants receiving study treatment
- Number of participants who completed the study treatment
- Number of participants discontinued the study treatment
- Reasons for discontinuation of study treatment

The Summary for the study disposition will be as follows:

- Number of participants enrolled
- Number of participants receiving study treatment
- Number of participants completed the study
- Participants who terminated study prematurely
- Reasons for termination of study

The number of participants in the following disposition categories (discontinued) will be summarized throughout the study under the following categories:

- Adverse Event
- Death
- Lost to Follow-Up
- Non-Compliance with Study Drug
- Withdrawal by Subject
- Pregnancy
- Other

Listings of participants will be provided for the following categories:

- Participants who discontinued study treatment
- Participants who terminated study prematurely

4.3. Treatment Compliance

Study treatment compliance is calculated as the actual total number of tablets taken divided by the expected total number of tablets during this study. Percentages of completed doses for categories (<80, 80-<100%, equal to 100%) will be summarized.

Compliance rate (%) = 100 $\times$ the actual total number of tablets/ the expected total number of tablets, where the actual number of tablets = Σ (number of intervention dispensed tablets – number of missing tablets) and the expected number of tablets = per protocol daily expected number of

tablets (e.g. the total daily tablets = 2 given 1 tablet once but oral twice daily) × 24 (in a 24-week treatment phase) ×7 (per week 7 days).

4.4. Extent of Exposure

Total treatment duration (in Weeks), number of participants with, without dose modification, number of participants who received Canagliflozin 50mg + Metformin hydrochloride 500mg and Canagliflozin 50mg + Metformin hydrochloride 1000mg will be summarized. Participants who received study dose will be listed.

The total treatment duration is defined as [{(last dose date - first dose date) + 1}/7]

4.5. Protocol Deviations

Major protocol deviations will be defined. Participants with major protocol deviations will be summarized based on all Enrolled analysis set. A listing of participants with a major protocol deviation will be provided.

A listing of participants with a COVID-19 related major protocol deviation will be provided separately.

4.6. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study treatment. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study treatment, including those that started before and continue on after the first dose of study treatment.

Prior and concomitant medications will be summarized by ATC code 2 and decoded CM term.

The data on prior and concomitant medications will be provided in separate listings. Listings will be repeated for participants who had covid-19 infection.

Considerations to be taken while mapping the Prior and Concomitant medications:

- If both start date and end date are missing, then this medication will be considered as both prior and concomitant medications.
- If a medication record misses components of its start and/or end dates (day and/or month and/or year) will be handled as:
    - In case of partial start or end dates, the medication records will be allocated using the available partial information, without imputations. If, for example, only month and year are available, these will be compared to the month and the year of the date/time of the study treatment intake.
- In case of a completely missing start date, the medication will be considered as having started before the study (prior of the study treatment intake).

- In case of a completely missing end date, the medication will be considered as 'ongoing' at the end of the study.

Rescue medication

New Antidiabetic medication started after the study drug is initiated. Concomitant medications with rescue medications will be summarized and listed.

4.7. Medical History

Medical History will be summarized and listed for all participants on all enrolled analysis set.

A listing for pre-planned surgery/procedure will be provided.

5. SAFETY

All safety analyses will be performed on the safety analysis set based on actual treatment received, unless otherwise specified.

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 treatment. Safety evaluations include the hypoglycemic episodes, safety laboratory tests (including chemistry, hematology, and urinalysis), vital signs, body weight, height, physical examinations.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, 95% CI, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

5.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the available version of the Medical Dictionary for Regulatory Activities (MedDRA version 24.1). Any AE occurring at or after the initial administration of study treatment through the day of last dose plus 28 days is considered to be treatment emergent. Treatment-emergent adverse events are adverse events with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study treatment based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized.

Summary tables will be provided for:

- TEAEs
- Serious TEAEs (SAEs)

- TEAEs leading to discontinuation of study treatment
- TEAEs leading to termination of study participation
- TEAEs by severity (Mild, Moderate, Severe)
- TEAEs by relationship to study treatment (Not Related, Doubtful, Possible, Probable, Very Likely)
- TEAEs by SOC and PT

In addition listings will be provided for participants who had:

- TEAEs
- Serious TEAEs (SAEs)
- TEAEs leading to discontinuation of study treatment
- TEAEs Leading to Death

Listings will be repeated for participants who had covid-19 infection.

A list of anticipated AEs is attached in the Section 7 appendix. A listing of unexpected AEs will be provided if unexpected AEs are identified.

5.2. Clinical Laboratory Tests

All clinical laboratory tests will be displayed for the participants included in the safety analysis set. This includes assessment of Chemistry, Hematology and Urinalysis.

Abnormality is defined as any lab value which is outside the normal range. The normal ranges will be based on standard units for the lab parameters.

The following summary tables will be provided:

- Descriptive statistics for all chemistry, hematology and urinalysis laboratory tests and change from baseline at each scheduled time point of measurement.
- Number of participants with abnormal laboratory values will be summarized.

In addition to the summary tables, the following listings will be provided:

- Clinical laboratory test results and change from baseline.
- Participants with abnormal laboratory values.
- Normal reference ranges.

5.3. Vital Signs and Physical Examination Findings

Vital sign parameters including pulse rate, blood pressure (systolic and diastolic) will be summarized using mean, standard deviation, median, minimum and maximum at each assessment time point.

Body Mass Index will be calculated as weight (kg)/(height (m))2, at each time point that body weight is measured. The height measurement collected at screening will be used in the calculation.

Three consecutive blood pressure reading will be taken and recorded at intervals of at least 1 minute apart. The value with highest blood pressure will be considered the 'Visit' blood pressure result for each assessment time points.

Abnormality is defined as any value which is outside the normal range specified in Table 2.

Change from baseline will also be summarized at each time point. Descriptive statistics for change from baseline (mean, standard deviation, 95% CI, median, minimum and maximum) will be presented.

Incidence of abnormalities in vital signs will be summarized for participants who had a baseline assessment and at least 1 postbaseline assessment for that vital sign.

Listing of vital sign measurements and change from baseline will be presented for all participants.

A listing of abnormal vital signs will be presented, including unscheduled visits.

Table 2: Normal Ranges for Vital Signs

Vital Signs Parameter	Range
Pulse	50 Beats/min to 100 Beats/min
SYSBP	90 mmHg to 140 mmHg
DIABP	50 mmHg to 90 mmHg

Abnormal physical examination results will be listed.

5.4. Electrocardiogram

All ECG parameters will be listed by participant.

5.5. Hypoglycemia episodes

Summary of participants with Hypoglycemic episodes (0,1,2 or > 3) prior to rescue medication will be provided. A separate listing will for Hypoglycemia episodes will also be provided.

6. EFFICACY

6.1. Efficacy Endpoint

Analysis for efficacy endpoints will be based on efficacy analysis set.

6.1.1. Definition

The primary measure of efficacy is HbA1c (Glycosylated Hemoglobin). Change in HbA1c (%) from baseline to week 12 and week 24 will be evaluated.

6.1.2. Analysis Methods

Change from baseline to week 12 and week 24 will be summarized descriptively for Glycosylated Hemoglobin (HbA1c) %.

Summary tables will also be generated for below subgroups:

- eGFR categories (<60, 60-<90, >=90) (mL/min/1.73m^2)
- Age categories (<35, 35-<65, >=65) (years)
- BMI categories (<30, 30-<35, >=35) (kg/m^2)

6.2. Secondary Efficacy Endpoints

Analysis for secondary efficacy endpoints will be based on efficacy analysis set.

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%.

6.2.1. Definition

Secondary measures of efficacy include changes from baseline in parameters like FPG, PPG, body weight, waist circumference and blood pressure. Secondary parameters will be evaluated at week 12 and week 24. The proportion of participants with HbA1c <7.0% at Week 24 will also be a key endpoint.

6.2.2. Analysis Methods

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for FPG, PPG, BP, Weight, waist circumference and their change from baseline to week 12 and week 24 will be presented based on efficacy analysis set for each of the following parameters:

- Fasting Plasma Glucose (FPG) in mg/dL
- 2-hr Post-prandial Plasma Glucose (PPG) in mg/dL
- Blood Pressure (BP) in mmHg
- Body Weight in Kg
- Waist Circumference in cm

The proportion of participants with HbA1c <7.0% will be summarized at baseline, Week 12 and Week 24.

A separate listing for all the efficacy endpoints (HbA1c, FPG, PPG, BP, Weight, waist circumference) will be provided for all participants based on efficacy analysis set.

7. Appendix

7.1. Anticipated Events

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

8. REFERENCES

Not applicable.