Janssen Research & Development*

Clinical Protocol

Protocol Title
Canagliflozin: Impact on Health Status, Quality of Life, and Functional Status in Heart Failure

CHIEF-HF

Protocol 28431754HFA3002; Phase 3B
AMENDMENT 3

JNJ-28431754 (canagliflozin) (INVOKANA)

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US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

Status: Approved
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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 3	23 February 2021
Amendment 2	02 June 2020
Amendment 1	07 February 2020
Original Protocol	07 November 2019

Amendment 3 (23 February 2021)

Overall Rationale for the Amendment: The overall rationale for the amendment is to clarify the adverse event (AE) reporting requirements and time frames for the study.

Section number and Name	Description of Change	Brief Rationale
Synopsis (Adverse Event Data Collection, Adverse Event Evaluations, Adverse Event Analyses); 3. Objectives and Endpoints (Adverse Event Data Collection); 8.3. Adverse Events and Serious Adverse Events and Special Situations; 8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 9.4.3 Adverse Event Analysis	The following text was modified: "Due to the virtual method of data collection for this study, there will be 2 types of adverse event data collection**,** one ~~will be done~~ by participants instructed to self-report any adverse events ~~from the study intervention~~ to a call center, and the other by an analysis of medical claims data from the participant's provider to their insurance system. **Participant-reported adverse events to the call center will be captured from the time of informed consent until 30 days after the end of treatment (ie, the last dose of study intervention) and adverse events from medical claims data from the time of informed consent to the end of study.** ~~Adverse events will be captured from the time of informed consent through the end of treatment (Month 3) plus 30 days.~~ **After the treatment period plus 30 days, serious adverse events will be identified solely through medical claims data. Adverse events that occur during the treatment period plus 30 days identified from medical claims will be aggregated by treatment assignment when unblinding is available. In addition, for this time period, self-reported adverse events from the call center will be summarized in a listing. Serious adverse event data from medical claims for the 9-month study period will be aggregated by treatment assignment.** ~~Medical claims adverse event data will be reviewed and evaluated in aggregate at the end of the 3-month, double-blind treatment period when the unblinded data are available.~~"	To clarify that 1. Adverse events will be collected from medical claims as well as from the call center, from the time of informed consent through the end of treatment plus 30 days. 2. After the treatment period plus 30 days, serious adverse events will be identified from medical claims data. 3. Aggregated adverse events from medical claims data will be presented for the treatment period plus 30 days. In addition, for the same period, a listing will be provided for the self-reported adverse events from the call center. 4. Serious adverse events from medical claims will be summarized at the end of the 9-month study period.
1.3 Schedule of Activities (SoA)	Reporting of adverse events is extended from end of treatment to end of study in SoA table. Footnote 'e' revised to '**Participant-reported adverse events to the call center occurs** ~~Lasts~~ from the time of informed consent until 30 days after the end of treatment (ie, the last dose of	To clarify the duration of self-reported adverse events from call center and adverse events collected from medical claim data.

Section number and Name	Description of Change	Brief Rationale
	study intervention). **Adverse events from medical claims data occurs from the time of informed consent to the end of study.**'	
10.1 Appendix 1: Abbreviations	Abbreviation list updated for an 'SAE'.	Minor errors were noted.
Throughout the protocol	Minor formatting and consistency changes were made.	

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1. PROTOCOL SUMMARY

1.1. Synopsis

Canagliflozin: Impact on Health Status, Quality of Life, and Functional Status in Heart Failure

Canagliflozin (JNJ-28431754) is an inhibitor of sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral antihyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM). The full chemical name for canagliflozin is (1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate.

Canagliflozin therapy has been shown to improve clinical outcomes including hospitalizations for heart failure (HHF) in patients with T2DM and HF based on results from the CANVAS program (CANVAS [DIA3008]/CANVAS-Renal [DIA4003]) and CREDENCE [DNE3001] study. An improvement in patient's symptoms of HF would be an important advance in the clinical management of HF. This randomized study is designed to assess whether canagliflozin therapy improves HF symptoms as assessed by the Total Symptom Score (TSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ) patient-reported outcome (PRO) scale in participants with HF and with or without T2DM in a real-world setting.

OBJECTIVES AND ENDPOINTS

Primary Objective

The primary objective is:

- to determine the superiority of the effectiveness of canagliflozin 100 mg daily versus placebo in participants with symptomatic HF in improving the overall KCCQ TSS.

Secondary Objectives

The first key secondary objective is:

- to determine the superiority of the effectiveness of canagliflozin 100 mg daily versus placebo in improving the total daily step count.

The second key secondary objective is:

- to determine the superiority of the effectiveness of canagliflozin 100 mg daily versus placebo in improving the KCCQ individual domain scores (physical limitation, quality of life, clinical summary, and overall).

Exploratory Objectives

The exploratory objectives are to assess the effectiveness of canagliflozin 100 mg daily in participants with symptomatic HF by:

- responses on the Patient Global Impression of Change (PGIC) and the Patient Global Impression of Severity (PGI-S)
- healthcare resource utilization (HRU) and health economics data
- associations (correlations and/or categorical association measures) between digital markers (step count and floors climbed), and clinical events such as need for outpatient intravenous therapies, emergency department (ED) visits, and hospitalizations
- daily floors climbed

- time to first hospitalization/readmission for heart failure
- time to first hospitalization/readmission for other events
- time to death
- the participant's satisfaction with their experience with the virtual design at the end of the study.

Endpoints

The primary effectiveness endpoint is the change in KCCQ TSS from baseline to Month 3.

The key secondary effectiveness endpoints are 1) change in total daily step count from baseline to Month 3, and 2) changes in KCCQ individual domain scores (physical limitation, quality of life, clinical summary, and overall) from baseline to Month 3.

The exploratory endpoints are the following:

- mean PGIC scores over time
- changes in PGI-S scores from baseline to Month 3
- change in number of daily floors climbed
- change in HRU and health economics data
- number of outpatient intravenous therapies, ED visits, and hospitalizations
- time to first hospitalization/readmission for heart failure
- time to first hospitalization/readmission for other events
- time to death

Adverse Event Data Collection

Due to the virtual method of data collection for this study, there will be 2 types of adverse event data collection, one by participants instructed to self-report any adverse events to a call center, and the other by an analysis of medical claims data from the participant's provider to their insurance system. Participant-reported adverse events to the call center will be captured from the time of informed consent until 30 days after the end of treatment (ie, the last dose of study intervention) and adverse events from medical claims data from the time of informed consent to the end of study. After the treatment period plus 30 days, serious adverse events will be identified solely through medical claims data. Adverse events that occur during the treatment period plus 30 days identified from medical claims will be aggregated by treatment assignment when unblinding is available. In addition, for this time period, self-reported adverse events from the call center will be summarized in a listing. Serious adverse event data from medical claims for the 9-month study period will be aggregated by treatment assignment.

Hypotheses

The primary hypothesis is that canagliflozin is superior to placebo as assessed by improvement in the TSS on the KCCQ scale during the 3-month, double-blind treatment period.

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, decentralized, virtual, interventional, superiority study conducted in the United States (US) in participants with symptomatic HF (stratified by heart failure with reduced ejection fraction [HFrEF] and heart failure with preserved ejection fraction [HFpEF]) to examine the improvement in the KCCQ TSS after 3 months of treatment with canagliflozin 100 mg or

placebo. The study will continue for an additional 6 months without any study intervention to collect participant follow-up in a real-world setting.

The study will enroll participants from large, integrated, health networks and large physician practices in the US with the participants conducting the majority of their study-related activities through an app on a smartphone and actigraphy data from a Fitbit device. There will be no in-person clinic visits required by the study.

The study consists of a screening period and a 3-month, double-blind treatment period. Approximately 1,900 participants will be randomized into the study in a 1:1 ratio to canagliflozin 100 mg daily or placebo groups (950 in each study intervention group). After Month 3 (the end of the double-blind treatment period), the study will continue for an additional 6 months when study intervention will no longer be provided. Data collection from medical claims, smartphone, Fitbit device, and selected PROs will continue until Month 9 for the purpose of secondary and further exploratory endpoints analyses. In addition, the KCCQ, PGIC, and PGI-S data will be collected at 6 and 9 months. An optional participant satisfaction survey about the virtual nature of the study will be provided to the participant at end of the study.

Participants will be of any gender, 18 years of age or older, and have clinically stable, symptomatic HF with or without T2DM with a KCCQ baseline overall summary score of ≤80 prior to randomization.

Study assessments include the KCCQ, Fitbit device data (step count and floors climbed), PGIC, PGI-S, participant satisfaction survey, medical and pharmacy claims data (including up to 36 months history for eligibility confirmation), HRU and health economics (including hospitalization/readmission due to HF or other reason, ED visits, the duration of stay at each hospitalization/readmission), review of medical claims for prohibited medications and new diagnoses that may require discontinuation, dates of deaths, and adverse events.

NUMBER OF PARTICIPANTS

Approximately 1,900 participants will be randomized in the study in a 1:1 ratio to canagliflozin 100 mg daily or placebo. Randomization of participants into the study will be stratified by the type of ejection fraction (ie, HFrEF or HFpEF) at study entry as recorded in the participant's electronic health record (EHR).

INTERVENTION GROUPS AND DURATION

The total duration of study participation for each participant is approximately 9 months. Participants will be randomly assigned to receive canagliflozin 100 mg daily immediate-release over-encapsulated tablets (capsules) taken orally or placebo capsules for the duration of the 3-month, double-blind treatment period, followed by a 6-month, no treatment period during which data will continue to be collected.

Description of Interventions

The study intervention, JNJ-28431754 (canagliflozin), will be provided as immediate-release, over-encapsulated tablets (as a capsule) or a placebo capsule taken orally once daily for the duration of the 3-month, double-blind treatment period.

Participant Unblinding

After each randomized participant completes the 3-month, double-blind treatment period of the study, they will be provided with their treatment allocation, whether they had been randomized to canagliflozin or placebo.

EFFECTIVENESS EVALUATIONS

Effectiveness evaluations include the KCCQ and daily step count.

SECONDARY AND EXPLORATORY EVALUATIONS

Secondary and exploratory evaluations include KCCQ individual domains, PGIC, PGI-S, participant satisfaction survey, the HRU and health economics data collected in this study, time to death, and associations (correlations and/or categorical association measures) between digital markers (step count and floors climbed) and clinical events such as need for outpatient intravenous therapies, ED visits, and hospitalizations.

ADVERSE EVENT EVALUATIONS

Adverse events will be captured through medical claims (from the time of informed consent to the end of study) and by the call center (from the time of informed consent until 30 days after the end of treatment). After the treatment period plus 30 days, serious adverse events will be identified solely through medical claims data. Adverse events that occur during the treatment period plus 30 days identified from medical claims will be aggregated by treatment assignment when unblinding is available. In addition, for this time period, self-reported adverse events from the call center will be summarized in a listing. Serious adverse event data from medical claims for the 9-month study period will be aggregated by treatment assignment.

STATISTICAL METHODS

Sample Size Determination

The primary effectiveness endpoint is the change from baseline in the KCCQ TSS at the end of the 3-month, double-blind treatment period. Although a 5-point improvement in the KCCQ TSS is generally viewed as clinically meaningful, recent studies have shown that improvements in the range of 3 to 5 points on the KCCQ TSS are equally meaningful in the overall HF-related health status measured by the KCCQ over a 12-week time period. Based on the evidence from these studies, the current study is powered to detect a mean change from baseline of 3 points in the KCCQ TSS between canagliflozin 100 mg and placebo groups at 12 weeks. Assuming a significance level of 5% and a standard deviation of 18 points for mean change in KCCQ TSS, a total of 1,900 participants will be randomized in this study providing approximately 95% power. This sample size is adequate to account for a potential 5% dropout rate.

Effectiveness Analyses

Primary and Secondary Effectiveness Analysis

The primary and key secondary effectiveness analyses will be based on the intent-to-treat (ITT) analysis population (using all randomized participants).

As the KCCQ TSS is measured repeatedly over time (ie, at baseline, Weeks 4, 6, and 12 respectively), the primary effectiveness endpoint (change in KCCQ TSS from baseline to Month 3) will be analyzed by a mixed effect model repeated measures (MMRM) method simultaneously adjusting for study intervention group, stratification factor (HFrEF versus HFpEF), time, time by study intervention group, and baseline KCCQ TSS value as covariates. An unstructured covariance structure will be assumed across study intervention groups to model the within-participant errors. The primary comparison will be based on the difference in least squares means between treatments at Month 3. The treatment difference in the least-squares means and their 2-sided 95% confidence interval (CI) will be provided. An MMRM model accounts for data missing at random.

A responder analysis will also be performed when comparing proportions of participants with a 5- (or 10-) point improvement in KCCQ TSS from baseline between the groups. This will be based on a two-sample difference in proportions test along with a 95% confidence interval for the difference in 2 proportions. Additionally, empirical cumulative distribution functions of the KCCQ TSS and other domain scores will be presented.

Subgroups defined by age, gender, race and baseline disease/demographic characteristics will be pre-specified in the Statistical Analysis Plan (SAP) for the primary effectiveness analysis. Details about the imputation of any missing data will be provided in the SAP. Each subgroup will be analyzed following a similar MMRM model used in the analysis of the primary effectiveness endpoint (change in KCCQ TSS from baseline to Month 3). The treatment difference in the least-squares means and their 2-sided 95% CI will be provided from each subgroup analysis. Quantitative and/or qualitative interactions will be identified. Qualitative interactions will be investigated further by the Gail and Simon test and interpreted accordingly.

The first key secondary endpoint of daily step count will be tested once the primary endpoint is shown to be significant at the 5% significance level using a two-sided t-test. This approach will control for the overall Type I error rate at 5%.

For the second key effectiveness endpoint, an MMRM model (like that used in the analysis of the primary endpoint) will be employed to summarize changes in KCCQ individual domain scores (physical limitation, quality of life, clinical summary, and overall) from baseline to Month 3. This hypothesis will be independently tested at 5% without any control for overall Type I error rate.

Exploratory Analyses

Exploratory analyses include the following:

- summary statistics of PGIC and PGI-S scores
- associations (correlations and/or categorical association measures) between digital markers (step count and floors climbed) and clinical events such as need for outpatient intravenous therapies, ED visits, and hospitalizations
- tabulation and comparison of total HRU and health economics data across groups
- descriptive statistics (eg, mean, median, and standard deviation) of daily floors climbed
- association between the KCCQ change from baseline to Month 3 and the PGIC at Month 3 will be examined and summarized
- time to death
- descriptive statistics of the participant's satisfaction with his/her experience with the virtual design at the end of the study.

Adverse Event Analyses

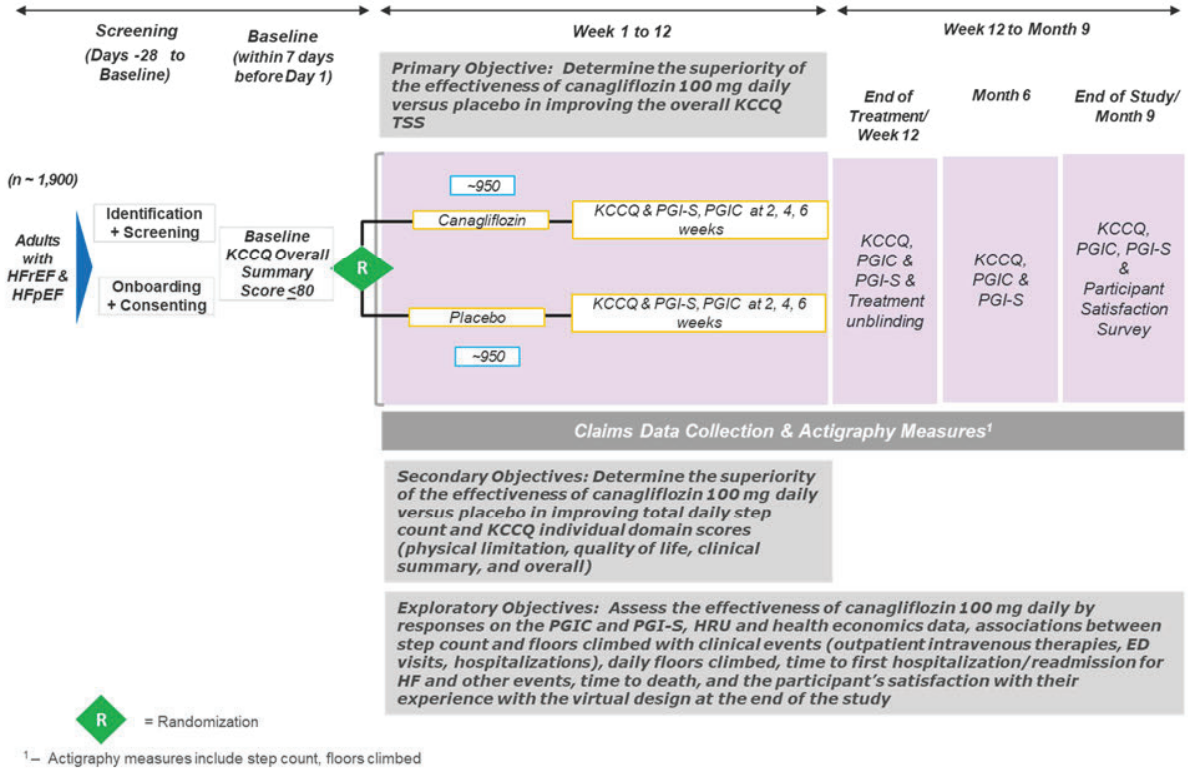
Adverse events reported to the call center will be assessed by Janssen Global Medical Safety (GMS) for causality and meeting suspected unexpected serious adverse reaction (SUSAR) reporting requirements. Self-reported adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be reported by preferred term by T2DM and non-T2DM. Adverse events collected from medical claims will be categorized by diagnosis code and reported by T2DM and non-T2DM. Discontinuations will be summarized based on any available data. Self-reported adverse events from the call center will be summarized in a listing.

Healthcare Resource Utilization (HRU) and Health Economics

Healthcare Resource Utilization and health economics data will be descriptively summarized by study intervention group.

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities (SoA)

Period	Screening	Baseline	Double-Blind Treatment					No Treatment		Notes
Day	Within 28 days before Baseline	Within 7 days before Day 1	1 (first dose)	14+3	28±3	42±3	84±3 End of Treatment	85-251-±7	252-±7 End of Study	Day –28 to 0=Screening; Day 1 = first dose, Day 84= end of treatment; Day 252=End of Study
Week			1	2	4	6	12	13-36		Week 12 is equivalent to Day 84 of treatment
Month		0					3	6	9	Month 3 is equivalent to Day 84 of treatment
Study Procedure										
Screening/Administrative										
Electronic Informed consent[a]	X									
Review medical history	X									
Inclusion/exclusion criteria[b]	X	X								All inclusion/exclusion verification should be completed within the 28-day screening period and before randomization
KCCQ baseline overall summary score ≤80		X								
Study Intervention Administration										
Randomization		X								
Dispense study intervention		X								
Administer study intervention		←	—	—	—	—	→			
Participant-reported adherence via app - weekly		←	—	—	—	—	→			
Assessments										
KCCQ				X	X	X	X	X[c]	X	Kansas City Cardiomyopathy Questionnaire
PGIC				X	X	X	X	X[c]	X	Patient Global Impression of Change
PGI-S		X		X	X	X	X	X[c]	X	Patient Global Impression of Severity
Step count and floors climbed		←	—	—	—	—	—	—	→	
Medical claims data collection[d]		←	—	—	—	—	—	—	→	
Participant Satisfaction Survey (optional)									X	

Period	Screening	Baseline	Double-Blind Treatment					No Treatment		Notes
Day	Within 28 days before Baseline	Within 7 days before Day 1	1 (first dose)	14+3	28±3	42±3	84±3 End of Treatment	85-251-±7	252-±7 End of Study	Day –28 to 0=Screening; Day 1 = first dose, Day 84= end of treatment; Day 252=End of Study
Week			1	2	4	6	12	13-36		Week 12 is equivalent to Day 84 of treatment
Month		0					3	6	9	Month 3 is equivalent to Day 84 of treatment
Health Resource Utilization and Health Economics										
HHF for any reason and duration		←							→	Hospitalizations for heart failure
Emergency department visits		←							→	
Readmissions and duration		←							→	
Ongoing Review of Participant Data										
Prohibited medications and new diagnoses		←							→	
Reporting of adverse events[e]	←								→	

Footnotes:

a. Must be signed before first study-related activity.

b. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations.

c. To be completed at Month 6.

d. Includes up to 36 months of historical medical and pharmacy claims data for eligibility confirmation. This data collection will begin upon signing of the informed consent.

e. Participant-reported adverse events to the call center occurs from the time of informed consent until 30 days after the end of treatment (ie, the last dose of study intervention). Adverse events from medical claims data occurs from the time of informed consent to the end of study.

2. INTRODUCTION

Canagliflozin (JNJ-28431754) is an inhibitor of sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral antihyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM). The full chemical name for JNJ-28431754 is (1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate.

The development program for canagliflozin has investigated the compound's efficacy and safety profile both as a monotherapy and in combination with other AHAs as adjunctive treatment to diet and exercise to improve glycemic control in the treatment of adult participants with T2DM. Three of the Phase 3 and Phase 4 studies evaluated canagliflozin in special populations, including older adults with T2DM and participants with T2DM who had moderate renal impairment. Recently completed cardiovascular (CV) safety studies have evaluated canagliflozin as a treatment to reduce the risk of major adverse CV events (MACE - CV death, nonfatal myocardial infarction (MI), and nonfatal stroke) in adults with T2DM who have established cardiovascular disease (CVD) or at least 2 risk factors for CVD. Canagliflozin therapy has been shown to be associated with improved clinical outcomes in patients with T2DM and heart failure (HF) based on results from the CANVAS program (CANVAS [DIA3008] /CANVAS-Renal [DIA4003]) and CREDENCE [DNE3001] studies.

Proposed mechanisms of action of sodium-glucose co-transporter 2 inhibitors (SGLT2is) and recent information from the DAPA-HF and DEFINE-HF studies[16,21] suggest that the effects of the SGLT2i class of medicines in patients with HF may extend to HF patients with or without T2DM.

This randomized study is designed to assess whether canagliflozin therapy improves HF symptoms as assessed by the Total Symptom Score (TSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ) patient-reported outcome (PRO) scale in participants with HF and with or without T2DM in a real-world setting.

CANVAS Heart Failure Data

Approximately 14.4% of all participants in the CANVAS Program had a prior history of HF. While the CANVAS Program met its primary endpoint,[15] the principal secondary endpoint (superiority of canagliflozin with respect to reducing all-cause mortality) did not meet statistical significance, hence the results of the subsequent analyses examining endpoints including hospitalization for HF (HHF) must be viewed as exploratory. The hazard ratio (HR) for HHF in the combined canagliflozin group versus placebo was 0.67 (95% CI: 0.52, 0.87), with similar effects seen in the canagliflozin 100 mg and 300 mg groups in the CANVAS study.[26] These HR results resulted in choosing the lower dose of canagliflozin 100 mg for this study.

Canagliflozin lowered the risk of HHF in both patient groups: primary (participants with only risk factors for CV disease) (HR: 0.64; 95% CI: 0.35 to 1.15) and secondary (participants with a history of CV disease) (HR: 0.68; 95% CI: 0.51 to 0.90) with no evidence of statistical heterogeneity (p=0.91).

An analysis of CANVAS[26] program demonstrated that canagliflozin decreased the risk of HHF in those with pre-existing history of HF (HR: 0.51; 95% CI: 0.33 to 0.78), and in those without a history of HF (HR: 0.79; 95% CI: 0.57 to 1.09) with no evidence of statistical heterogeneity (p = 0.47). This effect of reducing the risk of HHF in those with or without a history of HF was consistent irrespective of established treatments for the prevention or management of HF (ie, inhibitors of the renin-angiotensin-aldosterone system, beta-blockers, and diuretics).

Therefore, a study to demonstrate that canagliflozin improves patient symptoms of HF would be an important advance in the clinical management of HF patients and would offer an important and valuable therapeutic option.

CREDENCE Study

The CREDENCE study (NDA 204042 S-032, approved 27 September 2019, was a large, international, randomized, double-blind, event-driven study undertaken to formally test whether canagliflozin 100 mg, administered once daily, reduces the risk of kidney failure and CV events in participants with Stage 2 or 3 chronic kidney disease (eGFR ≥30 to <90 mL/min/1.73 m^2) and macroalbuminuria (urinary ACR >300 to ≤5,000 mg/g) and T2DM who were receiving Standard of Care (SoC) therapy. SoC was defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative consensus guidelines[22] and included a maximum tolerated labeled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB). This study was conducted between 21 February 2014 and 30 October 2018.

The renal protective effect of canagliflozin relative to placebo in a population with established CKD and T2DM was measured using a composite endpoint of doubling of serum creatinine, progression to end-stage kidney disease (ESKD) (defined as dialysis, renal transplantation, or sustained eGFR <15 L/min/1.73 m^2), and renal or CV death. The study also assessed the effects of canagliflozin on several adverse CV outcomes (CV death, HHF, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina), and all-cause mortality. The results demonstrated clinical benefit of the 100 mg dose of canagliflozin in reducing important cardiovascular and renal clinical endpoints in patients with T2DM and impaired renal function.[14] Specifically, HHF (which was a secondary endpoint) was significantly decreased in the canagliflozin versus placebo group (HR=0.61 [0.47-0.80]). Additionally, the rate of amputation was not shown to be statistically significantly increased with canagliflozin treatment in the CREDENCE study in the overall population (HR=1.11 [0.79-1.37]).

Recently, INVOKANA® was approved as the only diabetes medicine indicated to reduce the risk of ESKD, worsening of kidney function, cardiovascular death, and HHF in adults with type 2 diabetes and diabetic kidney disease (nephropathy) with a certain amount of protein in the urine.

Use of SGLT2is in Heart Failure With or Without T2DM

A mechanistic basis has been proposed for the SGLT2i class of medicines to exert beneficial effects in HF irrespective of the diabetic state and effects on glycemic control or osmotic diuresis.[25] Inhibition of sodium-hydrogen (Na/H) exchange in the kidney by SGLT2 inhibitors may reduce diuretic and endogenous natriuretic peptide resistance, and similar inhibition in the myocardium

may lead to a reduction in cardiac injury, hypertrophy, fibrosis, remodeling, and systolic dysfunction. Furthermore, the major pathophysiological derangements of HF and a preserved ejection fraction may be mitigated by the actions of SGLT2 inhibitors to reduce blood pressure, body weight, and fluid retention as well as to improve renal function.[25]

The use of canagliflozin in patients without T2DM has been studied in approximately 1,200 healthy subjects in multiple Phase 1 studies. A thorough QT/QTc study in healthy subjects (study DIA1010 NDA 204042 Sequence 0000 Module 5.3.4.1) demonstrated that canagliflozin at single therapeutic (300 mg) or supra-therapeutic (1,200 mg) doses does not lead to QT/QTc prolongation. At the 1,200 mg dose, canagliflozin C_{max} was approximately 1.4 times that for steady-state C_{max} at a 300 mg QD dose in T2DM subjects. This is important in light of the proarrhythmic myocardial substrate present in HF, in particular HFrEF, which is more prevalent in the non-type 2 diabetes population than in the type 2 diabetes population who experiences a higher incidence of HFpEF. For this study, the proposed dose of canagliflozin is 100 mg daily.

Additional evidence for the safety of canagliflozin in patients with HF comes from sub-group analyses of patients with T2DM in the CANVAS Program and in the CREDENCE study, in which there was no signal of increased arrhythmic death, or hyperkalemia – the latter of which is reassuring since many HF patients are on medications that are potassium-sparing, such as ACEis, ARBs, or mineralocorticoid receptor antagonists (MRAs), and diabetics are more predisposed to hyperkalemia with these agents than non-diabetics. CREDENCE in particular, which studied a population with a greater prevalence of kidney disease and a higher likelihood of hyperkalemia than the population in the CANVAS Program, demonstrated no increased incidence of hyperkalemia with canagliflozin versus placebo. In addition, in the CANVAS Program, there was no evidence of proportional differences in the risk of volume depletion, fracture, amputation, osmotic diuresis, acute kidney injury events, adverse events leading to discontinuation, and all serious adverse events (SAEs) between patients with or without HF at baseline (p interaction >0.160).[26]

A growing body of evidence is being generated for use of the SGLT2i class in HF. A randomized clinical study, DAPA-HF, in 4,774 HFrEF patients with (42%) and without (58%) T2DM demonstrated safety consistent with the known profile of dapagliflozin.[16] Ninety-four percent of patients were on ACEis or ARBs, and the mean eGFR was 66 mL/min/1.73m^2. In the study, dapagliflozin met the primary composite endpoint with a statistically significant and clinically meaningful reduction of cardiovascular death or the worsening of HF (defined as hospitalization or an urgent HF visit), compared to placebo. Based on these data, dapagliflozin was recently approved by the Food and Drug Administration (FDA) to reduce the risk of CV death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction with or without T2DM. This further supports more evaluations of this class of drugs in additional clinical trials in HFrEF and HFpEF, including measurement of symptomatic and functional improvement with tools such as the KCCQ.

Another recent randomized clinical study with dapagliflozin, DEFINE-HF in HFrEF, was completed in 510 patients with (62%) and without (36%) T2DM.[21] Results were consistent among

patients with or without T2DM, including safety analyses. Mean eGFR was 69 mL/min/1.73m^2. In the study, patients treated with dapagliflozin vs. placebo had clinically meaningful improvement in health status (KCCQ Overall Summary score ≥5 points).

Finally, there are multiple ongoing randomized studies with SGLT2 inhibitors in HF with or without T2DM (see below). As such, there is ample precedent to justify starting another study in HF patients irrespective of a diagnosis of T2DM.

Dapagliflozin:

- DEFINE-HF: biomarkers, symptoms, health status and quality of life in HFrEF patients (listed in clinicaltrials.gov March 2016)
- DELIVER: Outcomes study in HFpEF patients (listed in clinicaltrials.gov Aug. 2018)
- DETERMINE-REDUCED: Exercise capacity study in HFrEF patients (listed in clinicaltrials.gov March 2019)
- DETERMINE-PRESERVED: Exercise capacity study in HFpEF patients (listed in clinicaltrials.gov March 2019)

Empagliflozin:

- EMPEROR-Reduced: Outcomes study in HFrEF patients (listed in clinicaltrials.gov Feb. 2017)
- EMPEROR-Preserved: Outcomes study in HFpEF patients (listed in clinicaltrials.gov Feb. 2017)
- EMPERIAL-Reduced: Exercise capacity study in HFrEF patients (listed in clinicaltrials.gov Feb. 2018)
- EMPERIAL-Preserved: Exercise capacity study in HFpEF patients (listed in clinicaltrials.gov Feb. 2018)

Safety

The safety profile of canagliflozin is well established having been broadly evaluated for safety in several well-designed, randomized, clinical studies. The broader Phase 3/4 canagliflozin program was conducted in 22,645 patients, including 13,278 patients treated with canagliflozin and 9,367 patients treated with a comparator, in 15 double-blind, controlled, clinical studies; among them, more than 1,100 patients reported a history of HF at baseline. In addition, there is an extensive, real-world base of adverse event reporting based on approximately 1,475,000,000 person days treated worldwide. The SGLT2 inhibitor, dapagliflozin, was studied in HFrEF patients both with and without diabetes in the DAPA-HF and the DEFINE-HF studies[16,21] (those with HFrEF and type 2 diabetes). In those studies, the side effect profile was not different between those with or without T2DM or HF. Taken together, the evidence indicates that the safety profile of SGLT2 inhibitors, of which canagliflozin is a member, is well described and broadly understood in the study population included in this study.

For the most comprehensive nonclinical and clinical information regarding canagliflozin, refer to the latest version of the Investigator's Brochure[11] and Addenda for JNJ-28431754 (canagliflozin).

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.

The term “study intervention” refers to canagliflozin or placebo.

2.1. Background and Study Rationale

Outcomes in studies of antidiabetic agents improving HF outcomes include canagliflozin, empagliflozin, and dapagliflozin CV that have shown a strong signal for improvement in HF endpoints with SGLT2i, but further studies are needed to validate these findings. However, very recently, the FDA approved dapagliflozin to reduce the risk of HHF in adults with T2DM and established CV disease or multiple CV risk factors. Based on results of the DECLARE-TIMI 58, the possible role that SGTL2i may play in HF has been hypothesized but evaluation of the various pathways has not been performed.[30]

Heart failure contributes to one in nine deaths and is a leading cause of hospitalization in the US, yet there are limited treatment options for people living with this debilitating disease. It is highly prevalent and despite best available therapy, is associated with poor patient outcomes.[23,24] The CANVAS Program demonstrated that canagliflozin treatment in patients at cardiovascular (CV) risk was associated with improved clinical outcomes, including a reduction in the composite of CV death and HHF. A similar finding was observed with empagliflozin in the EMPA-REG cardiovascular outcomes study and dapagliflozin in DECLARE-TIMI 58.[19]

A meta-analysis of EMPA-REG OUTCOME, CANVAS PROGRAM, and DECLARE-TIMI 58 looked at a total of 20,060 T2DM patients and the CV outcomes of SGLT2i therapies. Enrolling 3,891 HF patients at baseline, this meta-analysis demonstrated similar significant reduction in HHF, regardless of the patient’s baseline HF status (HR 0.68 vs HR 0.71) for those with or without HF. The benefit for these groups was affected only by renal function, with greater benefit observed in patients with lower estimated glomerular filtration rate (eGFR).[18]

In addition, the OBSERVE-4D real-world meta-analysis is the largest retrospective observational study of effects of SGLT2i in this patient population. It compared the experience of over 140,000 new canagliflozin patients to over 100,000 empagliflozin and dapagliflozin new users, as well as 460,000 new users of non-SGLT2i. Patients treated with canagliflozin showed comparable HHF reduction to other SGLT2is on the market, and greater reduced risk for HHF and below knee lower extremity amputations when compared to non-SGLT2is. This held true even when comparing patients with established CV disease to the overall study population. While limitations exist in OBSERVE-4D pertaining to the length of treatment duration with canagliflozin, this may not be entirely comparable to the randomized clinical study data discussed above. However, findings in the OBSERVE-4D meta-analysis suggest similarity to reductions observed in randomized clinical studies and provide added confidence in the results of this meta-analysis.[27]

This meta-analysis (Table 1), as well as real-world data from CVD-REAL studies and the United States (US) Department of Defense Military Health System, support the effect of an SGLT2i on reducing HF-related hospitalizations; however, they did not seek to differentiate or provide any insight on the effect of these therapies specifically on HF with reduced ejection fraction (HFrEF) and HFpEF phenotypes, defining the need for further investigation.[20]

Table 1: Effects of Sodium-glucose Cotransports-2 Inhibitors (SGLT-2is) on Heart Failure Outcomes

Reference	Comparator groups	HF at baseline	n	Study design	Follow-up (weeks)	Hazard ratio for HHF
EMPA-REG OUTCOME[34]	Empagliflozin vs placebo	10%	7020	RCT	161	0.65 (0.50-0.85
CANVAS[33]	Canagliflozin vs placebo	14%	10 142	RCT	126	0.67 (0.52-0.87)
DECLARE-TIMI-58[35]	Dapagliflozin vs placebo	10%	17 160	RCT	218	0.73 (0.61-0.88)
CVD-REAL[40]	SGLT-2is vs oGLDs	6%	309 056	Retrospective cohort	64	0.61 (0.51-0.73
EASEL Cohort[43]	SGLT-2is vs oGLDs	11%	25 258	Retrospective cohort	83	0.57 (0.45-0.73)

HHF, heart failure hospitalization; oGLDs, other glucose lowering drugs; RCT, randomized controlled trial.
Nassif ME, Kosiborod M. Effects of sodium-glucose co-transporter type 2 inhibitors in heart failure. Diabetes Obes Metab. 2019;21(Suppl. 2):19-23.

HFpEF is well recognized as the predominant type of HF in patients with T2DM and is possibly related to insulin resistance and obesity. Such predisposing factors are thought to be at the crux of ineffectiveness of traditional HF therapies in treating HFpEF patients, making the need for impactful therapies in this patient population even more urgent.[2,6] While more studies are underway, some encouraging data comes from the Canagliflozin for Japanese Patients with Chronic Heart Failure and Type II Diabetes (CANOSSA) study,[28] which assessed the effect of canagliflozin on Japanese patients with T2DM and stable HF. The study enrolled 35 patients, of which 33 had HFpEF, and focused on canagliflozin's effect of weight and adipose tissue reduction on these patients. Beyond reduction in glycated hemoglobin (HbA1c) and fat volumes, the study demonstrated reduction in oxidative stress, improved diastolic disfunction, and decrease in left ventricular mass, potentially linking canagliflozin use to an improved HFpEF condition.

In addition to showing an improvement in HHF, improvement in clinical symptoms, physical functioning and quality of life would be a highly important clinical outcome for patients with HF. It is believed that canagliflozin, through its diuretic, blood pressure, and body weight reduction effects would have a clinically meaningful impact on these outcomes in these patients and represent an advance in the clinical management of these patients. This study is designed to assess whether canagliflozin can impact these important patient-centric outcomes not only in HFrEF patients but also in HFpEF patients for which there is no approved SGLT2i for treatment.

2.2. Benefit/Risk Assessment

Before randomization and throughout the study, the participant's physician(s) will continue to manage the participant's background medications to achieve goals for controlling the participant's HF and T2DM (if present). Participants enrolled in this study will be managed based on the standards of care for HF and T2DM (if applicable) according to established local and regional guidelines. An Independent Scientific Advisory Committee comprised of experts in the management of patients with HF and sponsor representatives will be commissioned for this study. Other medications in the SGLT2i class of medicines are being studied in patients with HF with or

without T2DM as outlined in Section 2, Introduction; however, none of these agents are currently indicated for the clinical improvement in HF symptoms or for use in patients with HFpEF.

The risks of participation in the study include exposure to study intervention, with the potential for side effects. Participant safety will be assured throughout the study by providing participants and their physicians access to a call center to ask questions and to report adverse events. In addition, the adverse effect profile of canagliflozin has been well described and will be outlined in the informed consent form (ICF). In addition, participant prescribing information with a listing of potential adverse events will be sent to the participant in their welcome kit.

This study was designed based in general accordance with the FDA[7] and European Medicines Agency (EMA) guidance[6] on the development of medications and clinical investigations for the use of canagliflozin for the reduction of HF symptoms of HF and in consultation with Health Authorities. In addition, the design was also based on the FDA's draft guidance to industry on drug development in HF which supports measures of patients' symptoms and physical function as endpoints.[8] This study will be conducted under FDA Investigational New Drug (IND) regulations. More detailed information about the known and expected benefits and risks of JNJ-28431754 (canagliflozin) may be found in the Investigator's Brochure, Canagliflozin.[11]

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES

Primary Objective

The primary objective is:

- to determine the superiority of the effectiveness of canagliflozin 100 mg daily versus placebo in participants with symptomatic HF in improving the overall KCCQ TSS.

Secondary Objectives

The first key secondary objective is:

- to determine the superiority of the effectiveness of canagliflozin 100 mg daily versus placebo in improving the total daily step count.

The second key secondary objective is:

- to determine the superiority of the effectiveness of canagliflozin 100 mg daily versus placebo in improving the KCCQ individual domain scores (physical limitation, quality of life, clinical summary, and overall).

Exploratory Objectives

The exploratory objectives are to assess the effectiveness of canagliflozin 100 mg daily in participants with symptomatic HF by:

- responses on the Patient Global Impression of Change (PGIC) and the Patient Global Impression of Severity (PGI-S)
- healthcare resource utilization (HRU) and health economics data
- associations (correlations and/or categorical association measures) between digital markers (step count and floors climbed), and clinical events such as need for outpatient intravenous therapies, emergency department (ED) visits, and hospitalizations
- daily floors climbed
- time to first hospitalization/readmission for heart failure
- time to first hospitalization/readmission for other events
- time to death
- the participant's satisfaction with their experience with the virtual design at the end of the study.

ENDPOINTS

The primary effectiveness endpoint is the change in KCCQ TSS from baseline to Month 3.

The key secondary effectiveness endpoints are 1) change in the daily step count from baseline to Month 3, and 2) changes in KCCQ individual domain scores (physical limitation, quality of life, clinical summary, and overall) from baseline to Month 3.

The exploratory endpoints are the following:

- mean PGIC scores over time
- changes in PGI-S scores from baseline to Month 3
- change in number of daily floors climbed
- change in HRU and health economics data
- number of outpatient intravenous therapies, ED visits, and hospitalizations
- time to first hospitalization/readmission for heart failure
- time to first hospitalization/readmission for other events
- time to death

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

Adverse Event Data Collection

Due to the virtual method of data collection for this study, there will be 2 types of adverse event data collection, one by participants instructed to self-report any adverse events to a call center, and the other by an analysis of medical claims data from the participant’s provider to their insurance system. Participant-reported adverse events to the call center will be captured from the time of informed consent until 30 days after the end of treatment (ie, the last dose of study intervention) and adverse events from medical claims data from the time of informed consent to the end of study.

After the treatment period plus 30 days, serious adverse events will be identified solely through medical claims data. Adverse events that occur during the treatment period plus 30 days identified from medical claims will be aggregated by treatment assignment when unblinding is available. In addition, for this time period, self-reported adverse events from the call center will be summarized in a listing. Serious adverse event data from medical claims for the 9-month study period will be aggregated by treatment assignment.

HYPOTHESIS

The primary hypothesis is that canagliflozin is superior to placebo as assessed by improvement in the TSS on the KCCQ scale during the 3-month, double-blind treatment period.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, decentralized, virtual, interventional, superiority study conducted in the US in participants with symptomatic HF (stratified by HFrEF and HFpEF) to examine the improvement in the KCCQ TSS after 3 months of treatment with canagliflozin 100 mg or placebo. The study will continue for an additional 6 months without any study intervention to collect participant follow-up in a real-world setting.

The study will enroll participants from large, integrated, health networks and large physician practices in the US with the participants conducting the majority of their study-related activities through an app on a smartphone and actigraphy data from a Fitbit device. There will be no in-person clinic visits required by the study.

The study consists of a screening period and a 3-month, double-blind treatment period. Approximately 1,900 participants will be randomized into the study in a 1:1 ratio to canagliflozin 100 mg daily or placebo groups (950 in each study intervention group). After Month 3 (the end of the double-blind treatment period), the study will continue for an additional 6 months when study intervention will no longer be provided. Data collection from medical claims, smartphone, Fitbit device, and selected PROs will continue until Month 9 for the purpose of secondary and further exploratory endpoints analyses. In addition, the KCCQ, PGIC, and PGI-S data will be collected at 6 and 9-months. An optional participant satisfaction survey about the virtual nature of the study will be provided to the participant at the end of the study.

Participants will be of any gender, 18 years of age or older, and have clinically stable, symptomatic HF (HFrEF or HFpEF) with or without T2DM with a KCCQ baseline overall summary score of ≤80 prior to randomization.

Participants should be receiving guideline recommended HF medications as prescribed by their treating physician(s) (such as ACEi, ARB, beta-adrenergic blocking agent or beta blocker [β-blocker], oral diuretics, MRA, angiotensin receptor-neprilysin inhibitor).

Study assessments include the KCCQ, Fitbit device data (step count and floors climbed), PGIC, PGI-S, participant satisfaction survey, medical and pharmacy claims data (including up to

36 months history for eligibility confirmation), HRU and health economics (including hospitalization/readmission due to HF or other reason, ED visits, the duration of stay at each hospitalization/readmission), review of medical claims for prohibited medications and new diagnoses that may require discontinuation, dates of deaths, and adverse events.

The total duration of study participation for each participant is approximately 9 months. Participants will be randomly assigned to receive canagliflozin 100 mg daily immediate-release over-encapsulated tablets (capsules) taken orally or placebo capsules for the duration of the 3-month, double-blind treatment period, followed by a 6-month, no treatment period during which data will continue to be collected.

Participants will be enrolled from large, integrated, health networks or large physician practices who have electronic health records (EHR) to identify participants. The primary and secondary endpoint data collection will be done via an app for a smartphone (being developed specifically for the study) as well as data from the Fitbit device.

Data integrity will be assured by automatic data collection directly from data sources (Fitbit device, Fitbit app on smartphone, structured electronic PROs on smartphone via the study app, and medical claims data from or to payers) without manual entry. Significant changes in actigraphy mid-study will be used to confirm that a Fitbit device remains associated with the participant to whom it is assigned. The Fitbit app on the participant's phone will collect all data from the Fitbit device, and significant latencies between wearable sensor data uploads via the app will be used to identify any smartphone and Fitbit device dissociation. In addition, the participant will be informed during the consenting process that the study Fitbit device must only be paired to the participant's smartphone and is to be used only by the participant.

There will be virtual study coordinating center support for initial participant onboarding to answer any study-related questions, assist with proper set up and use of the study app with the participant's smartphone and Fitbit device/app as data collection tools, confirming drug receipt and compliance, and to collect participant-reported adverse events and report them to the sponsor. The virtual study coordinating center will help participants appropriately set up their devices for the purposes of the study. In this particular instance, the main requirement for the Fitbit device is maximal wear time, as all of the sensor data will be collected passively. The blinded study intervention will be hand delivered directly to the participants from a drug distribution vendor. No formal on-site monitoring of the study will be performed as this is a decentralized clinical study, however, the sponsors' designee will centrally monitor participant medical claims, study app data, and Fitbit device data monthly for compliance with the study. For example, monitoring will include detecting non-use of the study app or Fitbit device. Medical claims data will also be monitored for inclusion/exclusion criteria, adverse events, prohibited medications, HRU, relevant concomitant medications, and new diagnoses that would require discontinuation. In addition, the study app will send reminders to participants of study items to complete assessments (KCCQ, PGI-S, PGIC), and will collect weekly study drug compliance. If lack of participation is detected by any of the monitoring, the virtual study coordinating center will contact the participants for follow-up information.

Participant Unblinding

After each randomized participant completes the 3-month, double-blind treatment period of the study, they will be provided with their treatment allocation, whether they had been randomized to canagliflozin or placebo.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Study Population

The study population selected represents participants with HF (HFrEF and HFpEF), with or without T2DM, who would potentially benefit from a drug intervention that could offer improvement in health status outcomes, such as clinical symptoms (eg, dyspnea and fatigue commonly experienced by these participants) and impaired quality of life (eg, physical limitations and emotional dysfunction such as depression and anxiety). Participants who meet the inclusion criteria for these conditions include adults of any gender 18 years of age and older, representing the demographic group in which these conditions are prevalent, and mortality and hospitalization rates are high, despite the recommendations of existing clinical practice guidelines.

Length of Study Periods

The screening period of 28 days allows for an appropriate length of time for screening procedures to determine study eligibility (with EHR reviews, app set-up, completion of the KCCQ, and consenting). The baseline period of 7 days begins upon randomization and allows for shipment of the study drug and Fitbit device to the participant. The 3-month, double-blind treatment period provides sufficient timepoints for effectiveness assessments to demonstrate treatment differences between canagliflozin and placebo.

Placebo Control, Randomization, Blinding, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention group. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Dose and Dosage Administration Regimen

In the CANVAS program, canagliflozin reduced the relative risk of the composite of CV death or HHF compared with placebo, with a HR of canagliflozin versus placebo of 0.78 (95% CI: 0.67, 0.91). The HRs were similar in the canagliflozin 100 and 300 mg groups. The HR for HHF in the combined canagliflozin group versus placebo was 0.67 (95% CI: 0.52, 0.87), with similar effects results seen in the canagliflozin 100 and 300 mg groups. These HR results resulted in choosing the lower dose of canagliflozin 100 mg daily for this study. In addition, because few participants

required titration to 300 mg/d in the CANVAS-R (DIA4003) study, and the treatment period in this study is relatively short, titration to the 300 mg/d dose is not necessary.

Kansas City Cardiomyopathy Questionnaire (KCCQ)

Patient-reported outcomes (PROs) are a measurement tool for the symptom burden and functional limitations in patients with HF and have demonstrated greater reproducibility than other clinical study measures like ejection fraction (EF) valve gradients,[13] 6-minute walk test, and a biomarker (B-type natriuretic peptide [BNP]).[29] The KCCQ (Section 10.3, Appendix 3) is a well-established PRO for use in patients with HF, with published validity and reliability. This instrument was developed and validated by Dr. John Spertus, the Lauer/Missouri Endowed Chair and Tenured Professor at the University of Missouri – Kansas City and the Clinical Director of Outcomes Research at Saint Luke's Mid America Heart Institute. After reviewing its extensive psychometric profile, the KCCQ has been endorsed by the Center for Devices and Radiological Health as a Certified Outcome Assessment through its Medical Device Development Tools Program.[17] In addition, the KCCQ was recently qualified by the Center for Drug Evaluation and Research as a PRO instrument for use in clinical investigations in heart failure.[4]

The KCCQ is a 23-item, self-administered questionnaire and requires, on average, 4 to 6 minutes to complete, with a resulting score of 0 to 100, and higher scores indicating better health. It was developed to measure the patient's perception of their health status, including their HF symptoms, impact on physical and social function and how their HF impacts the quality of life. The KCCQ has been repeatedly used as a clinically meaningful outcome measure in CV research, patient management, and quality assessment. It has been extensively tested for its validity, reliability, and responsiveness improvement in participants with HF, and is well suited as the primary endpoint for this study. In addition, the intent of the study is to enroll participants with New York Heart Association (NYHA) class II to IV. As it would be difficult to verify NYHA class with medical claims and EHR data, the sponsor will use a KCCQ overall summary score at baseline of ≤80, which is highly correlated to class II to IV in HFrEF and HFpEF based on the research published by Joseph, et al.[12]

Actigraphy Measurements

Total step count and total floors climbed will be collected continuously from the Fitbit device from each participant for the entire duration of the study. These actigraphy measures will be used to assess patient activity as it relates to treatment effect on the participant's daily activity.

Patient Global Impression of Change (PGIC)

The PGIC (Section 10.4, Appendix 4) is a commonly accepted, validated outcome measure used in clinical studies to assess the overall change in the participant's status as it relates to the participant's HF symptoms since starting the study as rated by the participant.

Patient Global Impression of Severity (PGI-S)

The PGI-S (Section 10.5, Appendix 5) is a commonly accepted, validated outcome measure used in clinical studies to assess the change in the severity of the participant's HF symptoms since starting the study as rated by the participant.

Health Resource Utilization and Health Economics Data Collection

Treatment of patients with symptomatic HF with JNJ-28431754 (canagliflozin) versus placebo may result in lower utilization of any incident of hospitalization/readmission due to HF or other reason, ED visits, the duration of stay at each hospitalization/readmission, and discharge destination; therefore, comparison will be done across study intervention groups.

Participant Satisfaction Survey

Participants will be provided with an optional participant satisfaction survey at the end of the study to provide feedback on this virtual study and the use of the Fitbit device and smartphone to collect their information. This feedback may be important to consider when designing studies that use technology and devices.

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, including availability of an approved medicine for HF in the same SGLT2i class of medicines as canagliflozin, which now includes the recent approval of dapagliflozin for HFrEF. 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.

4.3. Justification for Dose

Canagliflozin 100 mg daily taken orally is the dose selected based on data from a similar study population in the CANVAS program that demonstrated a significant treatment effect, with no differences observed between the 100 and 300 mg doses. In addition, there are fewer dose-dependent adverse events such as volume-related adverse events associated with this dose. Refer to Section 4.2, Study Design Rationale for further details.

4.4. End of Study Definition

A participant will be considered to have ended the treatment period of the study (at 3 months), regardless of whether the participant has completed the study intervention, if he or she has completed assessments at Month 3 of the double-blind treatment period, withdrew earlier from the treatment, or died prior to the Month 3 assessment.

The end of study (at 9 months) is considered as the last visit shown in the Schedule of Activities for the last participant in the study. The final data from the study clinical research organization

partner will be sent to the sponsor (or designee) after completion of the collection of the study data from the Fitbit device and the claims in the time frame specified in the Trial Agreement.

5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before randomization into the study.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the participant or designee must consult with the call center to resolve any issues before enrolling in the study.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study at enrollment (consent date):

1. any gender

2. 18 (or the legal age of consent in the jurisdiction in which the study is taking place) years of age or older

3. Criterion modified per Amendment 2

   3.1. have clinically stable symptomatic HF (HFrEF or HFpEF)

   For HFrEF:

   a) EF ≤40% AND

   b) a primary diagnosis of HF OR 2 medical visits (including virtual) with a HF diagnosis code in any position in the past 18 months.

   For HFpEF:

   a) EF >40% AND

   b) a primary diagnosis of HF OR 2 medical visits (including virtual) with a HF diagnosis code in any position in the past 18 months, AND

   c) on a loop diuretic or spironolactone or eplerenone (mineralocorticoid receptor antagonists)[1,3] in the past 18 months.

4. Criterion modified per Amendment 2

4.1. have a KCCQ baseline overall summary score of ≤80 prior to randomization

5. be able to read and understand English

6, possess and have sole use (eg, not shared with other users) of smartphone compatible with the Fitbit device

7. willing/able to wear the Fitbit device on a regular basis for the 9-month study period

8. must sign an electronic informed consent form (eICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study, including follow-up.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria prior to enrollment (consent date) will be excluded from participating in the study:

1. Criterion modified per Amendment 2

   1.1. currently taking an SGLT2i or within the last 3 months

2. history of diabetic ketoacidosis or have type 1 diabetes mellitus (T1DM)

3. Criterion modified per Amendment 2

   3.1. have acute decompensated HF (exacerbation of symptomatic HF) requiring intravenous diuretics, inotropes, or vasodilators within the last 4 weeks

4. Criterion modified per Amendment 2

   4.1. have stage 4 or 5 Chronic Kidney Disease (ie, eGFR <30ml/min on dialysis) from the most recent assessment

5. Criterion modified per Amendment 2

   5.1. have a history of atraumatic amputation within past 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months

6. Criterion modified per Amendment 2

   6.1. have a diagnosis of hypotension within 30 days

7. Criterion modified per Amendment 2

7.1. had major surgery within 3 months or have any surgery, ie, cardiac surgery, planned during the 3-month treatment (except for minor surgery, ie, outpatient surgery under local anesthesia)

8. Criterion modified per Amendment 2

8.1. 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 or have a life expectancy of <6 months or current immobility

9. have known allergies, hypersensitivity, or intolerance to JNJ-28431754 (canagliflozin) or its excipients (refer to Investigator's Brochure, Canagliflozin[5])

10. be a woman participant who is pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study

11. are legally incompetent

12. Criterion modified per Amendment 2

12.1. currently enrolled in an investigational study receiving an investigational study medication

13. has a left ventricular assist device

14. patient identity or association with enrolling network cannot be verified

NOTE: The required source documentation to support meeting the enrollment criteria are noted in Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations.

5.3. Prohibitions and Restrictions

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 details in Section 6.5, Prohibited Medications.

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

5.4. Screen Failures

Individuals who do not meet the criteria for participation in this study may be rescreened. Generally, a participant may only be rescreened once, but an additional screening may be allowed with concurrence by the sponsor.

Participant Identification

All potential participants who opt in to participate in the study on the website will receive a unique identifier in the study database held by a third-party representative. All data entered and collected via the study app with the participant's smartphone and Fitbit device are time and date stamped for completeness. Those participants who electronically sign the remote e-consent but do not enroll in the study can be tracked up to the point that they no longer interact with the app. Reports will be available to permit a detailed listing of each participant from remote e-consent through the study.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

The study intervention, JNJ-28431754 (canagliflozin), will be provided as immediate-release, over-encapsulated tablets (capsules) or placebo capsules taken orally once daily before the first meal of the day for the duration of the 3-month, double-blind treatment period. The capsules should be swallowed intact and participants should not attempt to dissolve them in water. The following table provides a description of the study interventions.

Table 2: Description of Study Interventions

Group Name	Group 1	Group 2
Study Intervention Name	canagliflozin	placebo
Type	drug	placebo
Dose Formulation	over-encapsulated tablets (capsules)	capsule
Unit Dose Strength	100 mg	0 mg
Dosage Level	100 mg	0 mg
Route of Administration	oral	oral
Use	experimental	placebo-comparator
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Individual participant bottles	Individual participant bottles
	Child resistant	Child resistant
Brand Name	INVOKANA®	Not applicable

JNJ-28431754 (canagliflozin) will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure, Canigliflozin[11] for a list of excipients.

6.2. Preparation/Handling/Storage/Accountability

All study intervention must be stored at controlled temperatures ranging from 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) and kept out of the reach of children.

The drug depot can refer to the pharmacy manual investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

The drug depot is responsible for ensuring that all study intervention received at the depot is inventoried and accounted for throughout the study. The dispensing of study intervention to the participant must be documented at the drug depot.

Study intervention must be handled in strict accordance with the protocol and the container label and must be stored at the drug depot in a secure area under appropriate environmental conditions.

Study intervention will be delivered to the participant by a qualified member of the drug depot/vendor. Study intervention will be supplied only to participants participating in the study. Participants will be instructed on how to store study intervention and how to destroy any unused study intervention at the end of the 3-month, double-blind treatment period.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 study intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor before initiation of the study.

Randomization will be balanced by using randomly permuted blocks and will be stratified by EF (HFrEF or HFpEF) at study entry as recorded in the participant’s EHR.

The interactive web response system (IxR) will generate a randomization code, participant randomization number, and kit numbers once consent is completed and the participant is confirmed eligible by the virtual principal investigator. The kit number will dictate the study intervention assignment and the matching study intervention bottle(s) to be shipped to the participant directly from the drug distribution vendor.

Blinding

The IxR will provide the kit number of the study intervention bottle(s) to be dispensed for each randomly assigned participant to begin dosing on Day 1 of the double-blind treatment period. Based on these randomization codes, study intervention will be packaged and labeled in a manner that maintains the double-blinded nature of the study.

The drug depot will not be provided with randomization codes. The codes will be maintained within the IxR, which has the functionality to allow the virtual principal investigator or designee to break the blind for an individual participant.

Under normal circumstances, the blind should not be broken until participants have completed the 3-month, double-blind treatment period. The Study Responsible Physician or other sponsor physician designee may in an emergency determine the identity of the study intervention by contacting the IxR. Telephone contact with the sponsor or its designee will be available 7 days per week. The date and reason for the unblinding must be documented in the study database. The documentation received from the IxR indicating the code break must be retained. All randomization codes will be released after completion of the study. The translation of randomization codes into treatment and control groups will be disclosed only to those authorized. Participants who have had their intervention assignment unblinded should continue to perform their scheduled evaluations.

6.4. Study Intervention Compliance

Participants will be instructed and notified by the study app weekly to confirm the number of study intervention capsules that they took that week. Study intervention compliance data will be monitored bi-weekly and if compliance is not >80%, the participant will be contacted by the call center who will re-educate the participant on the importance of diary completion and taking study intervention daily.

6.5. Prohibited Medications

Prohibited medications include other SGLT2i medications (including commercially available canagliflozin); participants must not take any other investigational agents during the study.

Medications will be reviewed monthly through medical claims data by the sponsor or designee. The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued during the 3-month, double-blind treatment period if:

- the participant has started another SGLT2i
- the participant has been diagnosed with T1DM

- for safety reasons or tolerability reasons (eg, adverse event), it is in the best interest of the participant to discontinue study intervention
- the participant develops severe renal impairment or End Stage Renal Disease, or is on dialysis
- the participant becomes pregnant
- the participant develops diabetic ketoacidosis
- the participant develops a new active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity or has an amputation.

The participant may choose to discontinue the study intervention only and remain in the study. In this case, the participant will continue to perform assessments (KCCQ, PGI-S, PGIC) and allow continued passive data collection from the app, Fitbit, and medical claims. If contacted during the study, the call center or designee will inform the participant of the importance to the study and results to have ongoing ascertainment of assessments and vital status.

Additional information on informed consent for collection of vital status can be found in Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations.

7.1.1. Temporary Discontinuation of Study Intervention

Study intervention may be temporarily discontinued; however, these interruptions should be kept to a minimum. Study intervention can be resumed when the participant, the virtual principal investigator, or the participant's physician deems it is appropriate to do so.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- lost to follow-up
- withdrawal of consent
- death

In the event a participant withdraws consent and does not agree to any kind of follow-up and specifically refuses any further contact with the call center or designee, this must be documented in the study database. If a participant is lost to follow-up, vital status will still be attempted for collection at study end through the participant's physician, medical claims, or public information according to local guidelines and as allowed by local regulations.

If a participant is lost to follow-up, every reasonable effort must be made by the call center or designee to contact the participant to determine vital status (eg, alive or dead) and the reason for discontinuation/withdrawal. This should include repeated telephone calls, certified letters, email requests, etc. The study screeners and app will obtain primary telephone contact number (eg, smartphone numbers), as well as other contact information (eg, email addresses) from participants before randomization. In addition, the call center should emphasize the importance of follow-up information to the participant before randomization. Follow-up can also be done with the help of the study site personnel. The measures taken to obtain follow-up information must be documented.

Unless consent is specifically withdrawn, participants are expected to be followed up through 1 of the alternative follow-up mechanisms described above.

Before withdrawing from the study, participants who request to withdraw from the study should be asked if they agree to be contacted to obtain follow-up information.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (SoA) summarizes the frequency and timing of effectiveness, medical resource utilization, health economic, and safety measurements applicable to this study.

Study-Specific Materials

The participants will be provided with the following supplies prior to starting the study:

- study intervention supply
- Fitbit device
- instruction manual(s) and patient drug information handouts.

8.1. Effectiveness Assessments

The primary effectiveness endpoint (KCCQ TSS) will be assessed at baseline and Weeks 2, 4, 6, and 12 during the double-blind treatment period (first 3 months) and afterwards at 6 and 9 months when no study intervention is administered. The following sensor data will be obtained from the Fitbit: step count and floors climbed.

8.1.1. KCCQ Scores

The KCCQ is a 23-item, self-administered questionnaire on the study app and requires, on average, 4 to 6 minutes to complete. It was developed to measure the patient's perception of their health status, including their HF symptoms, impact on physical and social function and how their HF impacts the quality of life. It scored by assigning a number for each response beginning with 1 that implies the lowest level of functioning and summing items within each domain, dividing by the range and multiplying by 100.[10] Missing values within each domain are assigned the average of the answered items within that same domain, presuming that at least half of the items within that domain are completed. Scale scores are transformed into values ranging from 0 to 100, with higher scores indicating more favorable health status.[10]

The answers provided by participants to the KCCQ's questions are used to calculate scores for the following 10 scales:

- Physical Limitation: a measure of how much a patient's routine activities are hampered by symptoms of HF
- Symptom Stability: a measure of whether a participant's symptoms have changed over the past 2 weeks

- Symptom Frequency: a measure of how often a participant has HF symptoms
- Symptom Burden: a measure of how much the participant's symptoms bother them
- Total Symptom: a combined measure of the symptom frequency and burden scales
- Social Limitation: a measure of how much a participant's social and work activities are limited by their HF symptoms
- Self-Efficacy: a measure of how well a participant can manage her care, find answers and help
- Quality of Life: a measure of the overall impact of a participant's HF on their perceived quality of life
- Clinical Summary: a combined measure of symptoms and physical limitations, congruent with the considerations a physician uses in assigning their NYHA classification
- Overall Summary: a combined measure of the participant's physical limitation, total symptom, social limitation, and quality of life scores.

In this study, at screening/baseline, KCCQ overall summary score will be evaluated to determine participant eligibility into the study. All other KCCQ domains and summary scores will also be calculated at baseline and at subsequent post-baseline time points respectively.

8.1.2. Actigraphy Measurements

Once randomized into the study, data from the Fitbit device on each participant will be collected continuously pertaining to the total step counts and total floors climbed for the entire duration of the study. Actigraphy measures (ie, step counts and floors climbed) will be examined in relation to the PRO measures and clinical outcomes to better characterize treatment effect on daily activity.

8.2. Exploratory Assessments

8.2.1. Patient Global Impression of Change (PGIC) Scores

The PGIC is a global index that is used to rate the overall status of the participant related to the participant's condition. It is rated by the participant and is based on the single question, "Since the start of the treatment you've received in this study, your heart failure symptoms are", where 1=very much improved, 2=somewhat improved, 3=a little improved, 4=no change, 5=a little worse, 6=somewhat worse, and 7=very much worse. Refer to Section 10.4, Appendix 4: Patient Global Impression of Change (PGIC).

8.2.2. Patient Global Impression of Severity (PGI-S) Scores

The PGI-S is a global index that is used to rate the severity of a specific condition. It is rated by the participant and is based on the single question, "Considering all aspects of your heart failure symptoms right now, would you say your heart failure symptoms are", where 1=none, 2=mild, 3=moderate, 4=severe, and 5=very severe. Refer to Section 10.5, Appendix 5: Patient Global Impression of Severity (PGI-S).

8.2.3. Participant Satisfaction Survey

An optional participant satisfaction survey to assess the participant's satisfaction with the virtual design of the study and use of the Fitbit device in the study will be provided to the participant at the end of study. Refer to Section 10.6, Appendix 6: Participant Satisfaction Survey.

8.2.4. Healthcare Resource Utilization and Health Economics

Healthcare Resource Utilization (HRU) and health economics data associated with medical encounters will be collected for all participants during the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- number and duration of first hospitalizations/readmissions (overall inpatient visit length of stay) for HF or any other reason
- number and duration of first hospitalizations/readmissions (overall inpatient visit length of stay) for any other events
- number of emergency room visits
- discharge destination

8.3. Adverse Events and Serious Adverse Events and Special Situations

Participants will be instructed to self-report any adverse events to a call center. In addition, this information may be discovered by the call center during interaction with the participant. Once identified, the call center will complete and submit a solicited safety reporting form to Janssen Global Medical Safety (GMS) per the sponsor's standard operating procedure. Queries for these cases will go to the call center/and virtual principal investigator as appropriate. If follow-up is needed with the participant's treating physician, it will be done either through the virtual principal investigator, who may contact the treating physician directly, as agreed upon in the ICF. All SAEs will be assessed by Janssen GMS for potential suspected unexpected serious adverse reactions (SUSARs) for expedited regulatory reporting.

Medical claims adverse event data will be reviewed and evaluated including potential SUSAR assessment and regulatory reporting in aggregate at the end of the 3-month, double-blind treatment period when the unblinded data are available. In addition, for this time period, self-reported adverse events from the call center will be summarized in a listing. Serious adverse event data from medical claims for the 9-month study period will be aggregated by treatment assignment. Self-reported adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be reported by preferred term and by T2DM and non-T2DM. Adverse events collected from medical claims will be aggregated based on diagnosis codes for the incidences of non-endpoint SAEs (ie, SAEs leading to hospitalizations, ED visits) and adverse events of interest between groups reported by T2DM and non-T2DM. Discontinuations will be summarized based on any available data.

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

All Adverse Events

Adverse events will be captured through medical claims (from the time of informed consent to the end of study) and by the call center (from the time of informed consent until 30 days after the end of treatment). After the treatment period plus 30 days, serious adverse events will be identified solely through medical claims data. Adverse events that occur during the treatment period plus 30 days identified from medical claims will be aggregated by treatment assignment when unblinding is available. In addition, for this time period, self-reported adverse events from the call center will be summarized in a listing. Serious adverse event data from medical claims for the 9-month study period will be aggregated by treatment assignment.

8.3.2. 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 virtual principal investigator (and the head of the investigational institute where required) all SUSARs. The virtual principal 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. A SUSAR will be reported to regulatory authorities unblinded. The virtual principal investigator and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.3.3. Pregnancy

Female participants and male participants with a partner becoming pregnant will be instructed to call the call center for any pregnancy. The call center will report the pregnancy to the sponsor within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered adverse events and must also be self-reported by the participants to the call center. Any participant who becomes pregnant during the study must be promptly discontinued from the study intervention.

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

8.3.4. Adverse Events of Interest

Adverse events of interest include all severe hypoglycemic events, acute kidney injury, fractures, diabetic ketoacidosis, and lower limb amputation.

In addition, the following adverse events will be examined: hypotension; Fournier’s gangrene; genital mycotic infections; urinary tract infections (including urosepsis and pyelonephritis); increased urination; and hypersensitivity reactions including angioedema and anaphylaxis.

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 effectiveness and safety data is outlined below. Specific details will be provided in the SAP.

The primary study objective will be addressed by comparing the mean change in KCCQ TSS from baseline to Month 3 between the study intervention groups. The key secondary study objective will involve a comparison between the 2 randomized groups in terms of the mean difference in daily step counts from baseline to Month 3. For analyzing the primary, secondary, and exploratory objectives, an intent-to-treat (ITT) population comprising of all randomized participants will be used. Specific imputation rules for missing data (eg, missing KCCQ TSS, daily step count) will be applied, if warranted, and will be specified in the SAP before the final database lock. Descriptive statistics such as mean, median, standard deviation, interquartile range, minimum and maximum will be used to summarize continuous variables. Counts and proportions will be used to summarize categorical variables. Graphical data displays (eg, box plots) may be employed to summarize data. For time to event variables, Kaplan-Meier estimates over time will be plotted. All statistical tests will be two-sided and performed at the 5% significance level unless otherwise specified. No multiplicity adjustment to the overall Type I error rate will be applied when analyzing the exploratory variables.

9.1. Statistical Hypotheses

For the primary effectiveness endpoint, the null hypothesis is that the canagliflozin 100 mg is not different from placebo with respect to the mean KCCQ TSS change from baseline at Month 3. For the first key secondary effectiveness endpoint of daily step count, the null hypothesis is that canagliflozin 100 mg is not different from placebo with respect to the mean daily step count.

9.2. Sample Size Determination

The primary effectiveness endpoint is the change from baseline in the KCCQ TSS at the end of the 3-month double-blind treatment period. Although a 5-point improvement in the KCCQ TSS is generally viewed as clinically meaningful,[5,29] recent studies[16,21] have shown that improvements in the range of 3 to 5 points on the KCCQ TSS are equally meaningful in the overall HF-related health status measured by the KCCQ over a 12-week time period. Based on the evidence from these studies, the current study is powered to detect a mean change from baseline of 3 points in the KCCQ TSS between canagliflozin 100 mg and placebo groups at 12 weeks. Assuming a significance level of 5% and a standard deviation of 18 points for mean change in KCCQ TSS, a total of 1,900 participants will be randomized in this study providing approximately 95% power. This sample size is adequate to account for a potential 5% dropout rate.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 3: Analysis Populations

Population	Description
Enrolled	All participants who sign the ICF
Intent-to-Treat (ITT)	All randomized participants
Per Protocol (PP)	A subset of the ITT population. Randomized participants who received study drug and with major protocol deviations will be excluded from the PP population. Major protocol deviations will be defined in the SAP.

9.4. Statistical Analyses

9.4.1. Handling of Missing Data

Missing data affecting the primary endpoint change in KCCQ TSS will be addressed via the MMRM method that assumes missingness at random (MAR). Specific imputation rules including statistical modeling approaches may be employed when such an assumption is not valid. In cases where individual items in the KCCQ domains are missing or not completed at required times, appropriate rules to impute missing item scores will be specified based on the KCCQ manual. Sensitivity analyses will be conducted to assess impact of missing data on key study results. Further details about the imputation rules and sensitivity analyses will be provided in the SAP.

9.4.2. Effectiveness Analyses

9.4.2.1. Primary and Secondary Effectiveness Analyses

The primary and key secondary effectiveness analyses will be based on the ITT analysis population (using all randomized participants).

As KCCQ TSS is measured repeatedly over time (ie, at baseline, Week 2, Week 4, Week 6, and Week 12 respectively), the primary effectiveness endpoint (change in KCCQ TSS from baseline to Month 3) will be analyzed by a mixed effect model repeated measures (MMRM) method simultaneously adjusting for study intervention group, stratification factor (HFrEF versus HFpEF), time, time by study intervention group, and baseline KCCQ TSS value as covariates. An unstructured covariance structure will be assumed across study intervention groups to model the within-participant errors. The primary comparison will be based on the difference in least squares between treatments at Month 3. The treatment difference in the least squares means and their 2-sided 95% confidence interval (CI) will be provided. An MMRM model accounts for data missing at random.

A responder analysis will also be performed when comparing proportions of participants with a 5- (or 10-) point improvement in KCCQ TSS from baseline between the study intervention groups. This will be based on a two-sample difference in proportions test along with a 95% confidence interval for the difference in 2 proportions. Additionally, empirical cumulative distribution functions of the KCCQ TSS and other domain scores will be presented.

The primary effectiveness endpoint will also be analyzed by subgroups defined by age, gender, race and key baseline disease/demographic characteristics using the MMRM approach described above. Further details will be provided in the SAP. Quantitative and/or qualitative interactions for each subgroup and treatment will be identified. Qualitative interactions will be investigated further by the Gail and Simon test[9] and interpreted accordingly.

The first key secondary endpoint of daily step count will be tested once the primary endpoint is shown to be significant at the 5% significance level using a two-sided t-test. This approach will control for the overall Type I error rate at 5%.

For the second key effectiveness endpoint, an MMRM model (like that used in the analysis of the primary endpoint) will be employed to summarize changes in KCCQ individual domain scores (physical limitation, quality of life, clinical summary, and overall) from baseline to Month 3. This hypothesis will be independently tested at 5% without any control for overall Type I error rate.

9.4.2.2. Exploratory Analyses

Exploratory analyses will be performed with no adjustment for multiplicity and include the following:

- summary statistics of PGIC and PGI-S scores
- associations (correlations and/or categorical association measures) between digital markers (step count and floors climbed) and clinical events such as need for outpatient intravenous therapies, ED visits, and hospitalizations
- tabulation and comparison of total HRU and health economics data across groups.
- descriptive statistics (eg, mean, median, and standard deviation) of daily floors climbed
- association between the KCCQ change from baseline to Month 3 and the PGIC at Month 3 will be examined and summarized
- time to death
- descriptive statistics of the participant's satisfaction with his/her experience with the virtual design at the end of the study.

9.4.3. Adverse Events Analysis

Adverse events reported to the call center will be assessed by Janssen GMS for causality and meeting SUSAR reporting requirements. Self-reported adverse events will be coded according to MedDRA and will be reported by preferred term by T2DM and non-T2DM. Adverse events collected from medical claims will be aggregated based on diagnosis codes for the incidences of non-endpoint SAEs (ie, SAEs leading to hospitalizations, ED visits) and adverse events of interest between groups reported by T2DM and non-T2DM. Discontinuations will be summarized based on any available data. Adverse events reported from the call center will be reported separately from those obtained from the medical claims data. Self-reported adverse events from the call center will be summarized in a listing.

9.4.4. Healthcare Resource Utilization and Health Economics Analyses

Healthcare resource utilization (HRU) and health economics data will be descriptively summarized by intervention group.

9.5. Interim Analysis

No interim analysis is planned for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Abbreviations

ACEi	angiotensin-converting enzyme inhibitor
AE	adverse event
AHA	antihyperglycemic agent
ARB	angiotensin II receptor blocker
ARNi	angiotensin receptor-neprilysin inhibitor
BB	beta blocker
CANVAS	short title for study, Canagliflozin Cardiovascular Assessment Study
CANVAS-R	short title for study, Canagliflozin Cardiovascular Assessment Study-Renal
CI	confidence interval
CREDENCE	short title for study, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial
CV	cardiovascular
CVD	cardiovascular disease
DKA	diabetic ketoacidosis
DMC	Data Monitoring Committee
ED	emergency department
EHR	electronic health record
EMPA	empagliflozin
ESKD	End Stage Kidney Disease
GCP	Good Clinical Practice
GMS	Global Medical Safety
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HHF	hospitalization for heart failure
HR	hazard ratio
HRU	healthcare resource utilization
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INVOKANA	canagliflozin
IRB	Institutional Review Board
ITT	intent-to-treat
IxR	interactive web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
MACE	major adverse cardiovascular events
MAR	missing at random
MDDT	Medical Device Development Tools
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	mixed effect model repeated measure
NYHA	New York Heart Association
PGIC	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PQC	Product Quality Complaint
PRO	patient-reported outcome(s) (paper)
SAE	serious adverse event
SAP	statistical analysis plan
SGLT2	sodium-glucose co-transporter 2
SGLT2i	sodium-glucose co-transporter 2 inhibitor
SoA	schedule of activities

SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TSS	Total Symptom Score
US	United States

10.2 Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Virtual Principal Investigator Responsibilities

The virtual principal investigator or designee 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

The sponsor will not modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor. 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. 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 virtual principal investigator or designee 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. These will be recorded by the sponsor.

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 drug depot:

- 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 the principal investigator 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
- signed and dated statement of virtual principal investigator (eg, Form FDA 1572) and current curriculum vitae (CV), if applicable
- documentation of virtual principal investigator or designee qualifications (eg, curriculum vitae)
- completed virtual principal investigator or designee financial disclosure form, 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 virtual principal investigator or designee financial disclosure forms
- documentation of virtual principal investigator or designee qualifications (eg, curriculum vitae).

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the virtual principal investigator or designee (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)
- Investigator's Brochure, Canigliflozin[11] (or equivalent information) and amendments/addenda
- sponsor-approved participant recruiting materials
- information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- virtual principal investigator or designee 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.

During the study, the principal investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- revision(s) to ICF and any other written materials to be provided to participants
- if applicable, new or revised participant recruiting materials approved by the sponsor
- new edition(s) of the Investigator's Brochure, Canigliflozin[11] and amendments/addenda
- summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- reports of adverse events that are of interest, special interest, serious, unlisted/unexpected, and associated with the study intervention
- new information that may adversely affect the safety of the participants or the conduct of the study
- deviations from or changes to the protocol to eliminate immediate hazards to the participants
- report of deaths of participants under the virtual principal investigator's care
- notification if a new virtual principal investigator is responsible for the study
- development Safety Update Report and Line Listings, where applicable
- any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the virtual principal investigator or designee (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Other Ethical Considerations

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

FINANCIAL DISCLOSURE

The virtual principal investigator or designee 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. The virtual principal investigator is 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 (REMOTE E-CONSENT) PROCESS

Each participant must give remote e-consent according to local requirements after the nature of the study has been fully explained. The remote e-consent must be electronically signed within the study app before the performance of any study-related activity. The remote e-consent that is/are used must be approved by both the sponsor and by the reviewing IRB and be in a language that the participant can read and understand. The remote e-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. After having obtained the consent, a copy of the remote e-consent must be sent to the participant.

In this study, a remote e-consent process will be utilized. Before enrollment in the study, the participant will have an opportunity to read through the remote e-consent which will detail the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. The remote e-consent will explain 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 they will receive. Finally, they will be told that their records may be accessed by health authorities and authorized sponsor personnel without violating their confidentiality, to the extent permitted by the applicable law(s) or regulations. By electronically signing the remote e-consent the participant is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that they are agreeing to allow recontact by the study sponsor for the purpose of obtaining consent for additional evaluations, if needed.

If the participant has any questions about the study related to the remote e-consent process prior to providing their electronic signature, they will be provided with an opportunity to discuss these questions with the virtual principal investigator via phone and/or a contact at the study call center. Once the participant understands all aspects of the remote e-consent, consent should be appropriately recorded by means of the participant’s personally dated signature via electronic signature. After having obtained the consent, the participant will receive a copy of the remote e-consent via email (after the participant has verified his or her email address) for their records.

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 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.

The participant has the right to request through the virtual principal 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.

COMMITTEES STRUCTURE

An Independent Scientific Advisory Committee comprised of experts in the management of patients with HF and sponsor representatives will be commissioned for this study. Committee membership and responsibilities will be documented in the committee charter(s).

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding JNJ-28431754 (canagliflozin) 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, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The virtual principal 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 virtual principal investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-28431754 (canagliflozin), 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 virtual principal 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 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, if appropriate.

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 guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the virtual principal investigator. The virtual principal investigator has the right to publish data after the primary data are published. If the virtual principal 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, the principal investigator will recognize the integrity of the study by not submitting data for publication data until the results from the completed study have been submitted for publication, within 18 months after the study end date. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the International Committee of Medical Journal Editors 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 and the results of clinical studies as required by law.

DATA QUALITY ASSURANCE

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; record of all adverse events and follow-up of adverse events; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable. Many of the assessments in this study (date of signed informed consent, activity data, KCCQ data) will be collected directly from the participant and therefore the data received is from a direct source.

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 virtual principal investigator or designee before the study.

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, baseline KCCQ) and documented in the source documents.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the virtual principal investigator/call center will maintain 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 virtual principal investigator/call center 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 virtual principal investigator/call center as to when these documents no longer need to be retained.

If the virtual principal 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 virtual principal investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

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

STUDY AND SITE CLOSURE

Study Termination

The sponsor reserves the right to terminate the study at any time for any reason at the sole discretion of the sponsor.

10.3 Appendix 3: Kansas City Cardiomyopathy Questionnaire (KCCQ)

Appendix 3 provides a representative example of the scale questions that will be used in this study.

The KC Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	❑	❑	❑	❑	❑	❑
Showering/Bathing	❑	❑	❑	❑	❑	❑
Walking 1 block on level ground	❑	❑	❑	❑	❑	❑
Doing yardwork, housework or carrying groceries	❑	❑	❑	❑	❑	❑
Climbing a flight of stairs without stopping	❑	❑	❑	❑	❑	❑
Hurrying or jogging (as if to catch a bus)	❑	❑	❑	❑	❑	❑

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
❑	❑	❑	❑	❑	❑

Original US English

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
❑	❑	❑	❑	❑	❑

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
❑	❑	❑	❑	❑	❑

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

Original US English

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
❑	❑	❑	❑	❑	❑

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
❑	❑	❑	❑	❑

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
❑	❑	❑	❑	❑

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
❑	❑	❑	❑	❑

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
❑	❑	❑	❑	❑

Original US English

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
❑	❑	❑	❑	❑

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	❑	❑	❑	❑	❑	❑
Working or doing household chores	❑	❑	❑	❑	❑	❑
Visiting family or friends out of your home	❑	❑	❑	❑	❑	❑
Intimate relationships with loved ones	❑	❑	❑	❑	❑	❑

Original US English

10.4 Appendix 4: Patient Global Impression of Change (PGIC)

Appendix 4 provides a representative example of the scale questions that will be used in this study.

Since the start of the treatment you've received in this study, your heart failure symptoms are: (select one response)

1. Very much improved
2. Somewhat improved
3. A little improved
4. No change
5. A little worse
6. Somewhat worse
7. Very much worse

10.5 Appendix 5: Patient Global Impression of Severity (PGI-S)

Appendix 5 provides a representative example of the scale question that will be used in this study.

Considering all aspects of your heart failure symptoms right now, would you say your heart failure symptoms are: (select one response)

1. None
2. Mild
3. Moderate
4. Severe
5. Very Severe

10.6 Appendix 6: Participant Satisfaction Survey

Appendix 6 provides a representative example of the questions that will be provided to the participant.

For each of the statements below, please indicate your level of agreement:	Strongly Disagree 1	Disagree 2	Neutral 3	Agree 4	Strongly Agree 5
Trying something new to possibly treat my heart failure was important to me.					
The virtual study was easy for me to sign up for and get started.					
The Fitbit was easy to set up and use.					
The study app was easy to set up on my smartphone.					
The questionnaires were easy to complete on my smartphone.					
The reminders to complete the questionnaires were helpful.					
The study Fitbit provided helpful information to me.					
It was easy to reach the study team when I had questions or concerns.					
I would recommend participating in a study like this to my friends and family.					

10.7 Appendix 7: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) 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 non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) 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.

*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.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

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 JNJ-28431754 (canagliflozin), the expectedness of an adverse event will be determined by whether or not it is listed in the IB.

ATTRIBUTION DEFINITIONS

Assessment of Causality

The causal relationship to study treatment is determined by Janssen Global Medical Safety (GMS). The following selection should be used to assess all adverse events (AE).

Related

There is a reasonable causal relationship between study treatment administration and the AE.

Not Related

There is not a reasonable causal relationship between study treatment administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

SEVERITY CRITERIA

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

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, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson &

Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)

- exposure to a sponsor study intervention from breastfeeding.

Special reporting situations should be reported. Any special reporting situation that meets the criteria of a serious adverse event should also be reported.

PROCEDURES

All Adverse Events

Adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology on the solicited AE form. 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").

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
- call center name and 24-hour contact telephone number
- 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). Note: hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a participant in a study within 24 hours 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 by the call center to the sponsor within 24 hours after being made aware of the event.

If the product defect is combined with a serious adverse event, the call center 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.

10.8 Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	02 June 2020
Amendment 1	07 February 2020
Original Protocol	07 November 2019

Amendment 2 (02 June 2020)

Overall Rationale for the Amendment: The overall reasons for the amendment are to 1) clarify inclusion/exclusion criteria for recruitment centers, 2) more accurately identify patients with heart failure in inclusion/exclusion criteria, and 3) represent patients with heart failure in medical claims over time and between sites of care.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis (Objectives and Endpoints, Overall Design, Secondary and Exploratory Evaluations, Statistical Methods); 1.3. Schedule of Activities (SoA); 3. Objectives and Endpoints; 4.1. Overall Design; 8.1. Effectiveness Assessments; 9.4.2.2. Exploratory Analyses	The term 'stairs' was changed to 'floors'.	To align with the data obtained from the Fitbit device, which reports this metric as 'floors' climbed not 'stairs' climbed.
1.1. Synopsis (Adverse Event Data Collection, Adverse Event Evaluations); 3. Objectives and Endpoints	The word 'self-reported' was replaced by 'adverse' and 'date of the first dose of study intervention' was replaced by 'time of informed consent'.	To ensure consistency for adverse event (AE) collection and timepoints across the protocol.
1.1. Synopsis (Adverse Event Data Collection, Adverse Event Evaluations); 3. Objectives and Endpoints	The word 'adverse event' was added with respect to medical claims data.	To clarify that medical claims data include AE data.
1.1. Synopsis (Overall Design); 1.3. Schedule of Activities (SoA); 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 5.1. Inclusion Criteria (Criterion #4)	The upper threshold of the Kansas City Cardiomyopathy Questionnaire (KCCQ) for baseline overall summary score was changed from <80 to ≤80.	To include participants with KCCQ summary score of 80.
1.1. Synopsis (Overall Design); 1.3. Schedule of Activities (SoA); 4.1. Overall Design; 4.2. Scientific Rationale for Study Design;	The lower threshold (<40) of the KCCQ for baseline overall summary score was removed.	To ensure that a larger number of participants have an opportunity to experience measurable health status benefit from treatment as there is no *a*

Section Number and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria (Criterion #4)		*priori* reason to presume that more symptomatic participants can't benefit from treatment.
4.2. Scientific Rationale for Study Design	The participant eligibility was extended to include those with New York Heart Association (NYHA) Class IV.	
1.1. Synopsis (Overall Design); 4.1. Overall Design	'Dates of deaths' was added to the list of study assessments.	To correlate with the exploratory endpoint 'time to death' and also for consistency.
1.1. Synopsis (Secondary and Exploratory Evaluations, Statistical Methods); 9.4.2.2. Exploratory Analyses	The 'time to death' evaluation was added to the list of secondary and exploratory evaluations.	To maintain consistency across the protocol. The term was omitted by mistake in the previous versions.
1.1. Synopsis (Intervention Groups and Duration); 4.1. Overall Design	The term 'claims' was deleted from collection of data during the no treatment period.	To explain the wider scope of data collection during the no treatment period (not just claims data).
1.1. Synopsis (Adverse Event Analyses); 8.3. Adverse Events and Serious Adverse Events and Special Situations; 9.4.3. Adverse Events Analysis	The term 'self-reported' was added.	To clarify AE analysis process
1.2. Schema	The study schema was updated.	To align with the changes in the study design and Schedule of Activities.
1.3. Schedule of Activities (SoA)	Kept Screening and Baseline in separate columns.	To clarify that Screening and Baseline are 2 distinct periods in this study.
1.3. Schedule of Activities (SoA); 4.2. Scientific Rationale for Study Design; 5. Study Population	Screening window was increased from 21 days to 28 days.	To increase the screening period from 21 days to 28 days to accommodate various study set up activities like electronic health record (EHR) reviews, app set-up and coordination of consenting, participants discussing with their physicians, families, etc and to keep the 7-day baseline period and specify the baseline activities.
4.2. Scientific Rationale for Study Design (Length of Study Periods)	Provided clarity on requirement of baseline period of 7 days. The text was modified as: The screening period of ~~3 weeks~~ **28 days** allows for an appropriate length of time for screening procedures to determine study eligibility **(with EHR reviews, app set-up, completion of the KCCQ, and consenting). The baseline period of 7 days begins upon randomization and allows for shipment of the study drug and Fitbit device to the participant**.	
2. Introduction; 4.2.1. Study-Specific Ethical Design Considerations	Information on Food and Drug Administration approval of dapagliflozin was added.	To explain the dapagliflozin information and to illustrate the benefit of including participants with heart failure with preserved ejection fraction (HFpEF) in this study.

Section Number and Name	Description of Change	Brief Rationale
2.2. Benefit/Risk Assessment	The text 'or for use in patients with HFpEF ' was added.	To indicate that there may be a benefit in HFpEF participants where dapagliflozin doesn't have an indication.
4.1. Overall Design	Specified that inclusion/exclusion criteria, healthcare resource utilization, and relevant concomitant medications will be included in the claims data monitoring.	To maintain consistency with the other sections of the protocol.
4.2. Scientific Rationale for Study Design;	Information of KCCQ was updated.	To update that KCCQ was recently qualified by Center for Drug Evaluation and Research as a patient reported outcome instrument for use in clinical trials in heart failure.
4.2. Scientific Rationale for Study Design; 8.1.2. Actigraphy Measurements	Added description on actigraphy measurements.	To add the description on Fitbit data collection that was missed in the previous protocol version.
4.4. End of Study Definition	The following text was modified as: A participant will be considered to have **ended** ~~completed~~ the treatment period of the study (at 3 months), regardless of whether the participant **has completed** ~~is on~~ the study intervention, if he or she has completed assessments at Month 3 of the double-blind treatment period, ~~or~~ withdrew earlier from the treatment, or ~~at the time of death for participants who~~ died prior to the Month 3 ~~visit~~ assessment.	To clarify that the participant could have ended the treatment period but not have completed the study intervention.
4.4. End of Study Definition	The term 'clinical research organization' was added.	To clarify that the study partner prefers to a clinical research organization partner and not participant.
5.1. Inclusion Criteria; 5.2. Exclusion Criteria; 5.2. Exclusion Criteria (Criteria #1, 3, 5, 6, and 7)	Clarified that each potential participant was required to satisfy the inclusion/exclusion criteria 'prior to enrollment (consent date)'. The extra term 'prior to enrollment ' was deleted from exclusion criteria 1, 3, and 5. The extra term 'of the screening visit' was deleted from exclusion criterion 6. The extra term 'of consent' was deleted from exclusion criterion 7.	To clarify the timing for fulfillment of inclusion/exclusion criteria.
5.1. Inclusion Criteria (Criterion #3)	Definitions of heart failure with reduced ejection fraction (HFrEF) and HFpEF were updated. Added spironolactone and eplerenone to the definition of HFpEF.	To clarify and align with the information received from site principal investigators and Steering Committee on definitions of HFrEF and HFpEF for this virtual study and diagnosis confirmation within 18 months instead of 1 year.

Section Number and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria (Criterion #4)	The text 'from the most recent assessment' was added.	To clarify the timing of assessment of stage 4 or 5 chronic kidney disease for exclusion of participants from the study.
5.2. Exclusion Criteria (Criterion #8)	The text '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' was added.	To explicitly describe the exclusion of participants with compromised well-being or whose participation could prevent, limit, or confound the protocol-specified assessments.
5.2. Exclusion Criteria (Criterion #12)	The text 'receiving an investigational study medication' was added.	To clarify that participants with ongoing treatment with an investigational agent should be excluded from the study, but those in studies without an investigational agent are eligible to participate.
5.2. Exclusion Criteria (Criterion #13)	A new exclusion criterion #13 was added: 'has a left ventricular assist device'.	To exclude the factors that can alter the health status and would confound the ability to define a benefit from treatment with the study drug.
5.2. Exclusion Criteria (Criterion #14)	A new exclusion criterion # 14 was added: 'patient identity or association with enrolling network cannot be verified'.	To exclude those participants whose identity cannot be verified.
5.4. Screen Failures	Updated the criteria for rescreening of participants.	To allow and outline for the rescreening of participants.
5.4. Screen Failures	The following text was modified as: All potential participants who ~~electronically sign the remote e-consent~~ **opt in to participate in the study on the website** will receive a unique identifier in the study database held by a third-party representative.	To emphasize that the participants will receive a unique study number when they opt in to participate in the study which is prior to enrollment (signing of consent).
6.3. Measures to Minimize Bias: Randomization and Blinding	The following text was modified as: The IxR will provide the kit number of the study intervention bottle(s) to be dispensed for each randomly assigned participant **to begin dosing** on Day 1 of the double-blind treatment period.	To indicate that the kit numbers are not assigned on Day 1 but that study intervention dosing should begin on Day 1.
6.4. Study Intervention Compliance	Re-education of the participant on importance of dairy completion was added.	To indicate that diary should be completed to track the study intervention compliance data.
7.2. Participant Discontinuation/Withdrawal from the Study	The following text was modified as: If ~~applicable~~, **the participant is lost to follow-up**, vital status **will still be attempted** ~~to be obtained~~ **for collection** at study end through the participant's physician, medical claims, or	To specify that vital status should be obtained, if possible, in case participant is lost to follow-up.

Section Number and Name	Description of Change	Brief Rationale
	public information according to local guidelines and as allowed by local regulations	
7.2. Participant Discontinuation/Withdrawal from the Study	The information on home and work contact numbers were removed.	To indicate that the app can only store smartphone contact number.
7.2. Participant Discontinuation/Withdrawal from the Study	The following text was added: Follow-up can also be done with the help of the study site personnel.	To specify that besides the call center, study site can also help with follow-up.
8. Study Assessments and Procedures (Overview)	The following text was deleted: Health Resource Utilization (HRU) and health economics data will be collected. Refer to Section 8.2.4, Healthcare Resource Utilization and Health Economics for details.	To remove duplicate information.
8.2.4. Healthcare resource Utilization and Health Economics	Added 'discharge destination' information to the list of healthcare resource utilization and health economics data	To maintain consistency with text in the other sections of the protocol.
8.3. Adverse Events and Serious Adverse Events and Special Situations	The text was modified to indicate that the principal investigator may contact the treating physician as agreed in the informed consent form.	To update how the principal investigator may contact the participant's treating physician based on the confirmed process.
8.3. Adverse Events and Serious Adverse Events and Special Situations; 9.4.3. Adverse Events Analysis	Emergency department visits was added as a criteria for aggregation of AEs collection from claims.	To be consistent by including criteria for aggregation of AEs collection from claims in this section.
8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	The following text was modified as: All ~~participant reported~~ adverse events ~~suspected to be related to the study intervention~~, whether serious or non-serious, will be collected from the time a signed and dated ICF is obtained until the participant completes their participation in the 3-month treatment period plus 30 days.	To clarify that all AEs (not just those suspected to be related to study intervention) should be collected.
8.3.4. Adverse Events of Interest	Additional adverse events of interest were specified.	To expand the scope of AEs of interest to be collected in the study.
9.3. Populations for Analyses (Table 2)	Updated the definition of 'per protocol' population.	To clarify the definition of per protocol population.
10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations (Regulatory and Ethical Considerations [Protocol Amendments])	The following text was deleted: The data recorded in the source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.	To remove non-applicable data source in this virtual study.
10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations (Regulatory and Ethical Considerations [Protocol Amendments])	Specified that the departure from the protocol information will be recorded by the sponsor.	To provide clarity on who will record the departure from protocol information.
10.6. Appendix 6: Participant Satisfaction Survey	Added numeric grading of 1 to 5.	To provide the scoring used on the participant satisfaction survey which was omitted in previous versions.

Section Number and Name	Description of Change	Brief Rationale
10.7. Appendix 7: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting (Product Quality Complaint Handling)	Modified the text to indicate that instead of study site personnel, the call center will report the product quality complaint to the sponsor in case a product defect is combined with serious AE.	To provide clarity and for consistency across the study.
References	New references (#1, 3, 14) were added. Other reference numbers cited within the protocol were updated.	References added to support the study.
6.1. Study Interventions Administered	Assigned table number to 'Description of Study Interventions' table. Table numbering of other tables were updated.	Minor errors were noted.
8.3.3. Pregnancy	The following text was modified as 'Any participant who becomes pregnant during the study must be promptly ~~withdrawn~~ **discontinued** from the study ~~and discontinue further study~~ intervention'.	
Throughout the protocol	Minor grammatical, formatting, or consistency changes were made.	

Amendment 1 (07 February 2020)

Overall Rationale for the Amendment: The overall reason for the amendment is to remove Return of Results (RoR) to align with Janssen standard operating procedure (SOP), update the study overview schema to align with the protocol, and to define that the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score will be used for the baseline assessment.

Section Number and Name	Description of Change	Brief Rationale
Synopsis Overall Design; 1.3 Schedule of activities (SoA); 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 5.1. Inclusion Criteria; 8.1.1. KCCQ Scores	Clarified that KCCQ overall summary score will be evaluated at Screening/Baseline to determine participant eligibility and other KCCQ domains and summary scores will be calculated at baseline and subsequent postbaseline timepoints, respectively.	To clarify that KCCQ baseline overall summary score will be used to determine participant eligibility at screening/baseline.
Synopsis Objectives and Endpoints; Synopsis Intervention Groups and Duration; 3. Objectives and Endpoints; 4.1 Overall Design	The term of "Return of Results (RoR)" was removed and term "Participant Unblinding" was added. Text related to RoR including exploratory objective and endpoint was deleted.	Janssen SOP does not allow for "RoR" to participants for an approved drug.
1.2 Schema	Schematic Overview of the Study was replaced with an updated figure (1).	To align with protocol.
1.3 Schedule of activities (SoA)	SoA was updated to clarify study day for date of first dose and other timepoints. Also, footnote "d" related to claims data collection and reporting of adverse events were updated.	To specify the timepoints (in days) for clarity and added a baseline period of up to 7 days before Day 1.
Title Page	EudraCT number deleted	EudraCT number is not applicable for the current study.
6.3 Measures to Minimize Bias: Randomization and Blinding	Information related to blind breaking was updated. Clarified that "Study Responsible Physician "or "other sponsor physician" designee may in an emergency determine the	To update appropriate process for study unblinding.

Section Number and Name	Description of Change	Brief Rationale
	identity of the study intervention by contacting the IxR.	
9.4.3 Adverse event analysis	Clarified that adverse events reported from call center will be reported separately from those obtained from claims data.	To clarify the adverse event reporting
10.7 Appendix 7: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Clarified that the causal relationship to the study treatment is determined by Janssen Global Medical Safety. Text related to responsibility of virtual principal investigator was deleted.	To align with the protocol and the design of the study and to remove incorrect text. Clarified the responsibility of virtual principal investigator.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

JNJ-28431754 (canagliflozin) (INVOKANA)
Clinical Protocol 28431754HFA3002 Amendment 3

INVESTIGATOR AGREEMENT

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: _____

_____

_____

_____

Name (typed or printed): PPD _____

Institution: Janssen Scientific Affairs _____

Signature: PPD _____ Date: [redacted]
(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.

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Approved, Date: 23 February 2021