**SYNOPSIS**

<table>
<thead>
<tr>
<th>Name of Sponsor/Company</th>
<th>Janssen Research &amp; Development*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Investigational Product</td>
<td>JNJ-28431754 (canagliflozin)</td>
</tr>
</tbody>
</table>

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologies, BV; Janssen-Cilag International NV; Janssen Pharmaceuticals NV; Janssen, Inc; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term “sponsor” is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved
Date: 8 March 2019
Prepared by: Janssen Research & Development, LLC

**Protocol No.:** 28431754DNE3001

**Title of Study:** A Randomized, Double-blind, Event-driven, Placebo-controlled, Multicenter Study of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Subjects With Type 2 Diabetes Mellitus and Diabetic Nephropathy

**Study Name:** Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial

**EudraCT Number:** 2013-004494-28

**NCT No.:** NCT02065791

**Clinical Registry No.:** CR103517

**Coordinating Investigator:** Adeera Levin, MD, FRCPC - [Contact]

**Study Center(s):** 690 centers in 34 countries (198 centers in North America [24 in Canada, 36 in Mexico, and 138 in the United States (US)], 113 centers in Central/South America [51 in Argentina, 37 in Brazil, 5 in Chile, 14 in Colombia, and 6 in Guatemala], 187 centers in Europe [11 in Bulgaria, 16 in Czech Republic, 11 in France, 4 in Germany, 21 in Hungary, 19 in Italy, 3 in Lithuania, 10 in Poland, 16 in Romania, 6 in Serbia, 10 in Slovakia, 26 in Spain, and 34 in United Kingdom]), and 192 centers in the Rest of World [9 in Australia, 22 in China, 17 in India, 26 in Japan, 16 in Malaysia, 6 in New Zealand, 10 in the Philippines, 20 in Russia, 14 in South Africa, 15 in South Korea, 8 in Taiwan, 28 in Ukraine, and 1 in United Arab Emirates]


**Study Period:** 21 February 2014 (Date first subject signed informed consent) to 30 October 2018 (Date of last observation for last subject recorded as part of the database)

**Phase of Development:** 3

Status: Approved, Date: 8 March 2019
Objectives:

Primary Objectives
In subjects with T2DM, Stage 2 or 3 chronic kidney disease (CKD) and macroalbuminuria who were receiving standard of care, to assess the efficacy of canagliflozin relative to placebo in reducing the composite endpoint of doubling of serum creatinine, end-stage kidney disease (ESKD), and renal or CV death.

Secondary Objectives
In subjects with T2DM, Stage 2 or 3 CKD and macroalbuminuria who were receiving standard of care, to assess the efficacy of canagliflozin relative to placebo in reducing:

- The composite endpoint of CV death and hospitalized heart failure
- The composite endpoint of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke (ie, 3-point major adverse cardiovascular events [MACE])
- Hospitalized heart failure
- The renal composite endpoint of doubling of serum creatinine, ESKD, and renal death
- CV death
- All-cause death
- The CV composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalized heart failure, and hospitalized unstable angina

Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group, 2-arm study conducted at multiple sites worldwide that evaluated the effects of canagliflozin relative to placebo on progression to doubling of serum creatinine, ESKD, renal or CV death in subjects with T2DM, Stage 2 or 3 CKD and macroalbuminuria, who were receiving standard of care including a maximum tolerated labeled daily dose of an ACEi or ARB.

Subjects meeting all inclusion and none of the exclusion criteria, and successfully completing the 2-week run-in period were randomly allocated to either canagliflozin 100 mg or matching placebo in a 1:1 ratio. The target number of primary efficacy events was to occur in 844 unique randomized subjects, after which the global trial end date (GTED) was to be announced.

Several monitoring and adjudication committees were commissioned for this study, including an Academic Research Organization (ARO), a Steering Committee of external scientific experts, an internal Medical Safety Review Committee (MSRC), an Independent Data Monitoring Committee (IDMC), an Independent Endpoint Adjudication Committee (EAC) (which adjudicated all renal and CV events that were components in the primary and secondary composite endpoints in this study), and separate adjudication committees, which reviewed cases of potential pancreatitis, fracture, diabetic ketoacidosis (DKA), and renal cell carcinoma events.

Number of Subjects (planned and analyzed): As an event-driven study, a total of approximately 4,200 subjects were planned for recruitment. A total of 4,401 subjects were randomized, with 2,199 and 2,202 subjects assigned to placebo and canagliflozin 100 mg, respectively. Four randomized subjects (2 in each treatment group) did not receive study drug and were therefore excluded from the On-treatment and On-study analysis sets (4,397 subjects); however, the 4 subjects were included in the ITT analysis set (4,401 subjects).
Summary of Analysis Sets

<table>
<thead>
<tr>
<th>Analysis Set</th>
<th>Analysis Population</th>
<th>Data Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat</td>
<td>Randomized subjects</td>
<td>Day 1 to the last study contact date up to the GTEDa</td>
</tr>
<tr>
<td>On-study</td>
<td>Treated subjects</td>
<td>Day 1 to the last study contact date up to the GTEDa</td>
</tr>
<tr>
<td>On-treatment</td>
<td>Treated subjects</td>
<td>Day 1 to the last dose date plus Xb days or the last</td>
</tr>
<tr>
<td></td>
<td></td>
<td>study contact date, whichever was earlier</td>
</tr>
</tbody>
</table>

a For each subject, data collected up to the final visit was used for analysis. If the final visit could not be arranged, the reported data such as public search of mortality was bounded by the GTED.

b X is 2 days for laboratory and vital sign measurements, and 30 days for adverse events, CV, renal, and mortality endpoints.

Diagnosis and Main Criteria for Inclusion:

Men and women ≥30 years-old with a clinical diagnosis of T2DM, HbA1c ≥6.5% to ≤12.0%, eGFR ≥30 to <90 mL/min/1.73 m² (as determined using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation), urinary albumin-to-creatinine ratio (ACR) >300 mg/g to ≤5,000 mg/g (>33.9 mg/mmol to ≤565.6 mg/mmol), on a stable maximum tolerated labeled daily dose of ACEi or ARB for at least 4 weeks prior to randomization were eligible for this study.

Test Product, Dose and Mode of Administration, Batch No.: Batches to be added

Reference Therapy, Dose and Mode of Administration, Batch No.: Batches to be added

Duration of Treatment: The total study duration was planned to be 5 to 5.5 years, including a subject accrual phase of approximately 2 to 2.5 years. Subjects were expected to be followed for approximately 4.5 years on average. An interim analysis was planned when the mean duration of follow-up was at least 2 years and approximately 405 subjects had experienced an adjudicated primary composite endpoint, as confirmed by the Endpoint Adjudication Committee (EAC). An Independent Data Monitoring Committee (IDMC) was to review the results of the planned interim analysis and make a recommendation whether the study should be continued as planned, modified, or terminated prematurely due to efficacy, futility, or safety reasons. The interim analysis was conducted as planned on 09 July 2018, with 413 subjects having experienced a primary composite endpoint, as confirmed by the EAC. Based on the predefined stopping rules, the IDMC recommended to stop the study early, as the efficacy objectives specified in the IDMC charter were met. As a result, the GTED period was announced on 16 July 2018 and final visits conducted. A total of 585 primary composite endpoints were accrued through the end of the GTED on 30 October 2018.

Criteria for Evaluation:

Efficacy: The primary measure of efficacy was the composite of the time to first occurrence of doubling of serum creatinine, ESKD, and renal or cardiovascular (CV) death. Secondary measures of efficacy in the prespecified hierarchical hypothesis testing sequence were the composite of CV death and hospitalized heart failure; the composite of CV death, nonfatal MI, and nonfatal stroke (ie, 3-point MACE); hospitalized heart failure; renal composite of ESKD, doubling of serum creatinine, and renal death; CV death; all-cause death; and the CV composite of CV death, nonfatal MI, nonfatal stroke, hospitalized heart failure, and hospitalized unstable angina.

Safety: Safety was evaluated based on the following variables: adverse events, hypoglycemic episodes (as collected in a specific eCRF), safety laboratory tests (hematology, serum chemistry, urinalysis), and vital sign measurements (blood pressure and pulse rate), and 12-lead electrocardiograms (ECGs).
Statistical Methods:

Study Hypotheses: The primary hypothesis of the study was that canagliflozin reduces the risk of the composite endpoint of doubling of serum creatinine, ESKD, and renal or CV death, relative to placebo, in subjects with T2DM, Stage 2 or 3 CKD and macroalbuminuria, who were receiving standard of care including a maximum tolerated labeled daily dose of an ACEi or ARB.

Efficacy Analyses: The primary analysis was based on the ITT analysis set from study Day 1 up to the GTED. The comparison of canagliflozin versus placebo for the primary efficacy endpoint was analyzed using a stratified Cox proportional hazards model including treatment, with stratification of the baseline hazard by screening eGFR ($\geq 30$ to $<45$, $\geq 45$ to $<60$, $\geq 60$ to $<90\ \text{mL/min/1.73 m}^2$). The study was powered at 90% to detect a relative risk reduction of 20% in the primary composite endpoint at a 2-sided significance level of 0.05. This included a planned interim analysis using a 2-sided significance level of 0.01 (as determined by the alpha spending function), and if the study was not stopped at the interim, the primary composite endpoint would have been tested at a 2-sided significance level of 0.045 in the final analysis.

As the IDMC recommended early study termination due to efficacy, the primary composite endpoint was tested after the final study visit for the last subject who completed the study, with a 2-sided significance level of 0.022, based on the alpha spending function. Estimates of the relative risk reduction (RRR) (defined as 1 minus the hazard ratio [HR]), the HR and corresponding 95% confidence intervals (CIs) were provided.

Time from study Day 1 to the first occurrence of a major secondary efficacy endpoint was analyzed using the same approach as the primary analysis based on the ITT analysis set.

A closed testing procedure was implemented to control the family-wise Type I error for the primary and secondary endpoints. Testing of the major secondary efficacy endpoints was performed using a 2-sided alpha level of 0.038.

Safety Analyses: Treatment-emergent safety analyses and summaries were based on the On-treatment analysis set (unless otherwise specified). There was no imputation of missing values for clinical laboratory test results and vital sign measurements in the safety analyses, and there was no hypothesis testing for results from safety analyses.

The study objective regarding safety and tolerability was assessed based upon a review of the incidence of all adverse events, as well as laboratory results, and other safety and tolerability measurements.

RESULTS:

STUDY POPULATION:

Subject Disposition and Study Completion/Withdrawal Information: A total of 12,900 subjects were prescreened, of those, 8,932 were screened, and a total of 4,401 subjects were randomized, with 2,199 and 2,202 subjects assigned to placebo and canagliflozin 100 mg, respectively. Four randomized subjects (2 in each treatment group) did not receive study drug and were therefore excluded from the On-treatment and On-study analysis sets; however, the 4 subjects were included in the ITT analysis set.

A subject was considered as having completed the study, regardless of whether the subject was on or off study drug, if after randomization the subject was followed until a time point after the notification of the GTED or until the time of death for subjects who died prior to the GTED notification. Study completion information and vital status are summarized in the table below. The proportion of subjects who completed the study (99.1%) and the proportion with known final vital status (99.9%) were comparable in both treatment groups.

Status: Approved, Date: 8 March 2019
Approximately 70% of placebo-treated subjects and 75% of canagliflozin-treated subjects completed the study on study drug. The primary reasons for not completing the study in both treatment groups were lost to follow-up (0.5%) and withdrawal of consent (0.4%).

**Demographic and Baseline Characteristics:** Baseline demographic, anthropometric, and disease history characteristics were generally similar between treatment groups. The median age of subjects was 64 years, with a mean HbA1c of 8.27%, and mean duration of diabetes of 16 years. The mean eGFR at baseline was 56.2 mL/min/1.73 m² with approximately 60% of the population having a baseline eGFR of <60.0 mL/min/1.73 m². The mean urinary ACR level was 1,381 mg/g, and 46.6% of subjects had a urinary ACR level >1,000 mg/g. In addition, the proportion of subjects with prior CV disease was 50.4%; 14.8% had a history of heart failure; 5.3% had a history of amputation. While the entire study population had nephropathy at baseline, 64% of the population had at least 2 microvascular complications (ie, diabetic retinopathy and/or neuropathy in addition to diabetic nephropathy).

**Duration of Exposure to Study Drug:** The total exposure of subjects to study drug was 9,658.4 subject-years, with 4,915.8 and 4,742.6 subject-years in the canagliflozin and placebo groups, respectively. The mean duration of exposure to study drug was 114.62 weeks (116.59 and 112.64 weeks for canagliflozin and placebo, respectively), with 40.6% of all subjects having more than 130 weeks of exposure.

**Duration of Study:** The total duration of time that subjects were followed in the study (on or off study drug) was 11,490.6 subject-years, with 5,768.8 and 5,721.8 subject-years in the canagliflozin and placebo groups, respectively. The mean duration of follow-up of all subjects (on and off study drug) was 136.23 weeks, with comparable study durations between the canagliflozin and placebo groups.

**Efficacy Results:**

**Primary Efficacy Analysis:** Canagliflozin significantly reduced the risk of the primary composite endpoint compared with placebo by 30% (HR: 0.70, 95% CI: 0.59, 0.82, p-value <0.0001), thereby successfully meeting the primary objective of the study. The observed risk reduction was similarly favorable for all individual components of the primary composite endpoint as shown in the table below. The treatment effect was consistent across prespecified subgroups, including subgroups with different degrees of renal impairment and different degrees of albuminuria at baseline.
Analysis of the Primary Composite Endpoint Including the Individual Components
(Study 28431754-DNE3001: Intent-To-Treat Analysis Set)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>n/N(%)</th>
<th>EVRT[a]</th>
<th>n/N(%)</th>
<th>EVRT[a]</th>
<th>HR[b] (95% CI)</th>
<th>P-value[b]</th>
<th>PH P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite Endpoint</td>
<td>340/2199 (15.5)</td>
<td>61.24</td>
<td>245/2202 (11.1)</td>
<td>43.21</td>
<td>0.70 (0.59, 0.82)</td>
<td>&lt;0.0001</td>
<td>0.3116</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Doubling of Serum Creatinine</td>
<td>188/2199 (8.5)</td>
<td>33.78</td>
<td>118/2202 (5.4)</td>
<td>20.73</td>
<td>0.60 (0.48, 0.76)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>ESKD</td>
<td>165/2199 (7.5)</td>
<td>29.44</td>
<td>116/2202 (5.3)</td>
<td>20.37</td>
<td>0.68 (0.54, 0.86)</td>
<td>0.0015</td>
<td>0.0014</td>
<td></td>
</tr>
<tr>
<td>Renal Death</td>
<td>5/2199 (0.2)</td>
<td>0.87</td>
<td>2/2202 (0.1)</td>
<td>0.35</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td>140/2199 (6.4)</td>
<td>24.38</td>
<td>110/2202 (5.0)</td>
<td>19.01</td>
<td>0.78 (0.61, 1.00)</td>
<td>0.0502</td>
<td>0.0496</td>
<td></td>
</tr>
</tbody>
</table>

Note: [a] Event rate per 1000 patient-years.
Note: [b] Hazard ratio (canagliflozin compared to placebo), 95% CI and p-value are estimated using a stratified Cox proportional hazards model including treatment as the explanatory variable, and stratified by screening eGFR (≥ 30 to <45, ≥ 45 to <60, ≥ 60 to <90 mL/min/1.73m²).
Note: [c] Log-Rank Test stratified by screening eGFR (≥ 30 to <45, ≥ 45 to <60, ≥ 60 to <90 mL/min/1.73m²) is provided as a supportive analysis.
Note: P-value for testing proportional hazards (PH) is evaluated by including the interaction term of treatment and logarithm transformed time into the model for the primary analysis.
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Secondary Efficacy Analysis: Canagliflozin significantly reduced the risk of the following endpoints compared with placebo:

- Composite endpoint of CV death and hospitalized heart failure by 31% (HR: 0.69; 95% CI: 0.57, 0.83; p=0.0001)
- MACE (comprised of nonfatal MI, nonfatal stroke and CV death) by 20% (HR: 0.80; 95% CI: 0.67, 0.95; p=0.0121)
- Hospitalized heart failure by 39% (HR: 0.61; 95% CI: 0.47, 0.80; p=0.0003)
- Renal composite endpoint (comprised of doubling of serum creatinine, ESKD, and renal death) by 34% (HR: 0.66; 95% CI: 0.53, 0.81; p<0.0001)

The RRR of 22% for the secondary endpoint of CV death did not attain statistical significance; therefore, the 2 remaining secondary endpoints in the hierarchical testing sequence could not be formally tested and the p-values associated with these endpoints are considered nominal. Nevertheless, results for the subsequent secondary endpoints of all-cause mortality and expanded CV composite (comprised of CV death, nonfatal MI, nonfatal stroke, hospitalized heart failure, and hospitalization for unstable angina) showed that canagliflozin numerically reduced the risk of these endpoints relative to placebo by 17% and 26%, respectively.

SAFETY RESULTS:

Adverse Events

The incidence rate of any adverse events was lower in subjects receiving canagliflozin than placebo, as shown in the table below, with an incidence rate difference (per 1,000 subject-years) of -27.88 (95% CI: -51.62, -4.15). The incidence rates for adverse events leading to study drug discontinuation were similar between treatment groups, with an incidence rate difference of -5.73 (95% CI: -14.99, 3.53). The incidence rate for serious adverse events was also lower in subjects receiving canagliflozin than placebo, with an incidence rate difference of -19.19 (95% CI: -34.64, -3.73). Adverse events with fatal outcome were comparable between treatment groups, with an incidence rate difference of -3.41 (95% CI: -9.41, 2.60).

Status: Approved, Date: 8 March 2019
Adverse events observed in this study were consistent with the known profile of canagliflozin. Treatment with canagliflozin in this study was not associated with an increased risk for amputation (incidence rate difference of 1.16 [95% CI: -2.87, 5.18]), fracture (incidence rate difference of -0.29 [95% CI: -4.35, 3.77]), neoplasms (1.53 [95% CI: -4.26, 7.33]), renal-related adverse events (incidence rate difference of -22.00 [95% CI: -32.27, -11.73]), adjudicated pancreatitis adverse events (incidence rate difference of 0.58 [95% CI: -0.68; 1.83]), or hypoglycemia (incidence rate difference of -4.62 [95% CI: -13.12, 3.88]). The incidence of adjudicated DKA adverse events was 2.17 and 0.20 per 1,000 subject-years in the canagliflozin and placebo groups, respectively, with an incidence rate difference of 1.96 (95% CI: 0.51, 3.42).

There were no new adverse drug reactions identified in this study.

Safety Laboratory Assessments

Protocol-specified safety laboratory analyte parameters were evaluated based on review of summary statistics for mean changes over time and by assessing the incidence of safety laboratory analyte measurements meeting predefined limits of change (PDLC) criteria. In general, changes in serum chemistry values from baseline to end of treatment were small to moderate in magnitude and consistent with the known effects of canagliflozin.

Consistent with previous clinical experience, a higher proportion of subjects in the canagliflozin group compared with the placebo group had an elevation in serum magnesium that exceeded the PDLC (greater than the upper limit of normal [ULN] and >25% increase from baseline) (2.1% vs 0.6%, respectively), with the 95% CI for the comparison excluding 0 (0.79, 2.23). Of note, for the analytes of bicarbonate, calcium, sodium, creatine kinase, phosphate and urate, the number of subjects who met the PDLC of each specific analyte was balanced between the 2 treatment groups, with the 95% CIs for the treatment group comparisons including 0.

For adverse events of hyperkalemia, the incidence rates in the canagliflozin group were not increased compared with the placebo group, overall or in any eGFR stratum.
The percentages of subjects with any postbaseline elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) meeting thresholds of >3x ULN, >5x ULN, >8x ULN were small and similar for the 2 treatment groups, with all 95% CIs for the comparisons including 0. No subject in the canagliflozin group (compared with 4 subjects in the placebo group) met the laboratory criteria for Hy’s Law of a postbaseline ALT or AST value >3x ULN and a postbaseline bilirubin value >2x ULN.

More subjects in the canagliflozin group experienced a hemoglobin increase of ≥20 g/L for any postbaseline value and for the last postbaseline value.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSION(S):

☐ In subjects with T2DM, Stage 2 or 3 CKD (eGFR ≥30 to <90 mL/min/1.73 m²), and macroalbuminuria (urinary ACR >300 to ≤5,000 mg/g [≥33.9 to ≤565.6 mg/mmol]) who were receiving standard of care, canagliflozin reduced the rate of the composite endpoint of doubling of serum creatinine, ESKD and renal or CV death. Furthermore, all components of the primary composite endpoint contributed to the finding of significant benefit for canagliflozin above that seen in the placebo group.

☐ In subjects with T2DM, Stage 2 or 3 CKD and macroalbuminuria, who were receiving standard of care, canagliflozin reduced the rate of the composite endpoint of CV death and hospitalized heart failure, MACE, hospitalized heart failure alone, and the composite endpoint of doubling of serum creatinine, ESKD, and renal death.

☐ In subjects with T2DM, Stage 2 or 3 CKD and macroalbuminuria, who were receiving standard of care, canagliflozin reduced the rate of the composite endpoint of ESKD and renal or CV death.

☐ Safety findings were consistent with the known safety profile of canagliflozin, with no increase in amputation, fracture, or renal cell carcinoma risk. No new adverse drug reactions were identified in the study.