

Inclusion and Exclusion Criteria

Inclusion Criteria at Screening Visit

1. Man or woman ≥ 30 years-old with a clinical diagnosis of type 2 diabetes mellitus (T2DM).
2. Glycated hemoglobin (HbA1c) $\geq 6.5\%$ to $\leq 12.0\%$, ($\geq 6.5\%$ to $\leq 10.5\%$ in Germany).
3. Estimated glomerular filtration rate (eGFR) ≥ 30 to < 90 mL/min/1.73 m² (as determined using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation).

Note: An overall global target ratio for randomized cohort of approximately 60%:40% for CKD Stage 3 (i.e., eGFR ≥ 30 to < 60 mL/min/1.73 m²; first category):CKD Stage 2 (i.e., eGFR ≥ 60 to < 90 mL/min/1.73 m²; second category) will be monitored centrally. In an effort to limit exposure to investigational product and to ensure sufficient experiences in subjects with Stage 3 CKD, entry of subjects with Stage 2 CKD (i.e., eGFR ≥ 60 to < 90 mL/min/1.73 m²) may be restricted on a regional and/or site basis should the ratio drift substantially off target over the course of the recruitment period.

4. Urinary albumin:creatinine ratio (UACR) > 300 mg/g to ≤ 5000 mg/g (> 33.9 mg/mmol to ≤ 565.6 mg/mmol).
5. All subjects must be on a stable maximum tolerated labeled daily dose of ACEi or ARB for at least 4 weeks prior to randomization.

Note: A maximum tolerated labeled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) is defined as the maximum approved labeled dose for diabetic nephropathy (for agents with an approved indication for diabetic nephropathy in patients with T2DM, i.e., losartan and irbesartan) or the maximum approved dose for hypertension (for agents without an approved indication for diabetic nephropathy), unless side effects or adverse events limit the use of the maximum approved dose. For subjects who are not

on a maximum labeled daily dose of an ACEi or ARB, investigators will be required to document why a higher dose should not be used.

6. Women must be:

- postmenopausal, defined as
 - >45 years of age with amenorrhea for at least 18 months, or
 - >45 years of age with amenorrhea for at least 6 months and <18 months and a serum follicle stimulating hormone (FSH) level >40 IU/L, or
- surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal occlusion [which includes tubal ligation procedures as consistent with local regulations]), or otherwise be incapable of pregnancy, or
- heterosexually active and practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (e.g., condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, and consistent with local regulations regarding use of birth control methods for subjects participating in clinical studies, for the duration of their participation in the study, or
- not heterosexually active.

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

7. Women of childbearing potential (i.e., those subjects who do not meet the postmenopausal definition above), regardless of age, must have a negative urine pregnancy test at baseline (Day 1) and at screening if required by local regulations.

Note: A serum pregnancy test is acceptable in lieu of a urine pregnancy test if required by local regulations.

8. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.
9. Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study. Each subject must also sign a separate informed consent form if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a subject from participation in the study.

Inclusion Criterion for Randomization

10. Subjects must have $\geq 80\%$ compliance (by pill count) with single-blind placebo.

Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

Diabetes-related/Metabolic

1. History of diabetic ketoacidosis or type 1 diabetes mellitus (T1DM).
2. History of hereditary glucose-galactose malabsorption or primary renal glucosuria.

Renal/Cardiovascular

3. Known medical history or clinical evidence suggesting nondiabetic renal disease.
4. Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant.

Note: Subjects with a history of treated childhood renal disease, without sequelae, may participate.

5. Uncontrolled hypertension (systolic blood pressure [BP] ≥ 180 and/or diastolic BP ≥ 100 mmHg) by Week -2.

Note: Subjects not fulfilling BP criteria at the initial screening visit may have their BP-lowering medication regimen adjusted, followed by re-evaluation up to the Week -2 run-in period (the ACEi or ARB regimen must be stable for at least 4 weeks before Day 1 to be eligible).

6. Blood potassium level >5.5 mmol/L during screening.

Note: Subjects in whom hyperkalemia was associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), β -blockers, or mineralocorticoid receptor antagonists (MRAs; e.g., spironolactone or eplerenone), who have been withdrawn from these drugs, and in whom usage of these drugs is not indicated in the view of the treating physician, may be included in the study.

7. Myocardial infarction, unstable angina, revascularization procedure (e.g., stent or bypass graft surgery), or cerebrovascular accident within 12 weeks before randomization, or a revascularization procedure is planned during the trial.

8. Current or history of heart failure of New York Heart Association (NYHA) class IV cardiac disease (The Criteria Committee of the NYHA).

9. Electrocardiogram (ECG) findings within 12 weeks before randomization that would require urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance).

Gastrointestinal

10. Known significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis).

Laboratory

11. Alanine aminotransferase (ALT) levels >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease.

Other Conditions

12. History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).

13. History of human immunodeficiency virus (HIV) antibody positive.

14. Major surgery within 12 weeks before randomization, or has not fully recovered from surgery.

15. Any condition that in the opinion of the investigator or sponsor's medical monitor would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified assessments.

16. 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 of screening (added May 5, 2016).

Medications/Therapies

17. Combination use of an ACEi and ARB.

18. Use of an MRA or a direct renin inhibitor (DRI).

Note: If deemed clinically appropriate at the discretion of the investigator, subjects may be removed from therapy with an MRA or DRI during screening. Subjects who are off therapy with an MRA or DRI for at least 8 weeks prior to randomization may be considered eligible for enrollment.

19. Current use of a sodium glucose co-transporter 2 (SGLT2) inhibitor (within 12 weeks prior to randomization).

20. Current participation in another canagliflozin study or previously exposed to canagliflozin in a prior canagliflozin study.

21. Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients.

22. Received an active investigational drug (including vaccines) other than a placebo agent, or used an investigational medical device within 12 weeks before Day 1/baseline.

General

23. Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study.

24. Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.

Note: Investigators should ensure that all study enrollment criteria have been met and determine that the subject has not had any interval change in clinical status since the time of the initial screening visit.

Before randomization, subjects whose clinical status changes after screening such that they now meet an exclusion criterion should be excluded from participation.