SYNOPSIS CANA/PHEN IN T2DM OVERWEIGHT AND OBESE SUBJECTS

A Randomized, Double-Blind, Parallel-Group 104-Week Study to Investigate the Safety and Efficacy of the Co-administration of Canagliflozin and Phentermine Compared With Placebo for the Treatment of Overweight and Obese Subjects With Type 2 Diabetes Mellitus

Canagliflozin (INVOKANA®) is a potent inhibitor of the renal sodium glucose co-transporter 2 (SGLT2) approved as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus (T2DM). In a Phase 2 study (OBE2002) of 26 weeks in nondiabetic overweight or obese subjects, the co-administration of canagliflozin 300 mg and phentermine 15 mg achieved a placebo-subtracted weight loss of -6.9% (p<0.001), while canagliflozin 300mg and phentermine 15 mg monotherapies achieved a placebo-subtracted weight loss of –1.3 and -3.5%, respectively.

OVERVIEW OF STUDY DESIGN

The current study is being conducted to investigate if the co-administration of canagliflozin and phentermine decreases body weight in overweight or obese subjects with Type 2 Diabetes Mellitus. Approximately 1,800 overweight or obese subjects with T2DM, 18 years of age and older, who have a BMI ≥27 kg/m² at screening are eligible to participate. Subjects will be randomly assigned to 1 of 5 treatment arms, as shown in the table below. Subject must (1) not currently be on AHA therapy, or (2) on a stable regimen of any approved AHA(s) in monotherapy or combination therapy used in accordance with local prescribing information.

<table>
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<th>Treatment arms</th>
<th>Baseline to Week 52</th>
<th>Week 53 to Week 104</th>
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<tbody>
<tr>
<td>1</td>
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<td>Randomized 1:1 to Placebo or canagliflozin 300 mg/phentermine 15mg*</td>
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<tr>
<td>2</td>
<td>Canagliflozin 300 mg/phentermine 15 mg</td>
<td>Canagliflozin 300 mg/phentermine 15 mg</td>
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<td>Canagliflozin 100 mg/phentermine 7.5 mg</td>
<td>Canagliflozin 100 mg/phentermine 7.5 mg</td>
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</table>

*For those subjects who have not discontinued study drug prior to Week 52.

At Week 52, placebo subjects in Treatment Arm 1 will be re-randomized to continue on placebo or switch to canagliflozin 300 mg/phentermine 15 mg. Subjects in the 4 combination treatment arms (ie, Treatment Arms 2, 3, 4, and 5) will remain on their respective treatment combinations through the remainder of the study as shown in figure 1. There are 3 sub-studies within the main study. Randomly selected subjects will participate in 1 of the 3 sub-studies, as selected sites.

Body Composition Substudy (n=350)
- At the baseline (Day 1), Week 24 and Week 52 visits changes in total fat and lean body mass, visceral and subcutaneous abdominal fat, and changes in hepatic fat content will be assessed.

Insulin Sensitivity and Beta-cell Function Substudy (n=250)
- After 52 weeks of treatment, approximately 250 subjects naive to AHA or currently treated with metformin will have insulin sensitivity and beta-cell function assessed.

Ambulatory Blood Pressure Monitoring Substudy (n=400)
- After 52 weeks of treatment, approximately 400 subjects will have systolic and diastolic blood pressure, and heart rate assessed via 24-hour ABPM.
Background Diabetes Therapy

Subjects on background AHA therapy with approved agents used in accordance with local prescribing information are eligible to participate if they meet all enrollment criteria.

During the 104-week double-blind treatment period, subjects should remain on a stable AHA regimen (agents and dosages) unless (1) down-titration or discontinuation of the AHA is considered clinically necessary to treat or avoid hypoglycemia, or to manage another safety or tolerability concern, (2) glycemic rescue therapy criteria are met, or (3) the subject has a change in their clinical status such that the dosage or use of the AHA is no longer consistent with prescribing guidelines (ie, per the local label). The reason for the change in background AHA therapy should be recorded in the eCRF. The study drug will not be up- or down-titrated.
Efficacy Evaluations

Endpoints

Primary Endpoint
The primary efficacy endpoint is the percent change in body weight from baseline to Week 52.

Secondary Endpoints
The key secondary measures of efficacy include proportion of subjects who lost at least 5% of their baseline body weight, proportion of subjects who lost at least 10% of their baseline body weight, HbA1c, change in IWQOL-Lite physical function, and CHES-Q physical health satisfaction scores, FPG, proportion of subjects with HbA1c <7.0% and change in SBP, at Week 52.

Exploratory Endpoints
Exploratory efficacy endpoints include the following measures over time:

- IWQOL-Lite Total and self-esteem, sexual life, public distress, and work domain scores
- CHES-Q emotional health satisfaction score
- PAM total score
- WPAI total score and individual items.

Substudy Endpoints

Body Composition Substudy
At the baseline (Day 1), Week 24 and Week 52 visits, a subset of approximately 350 subjects in the placebo and combination treatment groups will undergo:

- DEXA to investigate changes in total fat and lean body mass,
- Single slice abdominal CT at L4-L5 to assess changes in visceral and subcutaneous abdominal fat, and
- CT attenuation liver-to-spleen to evaluate changes in hepatic fat content.

Insulin Sensitivity and Beta-cell Function Substudy
After 52 weeks of treatment, in a subset of approximately 250 subjects naive to AHA or currently treated with metformin and who undergo a MMTT, the following endpoints will be evaluated:

Measures of insulin secretion (including AUC C-peptide/AUC glucose, and model-based parameters of beta-cell function)

- Insulin sensitivity estimated from the OGIS index corrected for UGE
- AUC-3h for plasma glucose
- Incremental AUC-3h for plasma glucose (defined as the positive area under the plasma glucose curve and above the pre-meal plasma glucose concentration)

Ambulatory Blood Pressure Monitoring Substudy
After 52 weeks of treatment, in a subset of approximately 400 subjects, the effect of the co-administration of canagliflozin and phentermine compared with placebo on the following endpoints will be evaluated by 24-hour ABPM:

Primary Substudy Endpoint
- 24-hour SBP

Secondary Substudy Endpoints
- 24-hour DBP and HR

PHARMACOKINETIC EVALUATIONS
Venous blood samples will be collected for determination of plasma trough concentrations of canagliflozin and phentermine in approximately 50% of randomized subjects. All subjects from selected study centers will have plasma samples collected per the time points specified in the Time and Events Schedule.

PHARMACOGENOMIC (DNA) AND BIOMARKER EVALUATIONS
A 10-mL pharmacogenomics (DNA) blood sample will be collected (where local regulations permit) at baseline, and fasting plasma, serum, and urine archive samples will be collected at baseline, Week 52 and Week 104, and could be used to assist in understanding mechanisms underlying the efficacy and safety findings in this study. Samples may also be used for future exploratory research to improve understanding of the pathophysiology of T2DM or obesity.

Subjects participation in the pharmacogenomics analysis is optional.

SAFETY EVALUATIONS
Safety evaluations, according to the time points provided in the Time and Events Schedule, will include the monitoring of all adverse events (including the use of PHQ-9 and C-SSRS questionnaires), vital signs measurements (SBP, DBP, HR, and RPP), clinical laboratory tests (including chemistry, hematology), pregnancy testing, lipid panel, FSH, physical examinations, body weight, SMBG, and collection of potential hypoglycemic episodes (eg, from the subject diary provided to subjects).

Major adverse CV events (MACE, defined as CV death, nonfatal MI, nonfatal stroke) and DKA and DKA-related events will be collected and adjudicated through the Week 104/end-of-treatment (EOT)/Early Withdrawal visit unless the subject is lost to follow-up.

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

SELECTION CRITERIA
Inclusion Criteria
1. A signed informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study. Each subject must also sign a separate ICF if he or she agrees to provide optional exploratory samples for research (where local regulations permit). Refusal to give consent for the optional exploratory samples does not exclude a subject from participation in the study.
2. Male or female ≥18 years of age at the screening visit with T2DM.
3. BMI ≥27 kg/m² at the screening visit.
4. An HbA₁c of ≥7.0% to ≤10.5% as determined by the central laboratory at the screening visit.
5. Stable weight (ie, change of ≤5% within 12 weeks before screening based on medical history).
6. Women must be either:
   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
   - permanently sterilized (eg, bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations]), hysterectomy or bilateral salpingectomy, bilateral oophorectomy; or otherwise be incapable of pregnancy, or
   - heterosexually active and practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly)
   - not heterosexually active (ie, woman agrees to refrain from heterosexual intercourse during the entire period of risk associated with the study drug)
7. Women of childbearing potential (ie, those subjects who do not meet the postmenopausal definition in the Inclusion Criteria above, regardless of age) must have a negative highly sensitive serum B-human chorionic gonadotropin (B-hCG) pregnancy test at baseline (Day 1).
8. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

Exclusion Criteria

Diabetes-Related/Metabolic
1. History of obesity with a known secondary cause (eg, Cushing’s disease/syndrome).
2. History of Type 1 diabetes mellitus (T1DM), DKA, pancreas or β-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy.
3. Fasting C-peptide <0.7 ng/mL (0.23 nmol/L) at screening visit.
4. History of hereditary glucose-galactose malabsorption or primary renal glycosuria.
5. Ongoing, inadequately controlled thyroid disorder as assessed by the investigator’s review of the subject’s medical history. Subjects taking thyroid hormone replacement therapy must be on stable doses for at least 6 weeks before the screening visit.

Renal/Cardiovascular
6. Myocardial infarction, unstable angina, revascularization procedure (eg, stent or bypass graft surgery), or cerebrovascular accident within 12 weeks before the screening visit, or if a revascularization procedure is planned during the trial.
7. Heart failure based on the New York Heart Association (NYHA) Class II-IV cardiac disease (The Criteria Committee of the NYHA) within 12 weeks of the screening visit (refer to Error! Reference source not found., NYHA Classification of Cardiac Disease).
8. Findings on 12-lead electrocardiogram (ECG) at the screening visit that would require urgent diagnostic evaluation or intervention.
9. An average of 3 seated blood pressure readings of SBP ≥160 mm Hg and/or DBP ≥100 mm Hg at the screening visit (see Error! Reference source not found., Method of Blood Pressure Measurement).

Gastrointestinal

10. Clinically active liver disease (eg, acute hepatitis, chronic active hepatitis, cirrhosis).

11. History of bariatric surgical procedure within 5 years before the screening visit.

Laboratory

12. Subject has an eGFR of <60 mL/min/1.73 m² at the screening visit using the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula (refer to Error! Reference source not found., Clinical Laboratory Tests).

   Note: a one-time repeat measurement is allowed, at the discretion of the investigator, if the value eGFR is not consistent with prior values.

13. Alanine aminotransferase level >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN at the screening visit (for elevations in bilirubin: if, in the opinion of the investigator and agreed upon by the Sponsor’s medical officer, the elevation in bilirubin is consistent with Gilbert’s disease, the subject may participate).

Other conditions

14. History of malignancy within 5 years before the screening visit (exceptions: squamous or basal cell carcinomas of the skin, carcinomas in situ of the cervix, or a malignancy that in the opinion of the investigator, with concurrence with the Sponsor’s medical monitor, are considered cured with minimal risk of recurrence).

15. History of a clinically significant eating disorder (eg, anorexia nervosa, bulimia, or binge-eating) within 3 years before the screening visit.

16. Major surgery (eg, requiring general anesthesia) within 12 weeks before the screening visit, or has not fully recovered from surgery, or planned surgery during the participation of the current study.

17. History of atraumatic amputation within past 12 months of screening, or a lower extremity skin ulcer requiring oral or parental antibiotic therapy, or osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening.

Medications/Therapies

18. Current or past participation in a study with canagliflozin, phentermine or phentermine containing combination therapies.

19. Known allergies, hypersensitivity, or intolerance to excipients of cangliflozin and phentermine.

20. Treatment with prescription (including but not limited to orlistat, lorcaserin, naltrexone/bupropion [or its individual components], liraglutide 3 mg (Saxenda), topiramate/phentermine. [or its individual components]) or over-the-counter weight loss medications or therapies within 12 weeks before the screening visit or is planning to initiate non-study-related weight loss treatment during the study which is not following the Standardized Non-Pharmacologic Weight Reduction Therapy provided by the Sponsor.

21. Use of the following medications within 12 weeks before the screening visit:
   - Oral, IV, or IM corticosteroids, or likely to require treatment with an oral, IV, or IM corticosteroid (for longer than 2 consecutive weeks in duration)
Note: Subjects using inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses may participate

- Antipsychotic drugs
- SGLT2 inhibitors
- Anticonvulsants, including barbiturates, GABA analogues, hydantoins, phenyltriazines, succinimides, valproic acid and its derivatives, carbamazepine, zonisamide, and felbamate
- Tricyclic antidepressants, lithium, levodopa, and dopamine receptor agonists
- Highly Active Anti-Retroviral Therapy.

22. Use of selective serotonin reuptake inhibitors (including but not limited to fluoxetine, sertraline, paroxetine, escitalopram, citalopram, dapoxetine, seproxetine, zimelidine, mesembrine, reboxetine) and serotonin-norepinephrine reuptake inhibitors (including but not limited to venlafaxine, duloxetine, desvenlafaxine, milnacipran, fluvoxamine) that has not been stable for at least 12 weeks prior to the screening visit.

23. Treatment with a loop diuretic at the screening visit or anticipated to require loop diuretic use during the course of the study.

24. Received an investigational drug (including investigational vaccines), other than a placebo agent, or used an investigational medical device within 12 weeks prior to the screening visit.

Psychiatric-Related

25. Any history of major depressive disorder within the last 2 years.

26. Any history of other severe psychiatric disorders (eg, schizophrenia, bipolar disorder, etc.).

27. Any lifetime history of suicide attempt.

28. Any suicidal ideation of severity 4 or 5 or any suicidal behavior on the Columbia Suicide Severity Rating Scale (C-SSRS) in the last month.

29. Patient Health Questionnaire 9 (PHQ-9) score ≥15 (indicative of at least moderately severe depression at baseline).

Note: Subjects with a PHQ-9 score of 10 to 14 will be referred to a Mental Health Professional (MHP).

General

30. Significant change in smoking habits within 12 weeks before the screening visit.

31. Pregnant or breastfeeding or planning to become pregnant or breast-feed during the study.

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

33. 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.

Related to phentermine

34. Use of monoamine oxidase inhibitors within 14 days before screening or anticipated need for monoamine oxidase inhibitors during the study or within 30 days after the last dose of study drug.
35. Glaucoma or history of glaucoma.
## TIME AND EVENTS SCHEDULE

<table>
<thead>
<tr>
<th>Pretreatment/Administrative</th>
<th>Pretreatment</th>
<th>Screen-ing</th>
<th>Base line</th>
<th>Core Double-Blind Treatment Phase (Year 1)</th>
<th>Double-Blind Extension Treatment Phase (Year 2)</th>
<th>Posttreatment</th>
<th>EOT/ EW</th>
<th>TC Follow-Up</th>
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<td>Wk -3</td>
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<td>Follow-Up</td>
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**Clinical Laboratory Assessments (cont.)**

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<td>PK Samplingb</td>
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**Patient-Reported Outcomes - Efficacy**

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**Patient-Reported Outcomes - Safety**

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**Additional Assessments**

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**Ongoing Review**

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<td>Dispense glucose meter, glucose testing supplies and subject diarya</td>
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<td>SMBGi instructionsa</td>
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<td>Counseling regarding hypoglycemiaa</td>
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<td>Review subject diarya</td>
<td>X</td>
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<td>Review threshold for glycemic rescue&quot;</td>
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<td>Adverse events assessmenta</td>
<td>X</td>
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<td>Record hypoglycemia eventa</td>
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<td>Pre-study and concomitant medicationsa</td>
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**ABBreviations**

ABPM = Ambulatory blood pressure monitoring; CHES-Q = Current Health Satisfaction Questionnaire; C-SSRS = Columbia Suicide Severity Rating Scale; CT = Computed Tomography; DEXA = Dual-Energy X-ray Absorptiometry; ECG = Electrocardiogram; EOT = End-of-treatment; EW = Early withdrawal; FPG = Fasting plasma glucose; FSH = Follicle stimulating hormone; HbA1c = Hemoglobin A1c; IWQOL = Impact of Weight on Quality of Life – lite version; MMTT = Mixed-meal tolerance test; PAM = Patient Activation Measure; PHQ-9 = Patient Health Questionnaire-9; PK = Pharmacokinetics; SMBG = Self-monitored blood glucose; TC = Telephone call; Wk = Week; WPAI = Work Productivity and Activity Impairment.

Draft, Date: 26 October 2016
Footnotes

a) If participating sites do not have a written policy that subjects typically are invited to the site in a fasting condition, an additional pre-screening visit will be necessary to obtain written informed consent prior to inviting subjects in a fasting state for the screening procedures.

b) The actual visit may occur within +/-4 day window.

c) At the discretion of the investigator, this can be an in-clinic visit. A telephone follow-up contact will be conducted for all subjects approximately 30 days after the last dose of study drug to collect serious adverse events since the last visit unless the subject has died, has been lost to follow-up, or has withdrawn consent. Subjects who prematurely discontinue study drug will require an immediate EOT assessment (as soon as possible following study drug discontinuation) as well as an off-drug clinic visit (ie, clinic visit or telephone contact) approximately 2 weeks after discontinuation. Subjects will continue to be followed up for specific data collection, including, vital signs, body weight, serious adverse events, and adverse events of interest. At this telephone contact, investigators should ask subjects about any foot problems and remind them about routine preventative foot care and early intervention for foot problems.

d) Informed Consent must be signed at the screening or the optional pre-screening visit before any study procedures are performed.

e) To participate in the optional pharmacogenomics component of the study, subjects must sign the pharmacogenomics informed consent indicating willingness to participate. The consent form must be reviewed and signed by the subject prior to the sample being drawn at Day 1.

f) Blood pressure and pulse: 3 seated readings will be recorded in the source and eCRF. Method of Blood Pressure Monitoring, Section 4, Inclusion Criteria, and Section 0, Exclusion Criteria.

g) Specific details about specimen collection, storage, packaging, and shipping will be provided in an operations manual from the central laboratory.

h) FSH will be measured in women >45 years of age with amenorrhea for at least 6 months and <18 months prior to screening.

i) Mixed-meal tolerance test (MMTT) will be performed in a subset of subjects who will participate in the insulin sensitivity and beta-cell functions sub-study. Blood samples for glucose, C-peptide and insulin will be collected at the following times (relative to the start of the standard meal, considered as time "0"): -15 minutes, "0" time (just prior to start of meal), and 30-, 60-, 90-, 120-, and 180-minutes after the start of the meal. See Section, Insulin Sensitivity and Beta-cell Function Substudy and, Procedures for Mixed-Meal Tolerance Test (MMTT) for additional information, including standard meal contents.

j) For the Day 1 MMTT, PK blood sample should be collected at the -15 minute collection time point (relative to the start of the standard meal, considered as time "0") along with other fasting blood samples scheduled for Day 1. The subject should be administered the first dose of study drug after collection of the 180-minute blood sample for the MMTT.

k) At Week 52, the dose of double-blind study drug should be administered approximately 30 minutes before the start of the standard meal for the MMTT. The PK sample and all other fasting laboratory tests for the Week 52 visit should be drawn prior to study drug administration (ie, prior to -30 minute time point, relative to the start of the standard meal). The blood collections time points for this visit will be: prior to -30 (for PK and fasting lab samples), -15, 0, 30, 60, 90, 120, and 180 minutes (for MMTT lab samples).

l) Serum (β-human chorionic gonadotropin [β-hCG]) pregnancy testing will be performed for all women of childbearing potential at the screening and baseline visits unless they are surgically sterile or unless there is a documented history of their post-menopausal status. Urine pregnancy tests will be performed at Weeks 24, 52, 76, and 104. Additional serum or urine pregnancy tests may be conducted throughout the study in sufficient number, as determined by the investigator or required by local regulations, to establish the absence of pregnancy during the study. Serum pregnancy test must be performed and the result reviewed before randomization.

m) Fasting plasma, serum, and urine archive samples to be collected for exploratory biomarker analysis.

n) PK samples will be collected in approximately 50% of randomized subjects (see Section 9.5.1.1). For PK sampling, subjects will be instructed to refrain from taking the study drug before the clinic visit. The subject will be instructed to take the dose of study drug immediately before their next meal. The subject must report the time that the study drug was taken on the day preceding the clinic visit. On clinic visit days, should the subject take the study drug prior the scheduled visit, the dosing time must still be recorded.

o) All PRO assessments are to be completed at the beginning of the visit (whenever possible) before any tests and procedures.
p) DEXA and abdominal CT scan will be performed in a subset of subjects. Both assessments can be obtained 2 weeks prior or up to the visit where they are required. Both assessments will not be performed at discontinuation visits.

q) DEXA and CT scans should be done at the EOT/Early Withdrawal visit ONLY if the subject discontinues from study drug prior to Week 52.

r) 24-hour ABPM will be obtained in a subset of subjects randomly assigned to participate in the ABPM substudy. Instructions for collecting ABPM measurements can be found in the procedural manual.

s) Subject should be counseled to maintain a diet and exercise regimen consistent with that outlined in the Standardized Non-Pharmacologic Weight Reduction Therapy.

t) Subjects will be provided with and instructed on the use of a home blood glucose monitoring system. A diary and glucose testing supplies will also be provided.

u) The subject will receive information regarding the signs and symptoms of and treatment for hypoglycemia.

v) Subjects will be provided with and instructed to return with their completed diaries to the study site for review by study research staff at each clinic visit (eg, for review of hypoglycemic events, SMBG values, concomitant medications).

w) Subjects meeting the protocol-specified glycemic rescue criteria will have rescue therapy initiated.

x) Adverse events will be monitored throughout the study from the time of signing the informed consent form until the end of the study.

y) Hypoglycemic events should be recorded on the hypoglycemia eCRF and also on the adverse event eCRF if considered an adverse event by the investigator.

z) Record any medications taken from up to 30 days before screening (and up to 6 months before screening for antihyperglycemic agents) until the first dose of double-blind study drug on Day 1 (baseline) as prestudy therapy in the corresponding eCRF. Concomitant therapy consists of all medications, including AHAs, since the first dose of study drug on Day 1; after study drug discontinuation, use of AHA therapies will be recorded at the final visit or contact.

aa) Full physical examination will include a full review of body systems (vital signs, as below, head and neck, eyes, chest and lungs, breast, CV, extremities and back, abdomen, and neurological examination). A pelvic/genitourinary system examination (ie, prostate, rectal, and gynecologic examinations) should be performed if considered clinically appropriate by the investigator. Consistent with standard diabetes treatment guidelines, all study participants should be provided with routine preventative foot care and early intervention for foot problems (see Section Error! Reference source not found., All Adverse Events for further detail).

bb) Only the routine preventative foot care and early intervention for foot problems will be performed at Week 24 and Week 76 visits.