SYNOPSIS  CANA/PHEN NON-2TDM OVERWEIGHT AND OBSESE 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 Nondiabetic Overweight and Obese Subjects

Canagliflozin (INVOKANA®) is a potent inhibitor of the renal sodium glucose co-transporter 2 (SGLT2) approved in multiple regions 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 nondiabetic overweight or obese subjects. Approximately 3,350 nondiabetic, overweight or obese subjects, 18 years of age and older, who have a BMI ≥30 kg/m² at screening; or ≥27 kg/m² at screening in the presence of hypertension and/or dyslipidemia are eligible to participate. Subjects will receive 1 of 9 treatments or treatment combinations. Three substudies are embedded within the main study:

- Prediabetes substudy: The combination of canagliflozin and phentermine could have a dual mechanism to improve beta-cell function and reduce the progression to T2DM. This substudy will randomize subjects who have prediabetes and are at high risk for developing T2DM, and compare the rate of diabetes progression through 104 weeks.

- Drug withdrawal substudy: At week 52, subjects without prediabetes will be re-randomized to continue on their originally assigned study medication or switched to placebo for an additional 12 weeks in order to investigate weight regain upon cessation of treatment.

- Factorial substudy: Weight loss in subjects receiving treatment with the individual components will be compared to their respective combination dose strengths.

These sub-study objectives will be investigated by stratifying subjects by pre-diabetic (n=1,675) or normoglycemic n=1,675) and studied as described below and randomized as shown in Figure 1.

Prediabetic subjects

For subjects who are pre-diabetic at screening (defined at screening as HbA1c of ≥5.7% and ≤6.4% or an FPG ≥100mg/dL [≥5.6 mmol/L] and ≤125 mg/dL [≤6.9 mmol/L]), the study is 104 weeks in duration.

- Placebo subjects will remain on placebo for 104 weeks.
- Subjects in the prediabetes substudy who are randomized to one of the 4 combination treatment groups will remain on their respective dosages of canagliflozin and phentermine for 104 weeks.
- Subjects in the prediabetes substudy initially randomized to one of the 4 monotherapy treatment groups will be switched at Week 52 to their assigned combination therapy for the remainder of the study (ie, to Week 104).

Normoglycemic Subjects

For subjects who are normoglycemic at screening, the study is 64 weeks in duration.

- Placebo subjects will remain on placebo for 64 weeks.
Subjects initially randomized to one of the 4 monotherapy treatment groups will be switched at Week 52 to their assigned combination treatment for the remainder of the study (ie, to Week 64).

Subjects initially randomized to one of the 4 combination treatment groups will be randomly assigned at Week 52 in a 1:1 ratio either to placebo or to remain on their active therapy for the remainder of the study (ie, to Week 64).

**Figure 1 Schematic Overview of the Study**

**Efficacy Evaluations**

**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, change in IWQOL-Lite physical function domain, change in CHES-Q physical health satisfaction scores and change in SBP, at Week 52.

**Exploratory Endpoints**
• IWQOL-Lite Total and self-esteem, sexual life, public distress, and work domain scores
• CHES-Q emotional health satisfaction score
• PAM total score
• WPAL total score and individual items

Prediabetes Substudy

At Week 104 or End of treatment, in subjects with prediabetes at the screening visit, the following endpoints will be evaluated:

Primary Substudy Endpoint
• The proportion of subjects that have progressed to T2DM, defined as HbA1c ≥ 6.5% and/or FPG ≥126 mg/dL (≥7.0 mmol/L) or initiation of AHA therapy

Secondary Substudy Endpoint
• The proportion of subjects who have reverted to normoglycemic values, defined as HbA1c <5.7% and FPG <100 mg/dL (<5.6 mmol/L)

Drug Withdrawal Substudy

At Week 64, in normoglycemic subjects participating in the drug withdrawal substudy, the following endpoints will be evaluated:

• Percent change in body weight from baseline to Week 64 (primary)
• Percent change in body weight from Week 52 to Week 64 (secondary)

Factorial Substudy

Primary Substudy Endpoint
• Percent change in body weight from baseline to Week 24

Secondary Substudy Endpoints
• Percent change in body weight from baseline to Week 52
• Proportion of subjects who lost at least 5% and at least 10% of their baseline body weight at Week 24 and 52

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, Week 64 (for subjects stratified to the normoglycemic stratum) and Week 104 (for subjects stratified to the prediabetes stratum), 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 obesity. Subject participation in the pharmacogenomic 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).

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.

3. BMI ≥30 kg/m² at the screening visit,
   OR
   BMI ≥27 kg/m² at the screening visit in the presence of hypertension and/or dyslipidemia.

   Note: hypertension is defined as being treated with pharmacotherapy for hypertension and/or having a SBP ≥140 mmHg and/or a DBP ≥90 mmHg at screening.

   Note: dyslipidemia is defined as being treated with pharmacotherapy for dyslipidemia and/or fasting LDL-cholesterol ≥130 mg/dL (≥3.36 mmol/L), and/or fasting HDL-cholesterol <40 mg/dL (<1.03 mmol/L) for men or <50 mg/dL (<1.29 mmol/L) for women, and/or fasting triglycerides ≥150 mg/dL (1.68 mmol/L) at screening.

4. Stable weight (ie, change of ≤5% within 12 weeks before screening based on medical history).

5. Women must be either:
   Postmenopausal, defined as:
   o >45 years of age with amenorrhea for at least 18 months, or
   o >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)

6. 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).

7. 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. Has an HbA1c of ≥6.5% or FPG ≥126 mg/dL (≥6.9 mmol/L) at screening.

   **Note:** a one-time repeat measurement is allowed, at the discretion of the investigator, if the value of HbA1c and/or FPG is not consistent with prior values.

   **Note:** Both the HbA1c and the FPG values must be below the specified exclusion criterion values at screening; subjects in which one meets the criterion but the other is too high must be excluded from the study.

3. History of Type 1 diabetes mellitus (T1DM), T2DM (treated with pharmacotherapy), DKA, pancreas or β-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy.

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 (The Criteria Committee of the NYHA) within 12 weeks of the screening visit (refer to Attachment 1, 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 Attachment 2, 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\(^{28}\) (refer to Attachment 5, 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 canagliflozin 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:

   1. 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

   2. Antipsychotic drugs

   3. Antihyperglycemic agents (including sulfonylureas, metformin, dipeptidyl peptidase-IV (DPP-IV) inhibitors, meglitinides, acarbose, thiazolidinediones, exenatide, glucagon-like peptide-1
[GLP-1] or GLP-1 analogs, pramlintide, SGLT2 inhibitors, insulin, colesevelam, or bromocriptine

4. Anticonvulsants, including barbiturates, GABA analogues, hydantoins, phenyltriazines, succinimides, valproic acid and its derivatives, carbamazepine, zonisamide, and felbamate

5. Tricyclic antidepressants, lithium, levodopa, and dopamine receptor agonists

6. Highly active anti-retroviral therapy.

22. Use of selective serotonin reuptake inhibitors (including but not limited to fluoxetine, sertraline, paroxetine, escitalopram, citalopram, dapoxetine, serpoxetin, 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. 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 breastfeed 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: PREDIABETIC SUBJECTS

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<td>Treatment</td>
<td>Posttreatment</td>
<td>EOT/ EW</td>
</tr>
</tbody>
</table>

### Pretreatment/Administrative

- **Informed consent**
  - Week -3: X
  - Week -2: X

- **Informed consent** (pharmacogenomics)
  - Week 2: X

- **Inclusion/exclusion criteria**
  - Week 52: X

- **Medical history and demographics**
  - Week 52: X

- **Preplanned surgery**
  - Week 52: X

### Study Drug Administration

- **Randomization**
  - Week 52: X

- **Dispense/administer study drug**
  - Week 52: X

- **Drug accountability**
  - Week 52: X

### Procedures

- **Physical examination, foot examination**
  - Week 1: X

- **Pulse and blood pressure**
  - Week 1: X

- **Height**
  - Week 1: X

- **Body weight**
  - Week 1: X

- **Waist circumference**
  - Week 1: X

- **12-lead ECG (local)**
  - Week 1: X

### Clinical Laboratory Assessments

- **FSH**
  - Week 1: X

- **Hematology**
  - Week 1: X

- **Serum chemistry**
  - Week 1: X

- **Fasting lipid panel**<sup>1, 2</sup>
  - Week 1: X

- **FPG**
  - Week 1: X

- **HbA1c**
  - Week 1: X

- **Urinalysis**
  - Week 1: X
### Pretreatment

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<tr>
<th>Optional Pre-Screening*</th>
<th>Screening</th>
<th>Baseline</th>
<th>Core Double-Blind Treatment Phase (Year 1)</th>
<th>Double-Blind Extension Treatment Phase (Year 2)</th>
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<tbody>
<tr>
<td>Visit*</td>
<td>Week -3</td>
<td>Week -2</td>
<td>Day 1 Wk 2 Wk 4 Wk 8 Wk 12 Wk 16, 20 Wk 24 Wk 28, 32 Wk 36 Wk 40, 44, 48 Wk 52</td>
<td>Wk 56, 60 Wk 64 Wk 68, 72 Wk 76 Wk 80, 84 Wk 88 Wk 92, 96 Wk 100</td>
<td>Week 104 Week 106</td>
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<td>PK Sampling*</td>
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</table>

### Patient Reported Outcomes - Efficacy

| IWQOL-Lite*             | X         | X        | X                                        | X                                             | X             |
| CHES-Q*                 | X         | X        | X                                        | X                                             | X             |
| PAM*                    | X         | X        | X                                        | X                                             | X             |
| WPAF*                   | X         | X        | X                                        | X                                             | X             |

### Patient Reported Outcomes - Safety

| PHQ-9*                  | X         | X        | X                                        | X                                             | X             |
| C-SSRS*                 | X         | X        | X                                        | X                                             | X             |

### Ongoing Review

| Diet and exercise counseling* | X         | X        | X                                        | X                                             | X             |
| Adverse events assessment*   | X         | X        | X                                        | X                                             | X             |
| Prestudy and concomitant medications* | X         | X        | X                                        | X                                             | X             |

Key: CHES-Q= Current Health Satisfaction Questionnaire; C-SSRS=Columbia Suicide Severity Rating Scale; 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; PAM=Patient Activation Measure; PHQ-9=Patient Health Questionnaire-9; PK=Pharmacokinetics; SMBG=Self-monitored blood glucose; TC=Telephone call; Wk=Week; WPAF=Work Productivity and Activity Impairment.
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. 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 2 weeks 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. Early withdrawal from study treatment will require the immediate collection of key data as soon as possible after stopping the study drug as well as an of drug clinic visit 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.

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

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. See Attachment 2 Method of Blood Pressure Measurement, Section 4.1, Inclusion Criteria, and Section 4.2, 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. Fasting is defined as “no caloric intake for at least 8 hours.”

j. LDL-C will be calculated using the Friedewald equation (or directly measured if triglycerides≥400 mg/dL).

k. 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.

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

m. 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 day, should the subject take the study drug prior to the scheduled visit, the dosing time must still be recorded.

n. All patient-reported outcome (PRO) assessments are to be completed at the beginning of the visit (whenever possible) before any tests and procedures.

o. Subject should be counseled to maintain a diet and exercise regimen consistent with those outlined in the Standardized Non-Pharmacologic Weight Reduction Therapy (Attachment 4).

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

q. 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 (if applicable).

r. 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/gynecological system examination (ie, prostate, rectal, and gynecological examinations) should be performed if considered clinically appropriate by the investigator. All study participants should be provided with routine preventative foot care and early intervention for foot problems (see Section 12.3.1, All Adverse Events for further detail).
# TIME AND EVENTS SCHEDULE: NORMOGLYCEMIC SUBJECTS

<table>
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<th>Pretreatment</th>
<th>Treatment</th>
<th>Posttreatment</th>
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<tbody>
<tr>
<td>Optional Pre-Screening †</td>
<td>Screen. Bas.</td>
<td>Core DBTTPY1</td>
<td>Double-Blind Extension Treatment Phase</td>
</tr>
<tr>
<td>Visit ‡</td>
<td>Week -3</td>
<td>Week -2</td>
<td>Day 1</td>
</tr>
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<td>Pretreatment/Administrative</td>
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<tr>
<td>Informed consent ‡</td>
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<tr>
<td>Informed consent (pharmacogenomics) ‡</td>
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<tr>
<td>Inclusion/exclusion criteria</td>
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<td>Medical history and demographics</td>
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<td>Preplanned surgery</td>
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<td>Study Drug Administration</td>
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<td>Randomization</td>
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<td>Dispense/administer study drug</td>
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<td>Drug accountability</td>
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<td>Procedures</td>
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<td>Physical examination, foot examination †</td>
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<td>Pulse and blood pressure ‡</td>
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<td>Height</td>
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<td>Body weight</td>
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<td>Waist circumference</td>
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<td>12-lead ECG (local)</td>
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<td>Clinical Laboratory Assessments ‡</td>
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<tr>
<td>Serum chemistry</td>
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<tr>
<td>Fasting lipid panel ‡</td>
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<tr>
<td>FPG</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>HbA1c</td>
<td>X</td>
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<td>Urinalysis</td>
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</tbody>
</table>

Note: DBTTPY1 = Core Double-Blind Treatment Phase (Year 1)

- **Weeks:** Wk 2, Wk 4, Wk 8, Wk 12, Wk 24, Wk 28, Wk 32, Wk 36, Wk 40, Wk 44, Wk 48, Wk 52, Wk 56, Wk 60, Wk 64, Week 66
- **Follow-Up:** TC

Draft, Date: 26 October 2016
<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Treatment</th>
<th>Posttreatment</th>
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<tr>
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<td>Optional Pre-Screening</td>
<td>Screening</td>
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<td>Week -3</td>
<td>Week -2</td>
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<td>Pregnancy test</td>
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<tr>
<td>Fasting plasma, serum, and urine archive samples</td>
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<td>PK Sampling</td>
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</table>

**Patient Reported Outcomes - Efficacy**

| | JWQOL-Lite | CHES-Q | PAM | WPAI |
| | X | X | X | X |

**Patient Reported Outcomes - Safety**

| | PHQ-9 | C-SSRS |
| | X | X |

**Ongoing Review**

| | Diet and exercise counseling | Adverse events assessment | Prestudy and concomitant medications |
| | X | X | X |

**Key:** CHES-Q = Current Health Satisfaction Questionnaire; C-SSRS = Columbia Suicide Severity Rating Scale; 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; PAM = Patient Activation Measure; PHQ-9 = Patient Health Questionnaire-9; PK = Pharmacokinetics; TC = Telephone call; Wk = Week; WPAI = Work Productivity and Activity Impairment.
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) 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 2 weeks 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. Early withdrawal from study treatment will require the immediate collection of key data as soon as possible after stopping the study drug as well as an off-drug clinic visit 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.

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

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 must 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. See Attachment 2 Method of Blood Pressure Measurement, Section 4.1, Inclusion Criteria, and Section 4.2, Exclusion Criteria.

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

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

i) Fasting is defined as “no caloric intake for at least 8 hours.”

j) LDL-C will be calculated using the Friedewald equation (or directly measured if triglycerides ≥400 mg/dL).

k) 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 and 52. 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.

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

m) 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.

n) All patient-reported outcome (PRO) assessments are to be completed at the beginning of the visit (whenever possible) before any tests and procedures.

o) Subject should be counseled to maintain a diet and exercise regimen consistent with those outlined in the Standardized Non-Pharmacologic Weight Reduction Therapy (Attachment 4).

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

q) 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 since the first dose of study drug on Day 1.

r) 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. All study participants should be provided with routine preventative foot care and early intervention for foot problems (see Section 12.2.1, All Adverse Events for further detail).