AMENDMENT #1 ENGLISH

Janssen Research & Development/Janssen Latin America

Clinical Study Protocol

CANA CGM Trial COMETA: Overview

Canagliflozin Continuous Glucose Monitoring (CANA CGM) Trial: A Pilot Randomized, Double-Blind, Controlled, Crossover Study on the Effects of the SGLT-2 Inhibitor (vs. the DPP-4 Inhibitor Sitagliptin) on Glucose Variability in Mexican Patients With Type 2 Diabetes Mellitus Inadequately Controlled on Metformin

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Protocol: **28431754DIA4026; Phase: Post-market**

JNJ-2843175 Canagliflozin

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 Biologics, BV; Janssen-Cilag International NV; Janssen, Inc.; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

This compound is approved for marketing in the following indication:

Canagliflozin (Invokana®) is a sodium-glucose co-transporter 2 (SGLT-2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Status: Approved

Date: 31 July 2017

Prepared by: Janssen Research & Development/Janssen Latin America

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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1. SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*/Janssen Latin America
Name of Product	Canagliflozin (JNJ-28431754)

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Title of Study: Canagliflozin Continuous Glucose Monitoring (CANA CGM) Trial: A Pilot Randomized, Double-Blind, Controlled, Crossover Study on the Effects of the SGLT-2 Inhibitor (vs. the DPP-4 Inhibitor Sitagliptin) on Glucose Variability in Mexican Patients With Type 2 Diabetes Mellitus Inadequately Controlled on Metformin

NCT No.: TBD

Clinical Registry No.: TBD

Coordinating Investigator: Fernando Javier Lavalle-González, MD, Facultad de Medicina de la Universidad Autónoma de Nuevo León, Madero y Dr. Aguirre Pequeño, Col. Mitras Centro sin número [redacted] Mexico [redacted] Tel: [redacted]

Study Centers: A total of five study centers in Mexico

Publication (Reference): None

Study Period (See Figure 1 and Table 4.)

Total = 97 days
Prestudy: 16 days: including prescreening period (6 days), screening period (3 days) and selection period (7 days)
Two active treatments: each 28 days (56 days)
Washout (with ongoing metformin): 16 days
Post-study follow-up: 9 days
Each visit day is surrounded by a ± 3-day scheduling window.
Visit 1 = Optional prescreening: Day −16.
Visit 2 = Screening: Day −10.
Visit 3 = Selection/CGM qualification: Days −7 to −1, including 6 days of CGM monitoring, from Day −7 to −2 study subject to perform calibration of CGM device by using glucometer.
Visit 4 = Selection/qualification: On Day −1, if CGM data from Days −7 to −2 meet eligibility criteria, study participation is offered to patient.
Visit 5 = Randomization: Day 0.
Visit 6 =Initiate treatment period 1: Day 0. Dispense study medication (treatment A or B) and instructions.
Visit 7 = CGM in: Insert CGM device for 6-day measurement (Day 22); study subject to perform calibration using glucometer during the 6 days of CGM measurement.
Visit 8 = CGM out: Remove CGM device after 6 days and download data from CGM device, Glucometer and enter manually patient log information into the system (Day 27).
Visit 9 = Treatment washout; Day 28, between treatment periods 1 and 2. Collect unused medications from treatment period 1 and perform pill count/compliance assessment (see below). Maintain ongoing metformin at stable dose.

Visit 10 = Treatment crossover visit: Day 44. Initiate treatment period 2. Dispense study medication (treatment B or A) and instructions (Day 44).
Visit 11 = CGM in: Insert CGM device for 6-day measurement (Day 66); study subject to perform calibration using glucometer during the 6 days of CGM measurement.
Visit 12 = CGM out: Remove CGM device after 6 days and download data from CGM device, Glucometer and enter manually patient log information into the system (Day 71).
Visit 13 = End-treatment follow-up visit: Day 72. Collect unused medications from treatment period 2 and perform pill count/compliance assessment (see below). Allow for up to 9 days (to final Day, 80) to follow and resolve any safety or tolerability issues. Maintain ongoing metformin at stable dose.

Phase of Development: Post-market

Objectives: This trial is designed to compare the effects on glycemic variability (GV) of the sodium-glucose co-transporter-2 (SGLT-2) inhibitor canagliflozin and the dipeptidyl dipeptidase-4 inhibitor sitagliptin when administered to Mexican subjects with type 2 diabetes mellitus (T2DM) who had inadequate glucose control on stable dosages of the biguanide metformin. The primary objective is to assess the effects of 4 weeks each of daily treatment with canagliflozin 300 mg versus sitagliptin 100 mg as treatment adjuncts to metformin (at stable dosages) on intrapatient glycemic coefficient of variation (CV), expressed as a ratio (%) of standard deviation (SD) to mean glucose levels.

Secondary efficacy objectives are to assess the effects of 4 weeks each of daily treatment with canagliflozin 300 mg versus sitagliptin 100 mg as add-ons to metformin (at stable dosages) on mean (SD) changes from baseline in:

- Glycemic SD for 24-hour glucose (mg/dL)
- Mean 24-hour glucose profile (mg/dL)
- Preprandial glucose (fasting PG; mg/dL)
- 2-hour postprandial glucose (PPG; mg/dL)
- Time (minutes), percent of 24 hours, or area under the PG time curve for 24 hours (AUC_{24h}) with glucose = 70−139 mg/dL (time spent in target range)
- Time (minutes), percent of 24 hours, or AUC_{24h} (mg/dL/hr) with glucose > 140 mg/dL (time above target range)
- Time (minutes), percent of 24 hours, or AUC_{24h} (mg/dL/hr) with glucose > 180 mg/dL (time spent markedly above target range)
- Time (minutes), percent of 24 hours, or area over the PG time curve for 24 hours (AOC_{24h} ; mg/dL/hr) with glucose < 70 mg/dL (time spent below target range)
- Frequency (%) of 2+ consecutive glucose readings < 70 mg/dL (and/or of hypoglycemic symptoms requiring personal support)

Exploratory efficacy objectives are to probe the effects of 4 weeks each of daily treatment with canagliflozin 300 mg versus sitagliptin 100 mg as add-ons to metformin (at stable dosages) on mean (SD) changes from baseline in:

- AUC for glycemic variability (mg/dL/hr) throughout the day (0−24 hours), after breakfast (0−5 hours), after lunch (5−11 hours), after dinner (11−15 hours), and during sleep (15−24 hours).
- Peak glucose (mg/dL) throughout the day (0−24 hours), after breakfast (0−5 hours), after lunch (5−11 hours), after dinner (11−15 hours), and during sleep (15−24 hours).
- Overall hyperglycemia: AUC_{total} (mg/dL/hr).
- Nadir glucose (mg/dL): lowest glucose level over 72 hours.
- Continuous overlapping net glycemic action (CONGA): the SD of summed differences between observations separated by *n* hours.
- Mean of daily differences in PG (MODD).

Further objectives are to assess the tolerability profile of each active treatment according to incidences (subjects and number of events) of treatment-emergent adverse events and the safety profile according to incidences of abnormal vital signs, 12-lead electrocardiograms (ECG), and clinical laboratory panels.

Methodology: This is a randomized, double-blind, actively controlled, crossover, post-market, multicenter (all 4 study sites within Mexico) study to evaluate the efficacy, safety, and tolerability of the addition of canagliflozin 300 mg or sitagliptin 100 mg (each once-daily by mouth), for 4 weeks each, to metformin at stable dosages in Mexican subjects

with T2DM who have inadequate glycemic control (i.e. hemoglobin A1c 7.5%−10.5%) while receiving metformin monotherapy at the prescreening (Visit 1 – optional) or screenining visit (Visit 2).

It is planned that approximately 60 subjects (≥18 years of age) with T2DM and inadequate glycemic control on metformin at screening will be randomly allocated in a 1:1 ratio (for treatment, period, and sequence) to two 4-week double-blind, actively controlled treatment phases with once-daily canagliflozin 300 mg or sitagliptin 100 mg added to ongoing metformin. Subjects are randomized to a sequence of either A/B (e.g. canagliflozin followed by sitagliptin) or B/A (vice versa). Metformin treatment at stable dosages will be administered during not only each active-treatment period but also a 16-day canagliflozin-sitagliptin washout interval between them. Randomization is stratified by gender-specific baseline body mass index tertile. The maximum total study duration for subjects who do not withdraw consent or otherwise discontinue is 97 days, including 1) a prestudy screening phase of 16 days (including an optional pre-screening phase of 6 days, a screening phase of 3 days, a selection phase of 7 days and a randomization phase) ; 2) 28 days for each active treatment phase; 3) 16 days for the washout phase (with ongoing metformin monotherapy); and 4) 9 days for follow-up after the final day of the second active treatment. A ±3-day window around each study date is permitted to enable individual-subject scheduling of visits.

During the screening period, potential subjects will wear the CGM device continuously for 6 days, an assessment of eligibility, as determined by a trained external monitor, will be made based on adherence to CGM requirements and successful CGM readings for ≥3 consecutive days (each day counted from hour 0 to hour 24) within the 6 days of the selection phase. A successful CGM reading is defined as a value that does not have (within 1 day) a continuous interruption of >120 minutes in any postprandial interval or a continuous interruption of >180 minutes during a nocturnal/sleep interval.

Diagnosis and Main Criteria for Inclusion: Men and women at least 18 years of age with a documented medical history of T2DM who meet the following (minimum) criteria at screening:

- Inadequate glucose control while using MET monotherapy for at least 8 weeks at stable daily doses of at least 1,500 mg
- Hemoglobin A1c of 7.5% through 10.5%
- Estimated glomerular filtration rate (eGFR) of at least 60 mL/min/1.73 m^2
- Body mass index of 22 through 45 kg/m^2

Excluded from participation were patients with a history of any of the following at screening:

- Diabetic ketoacidosis (DKA)
- Type 1 diabetes mellitus (T1DM)
- Pancreatic (e.g. β-islet cell) transplantation
- Diabetes secondary to pancreatitis or pancreatectomy
- Individual history of (or present) pancreatitis
- One or more episodes of severe hypoglycemia (requiring assistance from others), as documented in the history obtained at Visit 1
- Hereditary glucose-galactose malabsorption or primary renal glucosuria.
- Repeated FPG or fasting self-monitored blood glucose (SMBG) > 270 mg/dL during the pretreatment phase
- Treatment with parenteral antidiabetic medications (e.g. insulins).
- Current use of "Natural medicines" or natural medicinal products for diabetes (e.g. cactus-derived nutrients, celery).
- Unsuccessful initial CGM reading as indicated by a continuous interruption of >120 minutes in any postprandial interval, or a continuous interruption of >180 minutes in a nocturnal/sleep interval, over 3 consecutive days (each day counted from hour 0 to hour 24) within the 6 days of the selection phase

Test Product, Dose and Mode of Administration: Canagliflozin tablets containing 300 mg for oral administration. **[Batch No. TBD]**

Reference Therapy, Dose and Mode of Administration: Matching (blinded) sitagliptin phosphate tablets containing 100 mg for oral administration. **[Batch No. TBD]**

Duration of Treatment: As shown in **Figure 1** and as summarized above (page 7), the total duration of each subject's study participation is approximately 14 weeks and will not exceed 97 days, including a 17-day prestudy period. Around each visit day was a ±3-day visit scheduling window. The study consisted of an optional 6-day prescreening phase, a 3-day screening phase, and a 7-day selection period (all on metformin alone). This prestudy phase was followed by randomization on Day 0; two 4-week (28-day) active-treatment phases separated from each other by a 16-day washout of active treatments (with continued metformin monotherapy); and a 9-day end-treatment follow-up phase.

Evaluations: Efficacy evaluations will include continuous-glucose-monitoring (CGM) parameters, which are measured over 6-day periods, in order to obtain a continuous 72-hour reading (valid hours of measurement is hour 0 12:00 am to hour 72 which is 12:00 am after 3 days of continuous reading), at the end of the selection phase (Days −7 to −1) and each active treatment (Days 22−27 at the end of treatment period 1 and Days 66−71 at the end of treatment period 2). These parameters include intrapatient glucose CV %, glycemic SD, 24-hour glycemia, 2-hour PPG, and percent of time (or area-under-the time concentration curve) spent within, above, or below the reference range for glucose, including frequencies of hypoglycemia. During each CGM interval, subjects will maintain diaries (log sheets) of nutrition, physical activity, and clinical symptoms, medication, and capillary blood glucose readings.

Safety evaluations include physical examinations, vital signs, 12-lead electrocardiograms, and clinical laboratory tests at screening and the end-of-study visits. Heart rate, blood pressure, and body weight will be measured at each visit.

Statistical Methods:
Sample Size Determination: The effects of canagliflozin and sitagliptin on glycemic variability have never been assessed in a head-to-head study involving continuous glucose monitoring. However, effects on overall glycemia were compared in the Canagliflozin Treatment and Trial Analysis−DPP-4 Inhibitor Comparator Trial (CANTATA-D) trial. The mean (SD) difference in estimated average glucose between groups was 11.11 (26.28) mg/dL. According to a two-sided $\alpha = 0.05$ and a power of 80%, a total of 46 subjects with paired data are needed to detect a mean (SD) difference of 11.11 (16.28) mg/dL between canagliflozin 300 mg and sitagliptin 100 mg as assessed by paired Student t-tests. Using a conservative subject attrition rate of 30% for an approximately 12-week study, the required sample size for this crossover trial is 46 + 13.8 = 60 subjects, each randomly allocated in a double-blind manner to two treatments, two periods, and two sequences involving canagliflozin 300 mg compared to sitagliptin 100 mg as add-ons to metformin in T2DM subjects with glucose inadequately controlled on the biguanide as monotherapy who meet all eligibility criteria.

Subjects will be randomized 1:1 to each treatment sequence. The CANTATA-D study found that treatment with canagliflozin 300 mg was associated with a 2.1% to 2.9% reduction in body weight compared to sitagliptin 100 mg when each was added to ongoing metformin over 52 weeks (Lavalle-Gonzalez et al., 2013a; Lavalle-Gonzalez et al., 2016). The net reduction with canagliflozin 300 mg at 4 to 6 weeks was approximately 1.0% to 1.5%. Nevertheless, it is possible that, once subjects lose weight while randomized to canagliflozin 300 mg, they will become more physically active. To minimize the effects of this potentially important covariate with relation to GV, randomization will be stratified according to gender-specific tertiles of body mass index (BMI) (Kriska et al., 2003). For men, tertile 1 ranges from 17 to <28; 2, from 28 to <33; and 3 from 33 to <66, kg/m^2. For women, tertile 1 ranges from 16 to <30; 2, from 30 to <36; and 3, from 36 to <69 kg/m^2. Because the eligibility criteria in this trial require a range of BMI = 22 to 45 kg/m^2 for study entry, the tertiles are redefined as follows. For men, tertile 1 ranges from 22 to <28; 2, from 28 to <33; and 3 from 33 to <45, kg/m^2. For women, tertile 1 ranges from 22 to <30; 2, from 30 to <36; and 3, from 36 to <45 kg/m^2. This stratified randomization method will control for any influence of the covariate of baseline BMI (surrogate for body weight).

Efficacy: Three null hypotheses (NH) will be tested.

H_{0A}: There is no statistically significant difference between CANA 300 mg and SITA 100 mg in terms of their effects on mean intrapatient glucose CV % as measured by CGM over a 3-day period at baseline and after each active treatment.

H_{1A} [Alternative hypothesis (AH)]: There is a statistically significant difference between CANA 300 mg and SITA 100 mg in terms of their effects on mean intrapatientglucose CV % as measured by CGM over a 3-day period at baseline and after each active treatment.

H_{0B}: There is no statistically significant difference between CANA 300 mg and SITA 100 mg in terms of their effects on mean intrapatient glycemic SD for 24-hour glucose profiles from baseline as measured by CGM over a 3-day period at baseline and after each active treatment.

H_{1B}: There is a statistically significant difference between CANA 300 mg and SITA 100 mg in terms of their effects on mean intrapatient glycemic SD for 24-hour glucose profiles from baseline as measured by CGM over a 3-day period at baseline and after each active treatment.
H_{0C}: There is no statistically significant difference between CANA 300 mg and SITA 100 mg in terms of their effects on mean 24-hour glucose profiles from baseline as measured by CGM over a 3-day period at baseline and after each active treatment.
H_{1C}: There is a statistically significant difference between CANA 300 mg and SITA 100 mg in terms of their effects on mean 24-hour glucose profiles from baseline as measured by CGM over a 3-day period at baseline and after each active treatment.

Descriptive statistics will be presented as mean (SD) for normally distributed continuous variables, median [interquartile range (IQR)] for non-normally distributed continuous variables, and numbers (%) for categorical variables. Baseline sociodemographic and other characteristics will be compared using Fisher's Exact test for categorical variables and Student's t-test for normally distributed continuous variables.

The primary efficacy analyses will be conducted in the intent-to-treat (ITT) population: subjects who received at least one dose of medication and had CGM recordings at baseline and after each active treatment (i.e. >70% of tracings available). A secondary analysis will be conducted in the per-protocol population: members of the ITT population who completed the study without major protocol violations. Although a previous randomized controlled trial compared effects of another SGLT-2 inhibitor (and also open-label sitagliptin 100 mg) using a modified last observation carried forward approach (with linear interpolation) to missing data(Rosenstock et al., 2013), data will not be imputed in the present study, which has a limited number of visits (six) and duration (80 days).

As in a previous CGM study, the distribution of each glycemic indicator (except for SD; see below), as well as body weight, will be assessed for normality via the Shapiro-Wilk test (Nomura et al., 2011). For normally distributed data, the mean (SD) value will be presented and, for non-normally distributed data, the median and IQR. Most between-treatment differences will be assessed using a paired Fisher's Exact test for baseline categorical variables and paired t-tests or Wilcoxon signed rank sum tests for normally and non-normally distributed continuous efficacy endpoints (respectively), according to the Shapiro-Wilk test results.

Also paralleling a previous CGM study involving sitagliptin 100 mg, data for analyses of the CANA CGM Trial's secondary endpoints related to AUC_{24hr} (and AOC_{24hr} for hypoglycemia) will be included per subject only if >70% of his or her CGM readings are available during each assessment period (3-day CGM at the end of the baseline and each of two treatment intervals); and AUC values will be adjusted for preprandial (FPB) readings (Ellis et al., 2011). Some of these variables (e.g. percentage of time with PG in different ranges) are known to be non-normally distributed and, as in previous CGM studies, will be evaluated using paired Wilcoxon rank sum tests on median and IQR values (Nomura et al., 2011; Nishimura et al., 2015).

Body weight will be measured at each visit. In the event of a significant mean (SD) [or median (IQR)] difference in change from baseline in body weight or physical activity between canagliflozin 300 mg and sitagliptin 100 mg (according to a statistical assessment informed by the Shapiro-Wilk test), a statistical approach similar to that of a prior SGLT-2 (vs. SITA) trial will be taken (Rosenstock et al., 2013); namely, a sensitivity analysis using either: 1) a repeated-measures mixed-effect model with baseline CGM values as fixed effects and on-treatment body weight and subject as random effects; or 2) an analysis of covariance with visit-wise body weights and physical activity as covariates.

To evaluate carry-over effects, Grizzle's two-stage model will be employed to statistically test for treatment x period interactions (Shen, 2006). In the event of a significant carryover effect, the methodology enables comparison of the effects of CANA 300 mg versus SITA 100 mg on parameters of GV in one of the two treatment periods.
All tests will be conducted at a two-sided $\alpha = 0.05$ (i.e. *a priori* significance level of $p < 0.05$).

Safety: Subjects receiving at least one dose of active treatment will comprise the safety population. Safety will be assessed according to mean values for vital signs (pulse rate, blood pressure, respiration rate, body temperature), 12-lead ECGs, and clinical laboratory assessments at the screening and end-of-study visits in this population: baseline safety assessments may occur at Visit 1 (Day −16 to −11; prescreening [optional]) or Visit 2 (Day −10 to −8; screening) and the end-of-study visit occurs at Visit 13 (Day 72 to 80 after randomization). Heart rate and blood pressure will be measured at each visit, as detailed in Appendix 5. Incidences of abnormal safety evaluations will be based on predefined, local reference ranges and each Investigator's customary clinical practice. Adverse events will be elicited

by open-ended questioning at each visit post ICF signature and also coded as to system organ class, and preferred term using Medical Dictionary of Regulatory Activities (MedDRA) version 14 (or higher). Safety will be further assessed according to incidences of SAEs, AEs leading to treatment discontinuation, and serious drug-related AEs.

2. INTRODUCTION

Diabetes is a major, burgeoning public-health challenge for Latin American societies. Numbers of patients with diabetes in this region are projected to increase from about 13 million in 2000 to 33 million in 2030 (Wild et al., 2004). The Cardiovascular Risk Factor Multiple Evaluation in Latin America (CARMELA) study reported that the prevalence of type 2 diabetes mellitus (T2DM) was 7.0% (Escobedo et al., 2009). Mexico has among the highest prevalences of diabetes around the world (14.4%). Annual direct and indirect costs associated with this chronic disorder in Mexico have been estimated at US$15 billion (Guzman et al., 2010; Villalpando et al., 2010).

Evidence from the Diabetes En America Latina (DEAL) study suggests that management of T2DM is less than optimal among primary-care practitioners in Latin America (Stewart et al., 2007). Across nine countries, poor glucose control, as evidenced by a fasting plasma glucose (FPG) ≥ 110 mg/dL was reported in 78%, and HbA1c < 7.0% in 43.2%, of Latin American adults. In Mexico, only about 30% of adults had HbA1c below the 7.0% HbA1c cut point often identified as a treatment target (Stewart et al., 2007).

Regional consensus guidelines for T2DM management in Latin America were formulated before SGLT-2 inhibitors became widely available (Guzman et al., 2010). Consensus practice guidelines issued by other health authorities, such as the US American Diabetes Association (ADA), do not clearly specify which second-line medication to add in the event of inadequate T2DM management after lifestyle counseling and treatment with the biguanide metformin (MET) (American Diabetes Association, 2016).

According to the most recent guidelines from ADA, practitioners should consider combining one of six potential treatments with MET if the HbA1c target is not met within about 3 months: a sulfonylurea, thiazolidinedione, SLGT2 inhibitor, DPP-4 inhibitor, glucagon-like peptide-1 receptor agonist (GLP-1RA), or basal insulin. However, there is a paucity of evidence from active-comparator trials to inform the selection of one therapy over another. According to the ADA guidance, "there are numerous trials comparing dual therapy with [MET] alone, [but] few directly compare drugs as add-on therapy [to MET]." As potential criteria to determine which of the six therapies to add in the event of inadequate glucose control on behavioral modification and MET, the ADA lists patient preferences, disease and drug characteristics, as well as psychosocial, health-economic, and clinical factors (American Diabetes Association, 2016).

One such clinical factor is glycemic variability (GV), which is not captured by HbA1c; the latter variable indicates average glucose over a 1- to 2-month interval (Koenig et al., 1976). HbA1c only partially captures acute glycemic fluctuations from nadir (interprandial) to peak (postprandial) (Monnier and Colette, 2008; Di Flaviani A. et al., 2011). On a clinical level, the Diabetes Control and Complications Trial (DCCT) demonstrated that increases in HbA1c accounted for only 11% of the variance in diabetic retinopathy (Lachin et al., 2008).

In recent years, the biological consequences of within-day and day-to-day fluctuations in glucose profiles have come into increasingly greater focus (Kilpatrick, 2009; Nalysnyk et al., 2010; Hu et al., 2010; Di Flaviani A. et al., 2011; Tylee and Trence 2012; Lin et al., 2014; Xixiang et al., 2014). In short, oscillations in daily glucose profiles may play a pathogenic role in the development of diabetic complications beyond mean elevations in average plasma glucose (PG) or HbA1c (The Diabetes Control and Complications Trial Research Group, 1997; Hirsch and Brownlee, 2005; Brownlee and Hirsch, 2006; Di Flaviani A. et al., 2011).

Such variability may adversely affect endothelial function and oxidative stress, potentially raising both macrovascular (cardiovascular) and microvascular (including peripheral neuropathy) disease risk (Hirsch and Brownlee, 2005; Ceriello, 2005; Monnier et al., 2006; Ceriello et al., 2008; Bragd et al., 2008; Monnier et al., 2008; Buscemi et al., 2010; Kohnert et al., 2012; Ogawa et al., 2012; Saisho, 2014). Intermittently elevated glucose may contribute to worsening dysregulation of adipokine (adiponectin, resistin) production, also potentially via oxidative mechanisms (Sun et al., 2010). One surrogate marker of evolving cerebral atherosclerosis is the change in carotid-artery intima-media thickness (IMT). In a clinical trial involving DPP-4 inhibition, reductions in daily glucose excursions, but not in chronic hyperglycemia, were associated with declines in carotid IMT (Barbieri et al., 2013).

There are other potential clinical ramifications of instability in daily glucose profiles among patients with T2DM (Praet et al., 2006). Clinical trials have demonstrated associations between GV and reduced postprandial β-cell

function, increased incidences of hypoglycemia (in patients with T1DM and T2DM) diabetic complications, and clinical endpoints such as all-cause mortality, mortality during intensive care (even in patients without diabetes), diabetes-specific mortality (and morbidity), cardiovascular-specific mortality, and ischemic stroke (Muggeo et al., 1995;Muggeo et al., 2000; Kohnert et al., 2009; Nalysnyk et al., 2010; Takao et al., 2010; Krinsley, 2010; Hermanides et al., 2010; Lin et al., 2012; Devries, 2013; Lin et al., 2014).

In addition to these findings, increased GV has been independently associated with diminished health-related quality of life and sense of well-being (Penckofer et al., 2012). In patients with T1DM, hyperglycemia has been related to increased levels of tension and anger (Hermanns et al., 2007). In addition, fear of hypoglycemia among both patients and physicians comprises a treatment barrier that can erode patient adherence and discourage physicians from intensifying regimens (i.e. "clinical inertia"), further compromising the effectiveness of care (Cryer, 2008; Avignon et al., 2012; Lovshin and Zinman, 2013; Strain et al., 2014).

The use of self-measured blood glucose (or CGM) can reduce GV and, conversely, enhance glucose control (reducing the risk of hyperglycemia and hypoglycemia) as well as potentially reducing patient and physician concerns about experiencing (or causing) hypoglycemia and/or intensifying regimens (DeBlock C. et al., 2008; Reach, 2008; Rodbard et al., 2009; Kohnert et al., 2012). Clinical trials have demonstrated that the use of CGM was associated with significant reductions in markers of systemic inflammation and oxidative stress (Rizzo et al., 2012).

3. OBJECTIVES

The chief aim of this trial is to compare the effects of 4 weeks each of CANA 300 mg versus SITA 100 mg as add-on to metformin at stable dose on glycemic variability (GV; as measured using CGM), when each agent is added to MET at stable dosages in Mexican patients with T2DM and inadequate glucose control on MET monotherapy. The primary efficacy outcome measure is the intrapatient coefficient of variation of mean intrapatient CV (SD/mean FPG). Other central study purposes include comparisons between the effects of these adjunctive treatments on changes from baseline in:

1. Mean (SD) 24-hour glucose levels
2. Mean (SD) preprandial glucose [fasting plasma glucose (FPG)]
3. Mean (SD) 2-hour postprandial glucose (PPG)
4. Time, percent of time, or AUC_{24hr} (or AOC_{24hr} for hypoglycemia) with glucose in euglycemic, hyperglycemic, and hypoglycemic ranges.

A further objective is to evaluate the safety and tolerability profile of active treatments.

4. METHODS

4.1. Study Design

This multi-center (4-center), 2 x 2 randomized, double-blind, actively controlled crossover study randomly allocates patients with T2DM and inadequate glucose control on metformin (MET) monotherapy at stable doses (≥1500 mg/day) to oral once-daily treatment with canagliflozin 300 mg (CANA) or the dipeptidyl peptidase 4 (DPP-4) inhibitor sitagliptin phosphate 100 mg (SITA) once daily added to metformin (MET) at stable doses for 28 days, with a 16-day MET monotherapy washout. The interval between the first and last dose of randomized adjunctive treatment is hence 72 days. Given a 16-day prestudy interval (6-day optional prescreening; 3-day screening; 7-day selection) and a post-treatment follow-up period of up to 9 days, the maximum study duration for each subject who tolerates medications and does not withdraw consent or otherwise discontinue is thus 97 days. Each of these visits is surrounded by a ±3-day window to enable individual-subject scheduling. Patients are randomized in a double-blind manner to treatment, period, and sequence.

Figure 1 depicts the design of this multi-center (4-center), 2 x 2 x 2 (2 sequences, periods, and treatments) double-blind, actively controlled crossover study.

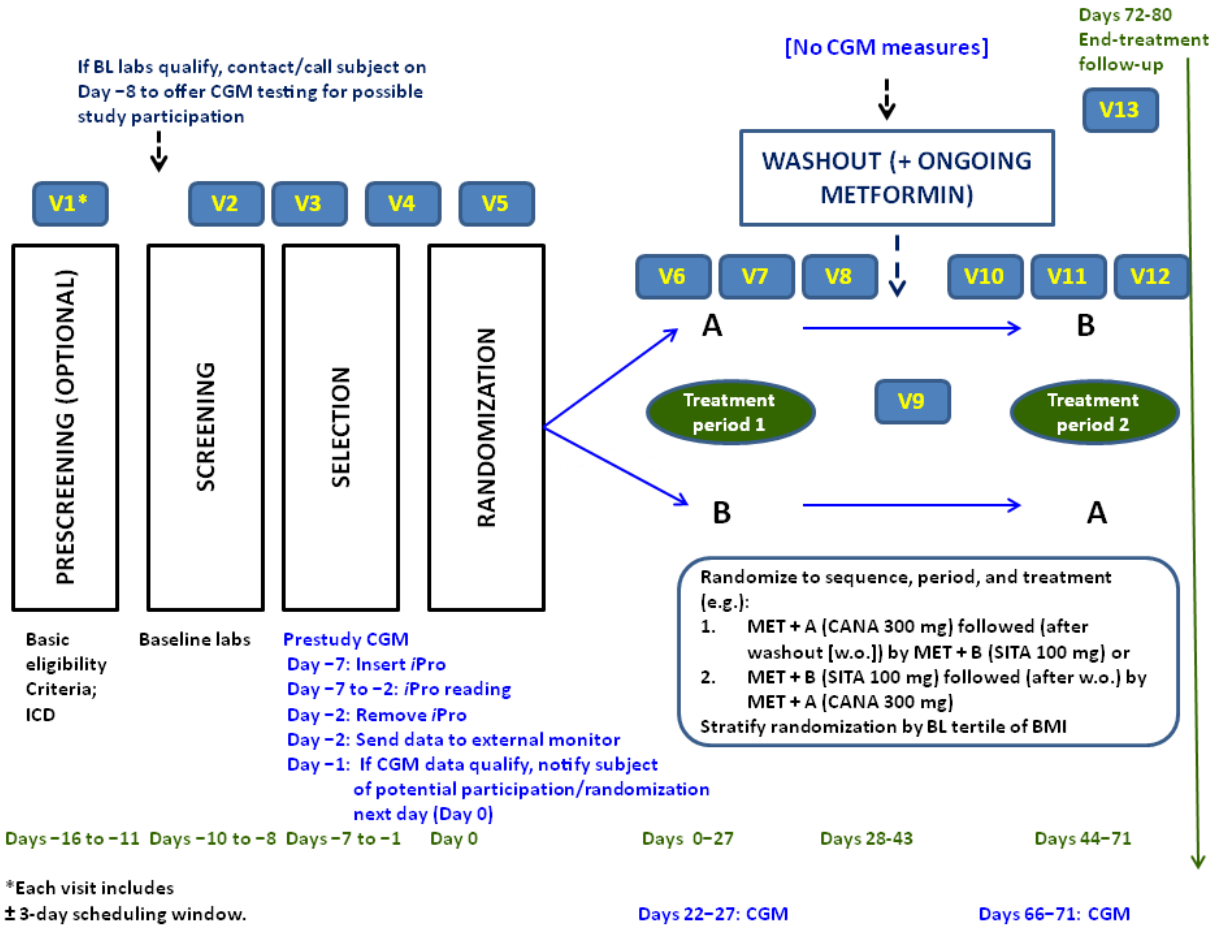

Figure 1. Study design schema and timeline for the CANA CGM trial. Because the prescreening visit is optional, Visit 1 can be the same as Visit 2. Study medications and instructions are dispensed at Visits 6 (Day 1; treatment period 1) and 10 (Day 44; treatment period 2); the CGM device is inserted at Visits 7 (Day 22; treatment period 1) and 11 (Day 66; treatment period 2) and removed (with downloading of data) at Visits 8 (Day 27; treatment period 1) and 12 (Day 71; treatment period 2), after 6 days of CGM measurements. Visit 9 is the washout visit and occurs on Day 28 (between the two treatment periods). Visit 13 is the end-treatment follow-up visit and occurs on Days 72 to 80.

4.1.1 Concise Summary of Procedures According to Visit and Subject (or Potential Subject), Investigator, and Study Site Personnel Responsibility

Following are key instructions for the investigator or other appropriately trained and authorized study site personnel. The guidance is expressed in greater detail in Section 5.4 of this document.

4.1.1.1 Optional Prescreening (Visit 1; Day −16 to −11 [with a ±3-day scheduling window])

- **Potential subject's responsibilities**:
  - Sign an Informed Consent Form (ICF) with 2 witnesses before participating in any protocol procedure (including assessment) after having the risks and benefits of protocol participating explained to you. If you do not understand these risks and benefits, ask the investigator or study site personnel to clarify them before signing the ICF.

- Meet with the investigator and answer his or her questions, including items about your current health status, medical history, and current medications. To participate in the study, you must be taking metformin at a stable dose for at least 8 weeks.

- **Investigator's responsibilities:**
  - Before any protocol procedure, including any assessment, discuss with the subject the potential benefits and risks of participation in the study. Obtain his or her written informed consent by distributing the study ICF and document this process within the medical charts. If needed, potential subjects have the right to an interpreter or to have the study explained orally and provide oral assent.

  - Baseline safety assessments can occur at this visit or the Screening Visit (Day −10; see below)

  - Measure vital signs: pulse rate, blood pressure (according to blood pressure measurement instructions in Appendix 5); pulse rate (Pulse rate will be measured once at each clinic visit) and blood pressure measurements and will be obtained after the subject has been in the sitting position for 5 minutes. Three consecutive blood pressure readings will be taken and recorded, at intervals of at least 1 minute apart. Respiration rate and body temperature. Perform12-lead ECG. Measure blood pressure according to instructions in Appendix 5. Document the data in the CRF and within the medical chart.

  - Perform (submit to central laboratory) fasting laboratory panels, including serum chemistries and hematology. If the baseline laboratory and other requirements meet qualifications, proceed to the selection (qualifying-CGM) phase. Document the data in the CRF and within the medical chart (appendix 10).

  - If the entire safety profile is not obtained (as above) measure pulse rate and blood pressure and record those in the CRF (measure blood pressure according to instructions in Appendix 5).

  - Measure body weight (in part because randomization is stratified by body mass index [BMI]). Body weight will be measured (at every visit) using the same calibrated and certified scale at each visit. Subjects will be weighed at approximately the same time of day on the same scale (with the subject wearing underwear and gown but no shoes). Subjects will be instructed to empty their bladder before being weighed. Document the data in the CRF and within the medical chart.

  - Through dialogue with the patient (interview), review the eligibility criteria. (See above, "Diagnosis and Main Criteria for Inclusion" [pp 7-8].) And document it within the medical charts.

  - Urine pregnancy testing will be performed for all women according to local procedures unless they are surgically sterile or unless there is a documented history of their postmenopausal status. 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. Pregnancy test must be performed in Central laboratory and the result reviewed prior to randomization (appendix 10).

  - If the subject meets all eligibility criteria (aside from the CGM and laboratory requirements below), proceed to the screening period.

- **Study site personnel's responsibilities**:
  - Make sure that the potential subject has signed the ICF and that it is properly filed.

  - If the subject meets all eligibility criteria (aside from the CGM requirement), request the potential subject's contact information, in order to arrange future study site visits.

  In the case that the site opts not to have the optional pre-screening visit, the site and patient will conduct this phase activities during Visit 2 (screening visit).

4.1.1.2 Screening (Visit 2; Day −10 to −8 [with a ±3-day scheduling window])

- **Potential subject's responsibilities**:

- Attend the study site for assessments.

- **Investigator's responsibilities**:
  - Perform a physical examination if not conducted at Visit 1 (optional prescreening) Physical examinations will include a full review of body systems (head and neck, eyes, chest and lungs, breast, cardiovascular (CV), extremities and back, abdomen, and neurologic examination). A pelvic/genitourinary system examination (ie, prostate, rectal, and gynecologic examinations) should be performed if considered clinically appropriate by the investigator. Whenever possible, the assessments should be made at the same time of day by the same investigator for each subject. Measure vital signs: pulse rate, blood pressure (according to blood pressure measurement instructions in Appendix 5); pulse rate (Pulse rate will be measured once at each clinic visit) and blood pressure measurements and will be obtained after the subject has been in the sitting position for 5 minutes and before taking blood samples. Three consecutive blood pressure readings will be taken and recorded, at intervals of at least 1 minute apart. Respiration rate and body temperature. Perform12-lead ECG. Measure blood pressure according to instructions in Appendix 5. Document the data in the CRF and within the medical chart.

  - If not conducted at Visit 1 (optional prescreening) perform (submit to central laboratory) fasting laboratory panels, including serum chemistries and hematology (Subjects must fast for at least 8 hours before blood sample collection). If the baseline laboratory and other requirements meet qualifications, proceed to the selection (qualifying-CGM) phase (appendix 10).

  - If the entire safety profile was obtained (as above) during the optional prescreening visit, measure only pulse rate and blood pressure and record them in the CRF and within the medical chart.

  - Measure body weight. Body weight will be measured (at every visit) using the same calibrated scale at each visit. Subjects will be weighed at approximately the same time of day on the same scale (with the subject wearing underwear and gown but no shoes). Subjects will be instructed to empty their bladder before being weighed. Document the data in the CRF and within the medical chart.

  - If not conducted at Visit 1 (optional prescreening) urine pregnancy testing will be performed for all women according to local procedures unless they are surgically sterile or unless there is a documented history of their postmenopausal status. 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. Pregnancy test must be performed in Central laboratory and the result reviewed prior to randomization (appendix 10).

- **Study site personnel's responsibilities**:
  - Take blood sample(s) for fasting laboratory panels, label and process samples, and inform the central laboratory to arrange for sample pick up.

  - Ensure that safety data have been recorded in the medical chart.

  - Ensure that the potential subject's laboratory samples have been collected by the local laboratory for analysis.

  - Advise the potential subject that study site personnel will contact him or her if the baseline laboratory results qualify for the next phase (selection).

  - Contact the potential subject on Day −8 if the baseline laboratory results qualify him or her for the next phase (selection).

4.1.1.3 Selection (Visit 3; Day −7 to −1 [with a ±3-day scheduling window] and visit 4; day -2)

This will be the potential subject's first experience using the CGM device. Following are the key steps, according to the responsibilities of the potential subject, investigator, and other appropriately qualified and trained study site personnel.

- **Potential subject's responsibilities**:

- Wear the CGM *i*Pro2 continuously for 6 days while following normal daily activities (see Appendix 7C).

- On Day 1, calibrate the device using the One Touch UltraMini™ (See instructions in Appendix 6.) by doing the following: After the CGM *i*Pro2 has been inserted (on the same day of insertion), measure your plasma glucose 3 times with the glucometer One Touch Ultra Mini ™: 1 hour after insertion, 2 hours after insertion, and once before bedtime, on the day of insertion (Appendix 6) and write down the results of these measurements in the Patient Log Sheet (Appendix 8).

- Use the same glucose meter and lot of strips for the entire study. Do not allow anyone else to use the glucose meter during the study.

- On each of the other 5 days of the selection phase (day 2, 3, 4, 5 and 6 of measurement), measure your plasma glucose with the glucometer One Touch Ultra Mini ™ 4 times a day: after you awake from sleep and after each of your 3 daily meals. Write down the results of each of these measurements in the Patient Log Sheet (Appendix 8)

- Receive the pedometer and learn how to use it.

- Receive the Glucometer and strips, making sure you understand how to use the glucometer appropriately (Appendix 6) during the different days of CGM readings (Appendix 7C).

- Receive instructions from the investigator and study site personnel regarding the use of the Patient Log Sheet (Appendix 8) and make sure that you understand it before leaving the clinic during your visit to the study investigator/personnel.

- Use the Patient Log Sheet (Appendix 8) to record what you eat at each meal; any exercise or strenuous activities and the times when these occur; times when you take your study medications (should be soon after awakening from sleep), numbers of daily steps as per pedometer readings, glucometer capillary blood glucose readings and any unusual signs or symptoms that you may experience (Appendix 7A, 7C). These may include side effects of the medication and/or signs or symptoms of hypoglycemia. The symptoms of hypoglycemia include:

- Excessive hunger, fatigue, sweating, unsteady feeling, or fainting

- Confusion or other mental effects
    - Irritability
    - Blurred vision
    - Sense of "pins and needles"
    - Anxiety
    - Slurred speech
    - Tremor

- Shakiness or light-headedness

- Nausea or vomiting

- Dry or tingling lips

- Sense of abnormal heart beat

Patient will be instructed that in the case of signs and symptoms of hypoglycemia, he or she will immediately consult to the nearest Emergency service or ambulance service. The information regarding which service will be reviewed with the site personnel.

- Keep the Patient Log Sheet accessible at all times (Appendix 8), so that you can immediately write down the needed information. Write down the time and date within 5 minutes of each blood glucose reading.

- Bring Patient Log Sheet to visit 4 to the site and make it available for the study personnel.
- Maintain ongoing treatment with Metformin at stable dose.

Investigator's responsibilities:

- On visit 3, insert the CGM device (*i*Pro2) subcutaneously in the patient's abdomen, according to manufacturer instructions (Day −7; Appendix 7A, 7B).
- On visit 3, distribute and thoroughly review the Patient Log Sheet (Appendix 8) with the potential subject. Ensure that the individual understands the key dietary, physical-activity, number of steps by pedometer readings, medication and clinical-symptom information that needs to be recorded, as well as capillary blood glucose readings.
- On visit 4, remove the sensor, within 24 hours of finishing the CGM reading period of 6 days, according to manufacturer's instructions (Day −1; Appendix 7A, 7B).
- Manually enter all data from the Patient Log Sheet into the system on the same day that the sensor is removed from the patient.
- Download data from the CGM *i*Pro2 as well as calibration data from the One Touch Ultra Mini™ glucometer on the same day that the sensor is removed from the patient. Glucose measurement data for calibration will be recorded in the Patient Log Sheet. Therefore, in case of problems downloading calibration data from the One Touch Ultra Mini ™ glucometer device, the data can be entered manually as well (Appendix 6).
- Send results of CGM baseline reading/CGM test to the External Monitor. The External Monitor will respond to each site within 24 hours of receiving the data (to confirm data acceptability and suitability for patient selection to participate and be enrolled/randomized).
- Measure body weight. Body weight will be measured (at every visit) using the same calibrated and certified scale at each visit. Subjects will be weighed at approximately the same time of day on the same scale (with the subject wearing underwear and gown but no shoes). Subjects will be instructed to empty their bladder before being weighed. Document the data in the CRF and within the medical chart.

Study site personnel's responsibilities:

- Receive training in the use of the CGM *i*Pro2 (Appendix 7A), as well as the web-based program for data collection (CareLink *i*Pro2) and the One Touch Ultra Mini™ glucose meter for CGM device calibration (Appendix 6).
- Set the glucose meter (one Touch Ultra Mini ™) to time and date according to instructions (Appendix 6).
- Review the following items with the potential subject, and make sure that he/she understands each; answer any questions or confirm that he/she has no questions about:
  - Using the CGM *i*Pro2 (Appendix 7A, 7C) and the One Touch UltraMini™ to calibrate the device (according to manufacturer's instructions; Appendix 6).
  - Telephone numbers to call in case of questions about: 1) the study overall; 2) adverse events in particular (including signs and symptoms of hypoglycemia); 3) the CGM *i*Pro2 and One Touch UltraMini™ (Appendix 6); and 4), including malfunctions and other mechanical issues of the devices
  - Complying with the Patient Log Sheet and understanding how to use it (Appendix 8).
  - Potential problems related to detachment of the CGM device.

- Taking all study medications as instructed.

- Returning to the study site, after 6 days of blood-glucose monitoring during the selection phase, so that the study personnel can: 1) download the CGM data and 2) review the Patient Log Sheet with the potential subject.

- Advise the potential subject that study site personnel will contact him or her if the CGM results qualify him or her for the next phase (Randomization).

- Contact the potential subject at least once during the 6-day CGM reading period to remind about Capillary blood glucose readings with the glucometer.

- Contact the potential subject on Day −1 if the CGM results qualify him or her for the next phase (Randomization) and schedule next visit within the next 3 days.

4.1.1.4 Randomization (Visit 5; Day 0 [with a ±3-day scheduling window])

Patients who meet overall eligibility criteria and have qualifying laboratory and CGM results will be offered an opportunity to participate in the study.

- **Subject's responsibilities**:
  - Report to the study site to receive:
    - Study medications
    - Assessments and instructions from the investigator and study site personnel

- **Investigator's responsibilities**:
  - Review the overall purposes of the study and remind subjects to:
    - Take their study medications as instructed.
    - Measure their fasting plasma glucose with the glucometer One Touch Ultra Mini ™ every morning during the study, additional to the additional measurements during the time they will be wearing the CGM as instructed.
    - Report any AEs (that occur between clinic visits) to the central study telephone number.
    - Return to the study site 6 days before the end of the treatment period (Day 22; approximately 3 weeks from the randomization visit) to receive CGM device and associated materials.
    - Measure pulse rate and blood pressure (according to blood pressure measurement instructions in Appendix 6).
  - Measure body weight. Body weight will be measured (at every visit) using the same calibrated scale at each visit. Subjects will be weighed at approximately the same time of day on the same scale (with the subject wearing underwear and gown but no shoes). Subjects will be instructed to empty their bladder before being weighed. Document the data in the CRF and within the medical chart.

- **Study site personnel's responsibilities**:
  - Reinforce the overall purposes of the study and remind subjects to:
    - Take their study medications as instructed
    - Report any AEs to the study telephone number
    - Return to the study site 6 days before the end of the treatment period to receive CGM and associated materials
  - Provide the central study telephone number so that the subject can report any AEs.

4.1.1.5 Study Treatment (Visit 6; Begin treatment period A; Day 0 [with a ±3-day scheduling window])

- **Subject's responsibilities**:
  - Receive blinded treatment period A study medication and instructions.

- Take medications (including metformin) as specified and be prepared to return to the study site for CGM monitoring and to return any unused medications.
- Measure your plasma glucose with the glucometer One Touch Ultra Mini ™ every morning after you awake from sleep before the first meal of the day. Write down the results of each of these measurements in in the log provided by the sponsor.
- Report to the site any repeated fasting plasma Glucose (FPG) measurements >280 mg/dl.
- Report any AEs to the central study telephone number provided.
- Return to the study site to receive and have inserted the CGM *i*Pro2 and receive the glucometer One Touch UltraMini™ and pedometer 6 days before the end of the treatment period (Visit 7; Day 22; **Figure 1**).

Investigator's responsibilities:

- Dispense study medications and instructions.
- Measure pulse rate and blood pressure (Appendix 5).
- Measure body weight. Body weight will be measured (at every visit) using the same calibrated scale at each visit. Subjects will be weighed at approximately the same time of day on the same scale (with the subject wearing underwear and gown but no shoes). Subjects will be instructed to empty their bladder before being weighed. Document the data in the CRF or within the medical chart.
- Address any questions or concerns from the subject or study personnel that are of a clinical nature and relate to the subject's continued safe and effective participation in the study.
- If subject reports any repeated fasting plasma Glucose (FPG) measurements >280 mg/dl, perform confirmatory FPG in Laboratory.

Study site personnel's responsibilities:

- Instruct the patient that in the case of signs and symptoms of hypoglycemia and/or Diabetic ketoacidosis (DKA), he or she will immediately consult to the nearest Emergency service or ambulance service. The information regarding which service will be reviewed with the site personnel.
- Contact the subject by telephone, in order to remind the subject to return to the study site at the appropriate time (Day 22) for the CGM visit.

4.1.1.6 Study Treatment ("CGM In"; Visit 7; Day 22 [with a ±3-day scheduling window])

Subject's responsibilities:

- Return to the study site to receive the CGM *i*Pro2 device, which will be inserted in your abdomen by the investigator.
- Wear the CGM *i*Pro2 continuously for 6 days while following normal daily activities (including taking your study medications) (Appendix 7C).
- On Day 1 with the CGM (Day 22 overall), calibrate the device using the glucometer One Touch UltraMini™ (See instructions in Appendix 6.) (Appendix 7C): After the CGM *i*Pro2 has been inserted, measure plasma glucose 3 times with the glucometer One Touch Ultra Mini ™ : 1 hour after insertion, 2 hours after insertion, and once before bedtime, on the day of insertion (Appendix 7A and 7C). Write the result of these measurements in the Patient Log sheet (Appendix 8)
- On each of the other 5 days of the CGM reading (day 2, 3, 4, 5 and 6 of measurement), measure your plasma glucose with the glucometer One Touch Ultra Mini ™ 4 times a day: after you awake from sleep and after each of your 3 daily meals. Record the results of each of these measurements in the Patient Log Sheet (Appendix8).

- Use the same glucose meter and lot of strips for the entire study. Do not allow anyone else to use the glucose meter during the study.

- Receive instructions from the investigator and study site personnel regarding the use of the Patient Log Sheet (Appendix 8) and make sure that you understand how to use it before leaving the clinic during your visit to the study investigator/personnel.

- Receive instructions from the investigator and study site personnel regarding the use of pedometer and Glucometer and make sure that you understand how to use it before leaving the clinic during your visit to the study investigator/personnel.

- Use the Patient Log Sheet (Appendix 8) to record: what you eat at each meal; any exercise or strenuous activities and the times when these occur; times when you take your study medications (should be soon after awakening from sleep); and any unusual signs or symptoms that you may experience, number of daily steps as measured by the pedometer. These may include side effects of the medication and/or signs or symptoms of hypoglycemia (as explained above).

- Keep the Patient Log Sheet (Appendix 8) accessible at all times, so that you can immediately write down the needed information. Write down the results of the plasma glucose measurements from the glucometer including time and date within 5 minutes of each blood glucose reading.

Investigator's responsibilities:

- On visit 7, insert the CGM (*i*Pro2) sensor subcutaneously in the patient's abdomen, according to manufacturer instructions (Day −7; Appendix 7A, 7B).

- Distribute and thoroughly review the Patient Log Sheet (Appendix 8) with the subject. Ensure that the individual understands the key dietary, physical-activity (including daily number of steps by pedometer measurements), medication, and clinical-symptom information that need to be recorded.

- Distribute pedometer and teach the patient how to use it.

- Distribute the Glucometer and strips, making sure the individual understand how to use it (Appendix 6) during the different days of CGM readings (Appendix 7C).

- On each visit, measure pulse rate and blood pressure (according to blood pressure measurement instructions in Appendix 5). Record data in the CRF.

- Measure body weight. Body weight will be measured (at every visit) using the same calibrated scale at each visit. Subjects will be weighed at approximately the same time of day on the same scale (with the subject wearing underwear and gown but no shoes). Subjects will be instructed to empty their bladder before being weighed. Document data in the CRF.

Study site personnel's responsibilities:

- Contact the subject at least once during the 6-day CGM reading period to remind about Capillary blood glucose readings with the glucometer and Remind the patient of schedule visit #8

4.1.1.7 Study Treatment ("CGM out"; Visit 8; Day 27 [with a ±3-day scheduling window])

Subject's responsibilities:

- Return to the study site to have the CGM *i*Pro2 sensor removed from your abdomen by the investigator.

- Return with your completed Patient Log Sheets.

Investigator's responsibilities:

- On visit 8, remove the CGM (*i*Pro2) sensor from the patient's abdomen, within 24 hours of finishing the CGM reading period of 6 days, according to manufacturer's instructions (Appendix 7A, 7B).

- Download data from the CGM *i*Pro2 as well as calibration data from the One Touch Ultra Mini™ glucometer on the same day that the sensor is removed from the patient. Glucose measurement data for calibration will be recorded in the Patient Log Sheet. Therefore, in case of problems downloading calibration data from the One Touch Ultra Mini™ glucometer device, the data can be entered manually as well (Appendix 6).

- Review data from the Patient Log Sheets with the subject.

- Manually enter all data from the Patient Log Sheet into the CareLink iPro2 system on the same day that the sensor is removed from the patient.

- Measure pulse rate and blood pressure (according to blood pressure measurement instructions in Appendix 5). Document data in the CRF and patient chart.

- Measure body weight. Body weight will be measured (at every visit) using the same calibrated scale at each visit. Subjects will be weighed at approximately the same time of day on the same scale (with the subject wearing underwear and gown but no shoes). Subjects will be instructed to empty their bladder before being weighed. Document data in the CRF and patient chart.

Study site personnel's responsibilities:

- Remind the subject to return to the study site the next day (Day 28) to begin the washout period.

4.1.1.8 Washout (Visit 9; Day 28 [with a ±3-day scheduling window])

Subject's responsibilities:

- If not returned in Visit 8, return to the study site with vial containing unused study medications.

- Return all unused medications to study site personnel (to enable compliance check).

- Take medication as directed during washout period

- Measure your plasma glucose with the glucometer One Touch Ultra Mini ™ every morning after you awake from sleep before the first meal of the day. Write down the results of each of these measurements in the log provided by the sponsor.

- Report to the site any repeated fasting plasma Glucose (FPG) measurements >280 mg/dl.

Investigator's responsibilities:

- Elicit any AEs from the subject via open-ended questioning. In a nonthreatening dialogue, ask the subject if he/she has any other ongoing questions or concerns about the study.

- Address any questions or concerns from the subject or study personnel that are of a clinical nature and relate to the subject's continued safe and effective participation in the study.

- Instruct the subject to take only metformin and no other study medications during the following 16 days.

- Measure pulse rate and blood pressure (according to blood pressure measurement instructions in Appendix 5). Record data in the CRF.

- Measure body weight. Body weight will be measured (at every visit) using the same calibrated scale at each visit. Subjects will be weighed at approximately the same time of day on the same scale (with the subject wearing underwear and gown but no shoes). Subjects will be instructed to empty their bladder before being weighed. Document data in the CRF and patient chart.

- If subject reports any repeated fasting plasma Glucose (FPG) measurements >280 mg/dl, perform confirmatory FPG in Laboratory.

- **Study site personnel's responsibilities**:
  - Collect all unused study medications. If no unused study medications are returned, ask the subject if he or she has taken all medication during the treatment period or has forgotten to return with unused medications.
  - Perform pill count and compliance check. Compute pill count as the number of pills taken (# of pills dispensed – # of pills counted). The number of pills expected to have been taken is calculated by multiplying the daily dose (1 tablet) by the number of days since the date dispensed (Lee JK et al. *Ther Clin Risk Manag* 2007; 3:685-90). An a-priori criterion of 80% to 120% will be applied to designate acceptable compliance.
  - If the subject has forgotten to return to the study site with unused study medications, schedule a follow-up return appointment as soon as possible to collect them.
  - Instruct subject to return to the study site 16 days after the Washout visit to begin the next treatment period (treatment period B).

4.1.1.9 Study Treatment (Visit 10; Begin treatment period B; Day 44 [with a ±3-day scheduling window])

- **Subject's responsibilities**:
  - Receive blinded treatment period B study medication and instructions.
  - Take medications (including metformin) as instructed.
  - Report any AEs to the central study telephone number provided.
  - Return to the study site
  - Measure your plasma glucose with the glucometer One Touch Ultra Mini ™ every morning after you awake from sleep before the first meal of the day. Write down the results of each of these measurements in the log provided by the sponsor.
  - Report to the site any repeated fasting plasma Glucose (FPG) measurements >280 mg/dl.

- **Investigator's responsibilities**:
  - Dispense study medications and instructions.
  - Remind subjects to:
    - Take their study medications as instructed.
    - Measure their fasting plasma glucose with the glucometer One Touch Ultra Mini ™ every morning. Write down their results of each of these measurements in the log provided by the sponsor and report to the site any repeated fasting plasma Glucose (FPG) measurements >280 mg/dl.
    - Report any AEs (that occur between clinic visits) to the central study telephone number.
    - Return to the study site to receive the CGM *i*Pro2 and the One Touch UltraMini™ 6 days before the end of the treatment period (Visit 11; Day 66; **Figure 1**).
  - Measure pulse rate and blood pressure (Appendix 5).
  - Measure body weight. Body weight will be measured (at every visit) using the same calibrated and certified scale at each visit. Subjects will be weighed at approximately the same time of day on the same scale (with the subject wearing underwear and gown but no shoes). Subjects will be instructed to empty their bladder before being weighed. Document the data in the CRF or within the medical chart.

- If subject reports any repeated fasting plasma Glucose (FPG) measurements >280 mg/dl, perform confirmatory FPG in Laboratory.

- Address any questions or concerns from the subject or study personnel that are of a clinical nature and relate to the subject's continued safe and effective participation in the study.

- **Study site personnel's responsibilities**:
  - Contact the subject by telephone 1 time each during Weeks 2 and 3, in order to remind the subject to return to the study site at the appropriate time (Day 66) for the CGM visit.

4.1.1.10 Study Treatment ("CGM In"; Visit 11; Day 66 [with a ±3-day scheduling window])

- **Subject's responsibilities**:
  - Return to the study site to receive the CGM *i*Pro2 device, which will be inserted in your abdomen by the investigator.

  - Wear the CGM *i*Pro2 continuously for 6 days while following normal daily activities (including taking your study medications) (Appendix 7C).

  - On Day 1 with the CGM (Day 22 overall), calibrate the device using the One Touch UltraMini™ (See instructions in Appendix 6.) (Appendix 7C): After the CGM *i*Pro2 has been inserted, measure plasma glucose 3 times with the glucometer One Touch Ultra Mini ™ : 1 hour after insertion, 2 hours after insertion, and once before bedtime, on the day of insertion (Appendix 7A and 7C). Write the result of these measurements in the Patient Log sheet (Appendix 8)

  - On each of the other 5 days of the CGM reading (day 2, 3, 4, 5 and 6 of measurement), measure your plasma glucose with the glucometer One Touch Ultra Mini ™ 4 times a day: after you awake from sleep and after each of your 3 daily meals. Record the results of each of these measurements in the Patient Log Sheet (Appendix8).

  - Use the same glucose meter and lot of strips for the entire study. Do not allow anyone else to use the glucose meter during the study.

  - Receive instructions from the investigator and study site personnel regarding the use of the Patient Log Sheet (Appendix 8) and make sure that you understand how to use it before leaving the clinic during your visit to the study investigator/personnel.

  - Receive instructions from the investigator and study site personnel regarding the use of the pedometer and glucometer and make sure that you understand how to use it before leaving the clinic during your visit to the study investigator/personnel.

  - Use the Patient Log Sheet (Appendix 8) to record: what you eat at each meal; any exercise or strenuous activities and the times when these occur; times when you take your study medications (should be soon after awakening from sleep); number of daily steps as measured by the pedometer and any unusual signs or symptoms that you may experience. These may include side effects of the medication and/or signs or symptoms of hypoglycemia (as explained above).

  - Keep the Patient Log Sheet (Appendix 8) accessible at all times, so that you can immediately write down the needed information. Write down the results of the plasma glucose measurements from the glucometer including time and date within 5 minutes of each blood glucose reading.

  - Report to the site any repeated fasting plasma Glucose (FPG) measurements >280 mg/dl.

- **Investigator's responsibilities**:
  - Insert the CGM (*i*Pro2) sensor subcutaneously in the patient's abdomen, according to manufacturer instructions (Appendix 7A, 7C).

  - Distribute pedometer and teach the patient how to use it.

- Distribute the Glucometer and strips, making sure the patient understand how to use it (Appendix 6) during the different days of CGM readings (Appendix 7C).

- Distribute and thoroughly review the Patient Log Sheets (Appendix 8) with the subject. Ensure that the individual understands the key dietary, physical-activity, medication, and clinical-symptom information that need to be recorded.

- Measure pulse rate and blood pressure (according to blood pressure measurement instructions in Appendix 5). Record data in the CRF.

- Measure body weight. Body weight will be measured (at every visit) using the same calibrated scale at each visit. Subjects will be weighed at approximately the same time of day on the same scale (with the subject wearing underwear and gown but no shoes). Subjects will be instructed to empty their bladder before being weighed. Record data in the CRF and medical chart.

- If subject reports any repeated fasting plasma Glucose (FPG) measurements >280 mg/dl, perform confirmatory FPG in Laboratory.

Study site personnel's responsibilities:

- Contact the subject at least once during the 6-day CGM reading period to remind about Capillary blood glucose readings with the glucometer and Remind the patient of and schedule visit #12

4.1.1.11 Study Treatment ("CGM out"; Visit 12; Day 71 [with a ±3-day scheduling window])

Subject's responsibilities:

- Return to the study site to have the CGM *i*Pro2 sensor removed from your abdomen by the investigator.

- Return with your completed Patient Log Sheets.

Investigator's responsibilities:

- On visit 12, remove the CGM (*i*Pro2) sensor from the patient's abdomen, within 24 hours of finishing the CGM reading period of 6 days, according to manufacturer's instructions (Appendix 7A, 7B).

- Download data from the CGM *i*Pro2 as well as calibration data from the One Touch Ultra Mini™ glucometer on the same day that the sensor is removed from the patient. Glucose measurement data for calibration will be recorded in the Patient Log Sheet. Therefore, in case of problems downloading calibration data from the One Touch Ultra Mini™ glucometer device, the data can be entered manually as well (Appendix 6).

- Review data from the Patient Log Sheets with the subject.

- Manually enter all data from the Patient Log Sheet into the CareLink iPro2 system on the same day that the sensor is removed from the patient.

- Measure pulse rate and blood pressure (according to blood pressure measurement instructions in Appendix 5). Document data in the CRF and patient chart.

- Measure body weight. Body weight will be measured (at every visit) using the same calibrated scale at each visit. Subjects will be weighed at approximately the same time of day on the same scale (with the subject wearing underwear and gown but no shoes). Subjects will be instructed to empty their bladder before being weighed. Document data in the CRF and patient chart.

Study site personnel's responsibilities:

- Remind the subject to return to the study site (Day 72) for the end-of-treatment follow-up visit.

4.1.1.12 End-of-treatment follow-up (Visit 13; Day 72 [with a ±3-day scheduling window])

- **Subject's responsibilities**:
  - Return to the study site.
  - Return all unused medications to study site personnel.
  - Undergo vital-signs and other end-of-treatment measures and receive further instructions.
- **Investigator's responsibilities**:
  - Measure pulse rate, blood pressure, and body weight. Perform other end-of-study assessments, including 12-lead ECG and fasting laboratory panels, to match the baseline safety screening.
  - Elicit any AEs from the subject via open-ended questioning.
  - Follow up any AE or abnormality in each of the 4 vital signs, ECG, or laboratory abnormalities, which are present on Day 72, over the remaining 9 days of the study (through Day 80). Record relevant data in the CRF.
  - Measure body weight. Body weight will be measured (at every visit) using the same calibrated scale at each visit. Subjects will be weighed at approximately the same time of day on the same scale (with the subject wearing underwear and gown but no shoes). Subjects will be instructed to empty their bladder before being weighed. Document the data in the CRF and within the medical chart.
  - Perform (submit to central laboratory) fasting laboratory panels, including serum chemistries and hematology (Subjects must fast for at least 8 hours before blood sample collection).
  - Remind the subject to continue taking his/her metformin at the same dose as at baseline and throughout the study.
- **Study site personnel's responsibilities**:
  - Collect all unused study medications. If no unused study medications are returned, ask the subject if he or she has taken all medication during the treatment period or has forgotten to return with unused medications.
  - If the subject has forgotten to return to the study site with unused study medications, schedule a follow-up return appointment as soon as possible to collect them.
  - The end-of-study visit will occur 1 day after the final CGM assessments. Refer to the instructions above for responsibilities related to CGM.
  - Ensure that all forms and other documents (e.g. CRFs, Patient Log Sheets), and any other study material (e.g. unused study medications, pedometers) have been returned.
  - Schedule a follow-up visit with the investigator within 9 days after the end-of-treatment visit if there are any ongoing or unresolved adverse events or abnormalities in vital signs, ECG, or laboratory panels.

4.1.2 CANA CGM Trial COMETA: Overview

The main agent being evaluated is CANA, which has a target indication of improving glycemic control in adults with T2DM, as an adjunct to diet and exercise. The active comparator is the DPP-4 inhibitor SITA, which shares CANA's target indication.

4.2 Endpoints and Hypotheses

4.2.1. Efficacy Endpoints

Efficacy endpoints will be measured in the intent-to-treat (ITT) population, which comprises all subjects who received at least one dose of medication and in whom CGM recordings at baseline and after each active treatment were

successful (>70% of tracings available). Efficacy will also be analyzed in the per-protocol (PP) population: members of the ITT population who complete the study without major protocol violations.

4.2.1.1. Primary Efficacy Outcome Measure

The primary efficacy endpoint is the mean (SD) intrapatient coefficient of variation (glucose CV %; SD/mean glucose), as assessed using CGM over a 3-day period at baseline and after each active treatment.

4.2.1.2. Secondary Efficacy Outcome Measures

Secondary efficacy endpoints include the mean (SD) change from baseline in each of the following as measured using CGM over a 3-day period at baseline and after each active treatment:

1. Glycemic SD for 24-hour glucose profile (mg/dL).
2. Mean 24-hour glucose profile (mg/dL).
3. Preprandial glucose (FPG; mg/dL).
4. 2-hour PPG (mg/dL).
5. Time (minutes), percent of 24 hours, or area under the glucose-time curve for 24 hours (AUC_{24h}) with glucose = 70−139 mg/dL (i.e. time spent with glucose in target range).
6. Time (minutes), percent of 24 hours, or AUC_{24h} (mg/dL/hr) with glucose > 140 mg/dL (i.e. time spent with glucose above target range).
7. Time (minutes), percent of 24 hours, or AUC_{24h} (mg/dL/hr) with glucose > 180 mg/dL (time spent with glucose markedly above target range).
8. Time (minutes), percent of 24 hours, or area over the glucose-time curve for 24 hours (AOC_{24h} ; mg/dL/hr) with glucose < 70 mg/dL (time spent with glucose below target range).
9. Frequency (%) of 2+ consecutive glucose readings < 70 mg/dL (and/or of hypoglycemic symptoms requiring personal support).

4.2.1.3. Exploratory Efficacy Outcome Measures

Exploratory endpoints in this pilot study will include mean (SD) changes from baseline in:

1. AUC for glycemic variability (mg/dL/hr) throughout the day (0−24 hours), after breakfast (0−5 hours), after lunch (5−11 hours), after dinner (11−15 hours), and during sleep (15−24 hours).
2. Peak glucose (mg/dL) throughout the day (0−24 hours), after breakfast (0−5 hours), after lunch (5−11 hours), after dinner (11−15 hours), and during sleep (15−24 hours).
3. Overall hyperglycemia: AUC_{total} (mg/dL/hr).
4. Nadir glucose (mg/dL): lowest glucose level over 72 hours.
5. Continuous overlapping net glycemic action (CONGA): the SD of summed differences between observations separated by *n* hours.
6. Mean of daily differences in PG (MODD).

Body weight and levels of physical activity (assessed by wearable pedometers) will also be evaluated at the screening visit, each active-treatment 3-day CGM visit, and the washout visit.

4.2.1.4. Safety and Tolerability Outcome Measures

Incidences of AEs related to safety and tolerability will be predicated on the safety population, which comprises subjects receiving at least one dose of active treatment.

4.2.1.4.1. Safety

Medical history, physical examination, vital signs (body temperature, pulse rate, blood pressure, and respiration rate), 12-lead electrocardiograms, serum chemistries, haematology, and urinalysis will be assessed at the screening and end-of-study visits. Pulse rate and blood pressure will be measured at every visit during the study.

4.2.1.4.2. Tolerability

Adverse events (AEs) will be elicited via open-ended questioning at each study visit. Treatment-emergent adverse events (TEAEs) will be defined as events that first occur, or are present at screening and worsen, after initial randomization and the randomized crossover.

4.2.2. Outcome Measures

Safety will be assessed according to mean values for vital signs, 12-lead ECGs, and clinical laboratory assessments at the screening and end-of-study visits in this population (Visits 1 and 6). Incidences of abnormal safety test results will be based on predefined, local reference ranges and each Investigator's customary clinical practice. Adverse events will be elicited by open-ended questioning at each visit and coded as to system organ class and preferred term using Medical Dictionary of Regulatory Activities (MedDRA) version 14 (or higher). Tolerability will be determined as the incidence of subjects with one or more TEAEs (by treatment group). Safety will be further evaluated according to incidences (number of patients and events) of SAEs, AEs leading to treatment discontinuation, and serious drug-related AEs.

4.3. Interim Analysis and End of Study

Consistent with the short-term (two 28-day active treatment phases), cross-over design of this study, there will be no pre specified interim analysis. In addition, the relatively small targeted enrollment (see below) largely precludes subgroup analyses.

4.4. Hypotheses

The primary hypothesis is that mean changes from baseline in mean intrapatient glucose CV % are statistically significantly lower after 28 days of treatment with CANA 300 mg (vs. SITA 100 mg) when each is combined with MET in patients with T2DM inadequately managed while using this biguanide as monotherapy. Specific null hypotheses and alternative hypotheses are stated in the Statistical Analysis Plan.

4.5. Treatments, Dosages, and Administration

4.5.1. Treatment of Interest: Canagliflozin

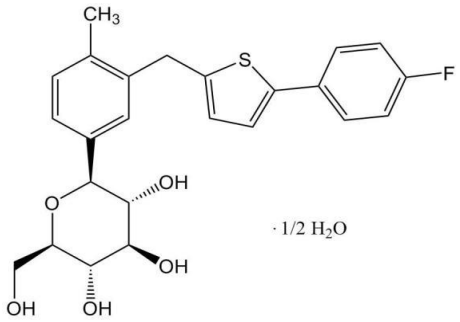

Figure 2. Molecular structure of canagliflozin (CANA).

4.5.1.1. CANA 300 mg will be administered once daily, before the first meal of the day.

CANA is a sodium-glucose co-transporter-2 (SGLT-2) inhibitor. SGLT-2 is expressed in the proximal renal tubules, mediating reabsorption of filtered glucose from the lumen of the tubule. By inhibiting the activity of this transporter, CANA elevates urinary glucose excretion, reducing reabsorption of filtered glucose. The dissociation constant for CANA's competitive inhibition of SGLT-2 is K_i = 0.84 ± 0.06 nM. In cultured SGLT-2−expressing cells, CANA decreases α-methyl-D-glucopyranoside (AMG) uptake with an IC_{50} value of 4.2 ± 1.5 nM. The IC_{50} value for inhibition of AMG by SGLT1−expressing cells is 555 ± 31 nM. Hence, CANA inhibits SGLT-2 with 109 times greater selectivity compared to SGLT1 (Kuriyama et al., 2014).

CANA significantly reduced fasting plasma glucose (FPG), by approximately 35−45 mg/dL, and PPG by 45−60 mg/dL, in clinical trials (**Figure 3**) (Inagaki et al., 2013; Stenlof et al., 2013; Janssen, 2013). One reason that CANA does not increase the risk of hypoglycemia is that the renal threshold for glucose (RT_G) typically remains above the hypoglycemia threshold (Sha et al., 2014). High-dose CANA may reduce PPG by nonrenal mechanisms (i.e. beyond urinary glucose excretion; potential enteral SGLT-1 mechanism) (Stein et al., 2014). CANA may be able to delay and attenuate PPG excursions (Sha et al., 2015). However, no clinical trial to date has specifically evaluated the effects of CANA + metformin (MET) vs. MET + a dipeptidyl peptidase 4 (DPP4) inhibitor on GV in patients with inadequate glucose control while using MET monotherapy.

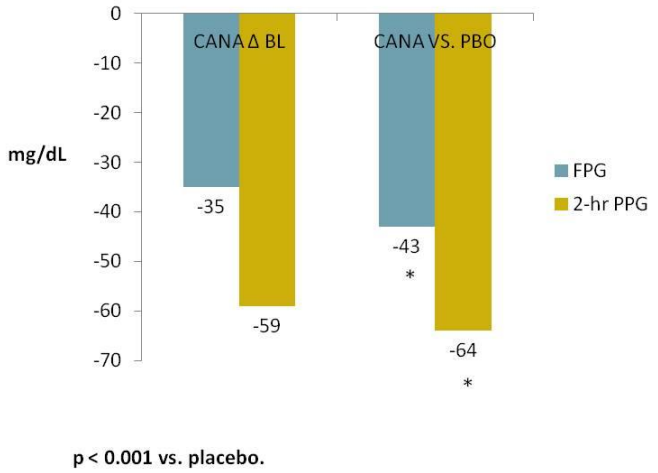

Figure 3. Effects of canagliflozin 300 mg (vs. baseline and placebo) on fasting plasma glucose (FPG; preprandial glucose) and 2-hour postprandial glucose (PPG) (Janssen, 2013).

Potential safety issues with CANA (when administered without insulin or insulin secretagogues) include hypotension (secondary to reductions in intravascular volume), hyperkalemia, hypersensitivity reactions, and genital mycotic infection. Because of its renal mechanism of action, CANA is contraindicated in patients who have severe renal impairment or end-stage renal disease and/or are undergoing dialysis. In randomized controlled trials, adverse drug reactions observed with CANA that had incidences of ≥5% included increased urination and genitourinary infections (Janssen, 2013).

During a routine review of unblinded interim data from an ongoing Phase 3 study, the Independent Data Monitoring Committee observed a non-dose-dependent increase in the incidence of non-traumatic, lower-extremity amputations (mostly of the toes) in the canagliflozin 100 mg and 300 mg groups compared to placebo. With a mean duration of follow-up in CANVAS of approximately 4.5 years, the annualized incidence of lower-extremity amputation was 0.73, 0.54, and 0.30 events per 100 patient-years in the canagliflozin 100 mg, canagliflozin 300 mg, and placebo groups,

respectively. Overall, treatment with canagliflozin was associated with an approximately 2-fold increase in amputation event rates (relative risk [RR] 2.15; 95% CI: 1.3 - 3.5). The Phase 3 study IDMC, which has access to unblinded CV outcomes data, notified the sponsor that "after consideration of all outcomes, the IDMC feels the study should continue." Infections were the events most commonly associated with amputations, and most amputations were of the toe. The factors associated with the greatest risk for amputation included prior amputation, peripheral vascular disease, and neuropathy.

Final results from two clinical trials – the CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-R (A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus) – showed that leg and foot amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo, which is an inactive treatment. The CANVAS trial showed that over a year's time, the risk of amputation for patients in the trial were equivalent to:
• 5.9 out of every 1,000 patients treated with canagliflozin
• 2.8 out of every 1,000 patients treated with placebo

The CANVAS-R trial showed that over a year's time, the risk of amputation for patients in the trial were equivalent to:
• 7.5 out of every 1,000 patients treated with canagliflozin
• 4.2 out of every 1,000 patients treated with placebo

Amputations of the toe and middle of the foot were the most common; however, amputations involving the leg, below and above the knee, also occurred. Some patients had more than one amputation, some involving both limbs.

For subjects who develop conditions that are associated with amputation such as a lower extremity infection, skin ulcer, osteomyelitis, gangrene, or critical limb ischemia, study drug should be interrupted until the condition has resolved in the opinion of the investigator. In the event of an amputation, restarting of dosing with canagliflozin should only be done after careful consideration of the individual risk:benefit and following discussion with the sponsor.

As of 11 May 2015, in the T2DM clinical development program, incidence rates of unblended serious adverse events of diabetic ketoacidosis (DKA), ketoacidosis, metabolic acidosis, and acidosis were 0.0522 (0.07%, 4/5337), 0.0763 (0.11%, 6/5350), and 0.0238 (0.03%, 2/6909) per 100 subject-years with canagliflozin 100 mg, canagliflozin 300 mg, and comparator, respectively. Of the 12 subjects with serious adverse events of DKA, ketoacidosis, metabolic acidosis, or acidosis (all of whom were hospitalized), 6 subjects on canagliflozin (3 on canagliflozin 100 mg and 3 on canagliflozin 300 mg), and none on comparator were reported to have autoimmune diabetes (latent autoimmune diabetes of adulthood [LADA] or type 1 diabetes) or tested positive for GAD65 antibodies after being diagnosed with a serious DKA-related event. Eight of the 10 subjects on canagliflozin were receiving insulin therapy. The blood glucose values around the time of admission in 9 of 10 subjects on canagliflozin ranged from 347 to 571 mg/dL (9.3 to 31.7 mmol/L). The remaining subject had blood glucose values ranging from 148 to 320 mg/dL (8.2 to 17.8 mmol/L). Diabetic ketoacidosis has also been reported during post-marketing surveillance and has occurred in patients with blood glucose values less than 250 mg/dL (13.9 mmol/L). As a result, DKA is considered a rare adverse drug reaction.

In preclinical studies in rats, hyperostosis (increased trabecular bone) was observed; mechanistic toxicology studies demonstrated that hyperostosis, like the tumors discussed above, related to carbohydrate malabsorption in rats treated with canagliflozin, with consequent marked hypercalciuria (which is not seen in human). A detailed analysis of bone safety was conducted in the Phase 3 program, including an assessment using DXA in a dedicated Phase 3 study (a study conducted in older subjects [ages >55 and <80 years] with T2DM) and a cross-program assessment of fracture incidence. Bone mineral density (BMD) was examined at 4 sites: at the lumbar spine, total hip, distal radius, and femoral neck. Minimal changes in BMD from baseline to Week 104 were seen in the lumbar spine (a cancellous bone region), femoral neck (a mixed cancellous and cortical bone region), and distal forearm. A decrease in BMD from baseline to Week 104 in the total hip, a site comprised of mixed cortical and cancellous bone (like the femoral neck), was observed for both canagliflozin treatment groups (-0.9% and -1.2% in the canagliflozin 100 mg and 300 mg groups, respectively, placebo adjusted). In a cardiovascular study of 4,327 subjects with known or at high risk for cardiovascular disease (Study DIA3008), the incidence rates of bone fracture were 1.6, 1.6, and 1.1 per 100 subject years of exposure to canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy. The final results of this same study (CANVAS program) reported an HR of 1.23 (95% CI, 0.99–1.52) for Low-trauma fracture for Canagliflozin vs placebo. In other

T2DM studies with canagliflozin, which enrolled a general diabetes population of approximately 5,800 subjects, no difference in fracture risk was observed relative to control.

4.5.2. Reference Treatment: Sitagliptin (Active Comparator)

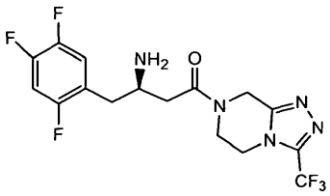

Figure 4. Molecular structure of sitagliptin.

SITA 100 mg will be administered once daily at the same time as CANA 300 mg (within each period, not concurrently with CANA 300 mg).

SITA is a dipeptidyl peptidase 4 (DPP-4) inhibitor with a molecular structure depicted in **Figure 4**. By inhibiting DPP-4, which catalyzes *N*-terminal amino-acid (alanine/proline) enzymatic degradation of the endogenous incretins glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide, DPP-4 inhibitors such as SITA promote glucose-dependent insulin release via the endocrine action of the hormone glucagon in enterocytes and other target cells; the activities of both GLP-1 and GIP cease when PG falls below 55 mg/dL (Richter et al., 2008). DPP-4 is expressed widely in the body, not only in the intestine; other sites of DPP-4 include the capillary endothelium, kidney, liver, and a variety of immune effector cells, including B and T lymphocytes and natural-killer cells. The aminopeptidase DPP-4 spans cell surfaces and transduces intracellular signals via both circulating and intracellular molecules (Richter et al., 2008).

DPP-4 is a member of a family of enzymes that also includes DPP-4β, DPP-6, DPP-8, DPP-9, quiescent cell proline dipeptidase, and fibroblast activation protein. Sitagliptin metabolites M1, M2, and M5 are (respectively) about 300-, 1,000-, and 1,000-fold less active as DPP-4 inhibitors compared to SITA; the IC_{50} values for these metabolites are about 5, >20, and >20 µM (respectively) compared to 18 nM for SITA. Sitagliptin is highly selective as a substrate for DPP-4 compared to DPP-8/9; binding to the latter molecules can result in severe toxicity (European Medicines Agency, 2007).

In randomized controlled trials, SITA 100 mg reduced FPG by approximately 23 mg/dL and 2-hour PPG by 52 mg/dL compared to placebo (**Figure 5**)(Merck, 2010).

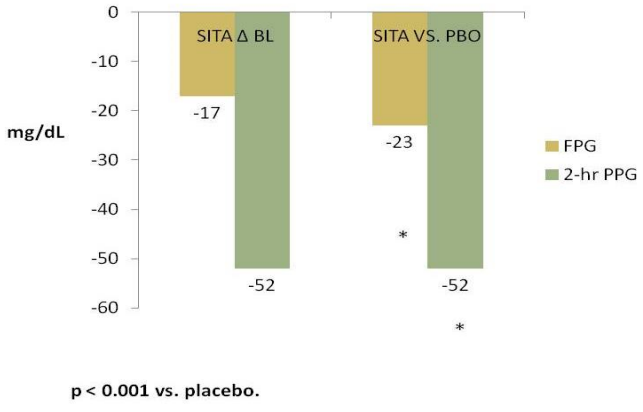

Figure 5. Effects of SITA 100 mg (vs. baseline and vs. placebo) on FPG (preprandial glucose) and 2-hour PPG (Merck, 2010).

Potential safety issues with SITA (when administered without insulin or insulin secretagogues) include potentially fatal necrotizing or hemorrhagic acute pancreatitis; acute renal failure; allergic and hypersensitivity reactions; and severe and disabling arthralgia. In randomized controlled trials, adverse drug reactions observed that had incidences of ≥5% with SITA included nasopharyngitis, upper-respiratory-tract infection, and headache (Merck, 2010).

4.6 Study Rationale

4.6.1 Background: Clinical Studies Involving Canagliflozin or Sitagliptin

The CANA CGM trial is unprecedented in comparing the effects of CANA (vs. SITA) on GV using CGM. One non-CGM study (with more than one report) compared the effects of CANA and SITA on glucose control (Schernthaner et al., 2013; Lavalle-Gonzalez et al., 2013; Lavalle-Gonzalez et al 2016). Previous CGM studies have mainly assessed the effects of these agents on glucose profiles at study conclusion (vs. baseline) or against other comparators (e.g. placebo). Some of these studies did not include CGM (**Table 1**)(Rosenstock et al., 2012; Schernthaner et al., 2013; Cefalu et al., 2013; Lavalle-Gonzalez et al., 2013b) and others did include this technology (**Table 2**)(Ellis et al., 2011; Guerci et al., 2012; Argento and Nakamura, 2016) (Janssen Protocol 28431754DIA2004).

In these clinical trials, subjects receiving CANA 300 mg had more marked reductions in parameters of glucose control when directly compared to SITA 100 mg in non-CGM studies (**Table 1** and **Figure 6**) and also greater reductions in mean (SD) glycemic SD when CANA 300 mg or SITA 100 mg was compared to placebo in CGM studies. Data in **Tables 1 and 2** inform sample size calculations in the Statistical Analysis Plan (see below).

Table 1. Effects of CANA vs. SITA in Non-CGM Studies

Trial/duration/ Population	**Treatment 1 mg/day (n =)**	**Treatment 2 mg/day (n =)**	**Mean (SD) difference in eAG*, mg/dL (CANA – SITA)**	**Other endpoints Mean (CANA – SITA)**
CANTATA-D (Latin American subgroup)(Lavalle-Gonzalez et al., 2016) (52-wk): adults with T2DM and HbA1c ≥ 7.0% to ≤10.5% on stable MET	SITA 100 (80)	CANA 300 (76)	**−41.00 (−38.55)**	Mean (SD) difference (CANA vs. SITA) in: • Body weight = −3.7% (−8.0%) • Systolic blood pressure = −4.0 (−22.3) mm Hg
Schernthaner et al(Schernthaner et al., 2013) (52-wk): adults with T2DM and HbA1c ≥ 7.0% to ≤10.5% on stable MET+SU	SITA 100 (378)	CANA 300 (377)	**Δ = −11.11** **(−26.28)**	2-hr PPG, mg/dL (no SD provided) • −39.9 (SITA) • −58.5 (CANA) Mean change in body weight: • +0.3% (SITA) • −2.5% (CANA; $p < 0.001$)
Rosenstock et al (12 wk)(Rosenstock et al., 2012)¶ : adults with T2DM and HbA1c ≥ 7.0% to ≤10.5% on stable MET	SITA 100 (65)	CANA 300 (64)	Δ = −5.4 [No SD provided]	—

*Estimated average glucose (eAG; mg/dL) was computed from hemoglobin A1c (%) using Nathan et al's formula eAG = (28.7 X HbA1c) − 46.7 (Nathan et al., 2008). 95% confidence intervals were converted to SD using the following formula: $SD = CI/3.96 \ X \sqrt[2]{N}$.

Table 2. Effects of CANA/SITA vs. PBO in CGM Studies

			Differences in measures of GV					
Trial/design/ duration/ population	**Treatment 1 mg/day (n =)**	**Treatment 2 mg/day (n =)**	**SD**	**SD**	**CV (SD/mean glucose)**	**CV (SD/MG)**	**Mean 24-hr glucose**	**Mean 24-hr glucose**
CANA trials			**mg/dL**	**mg/dL**	**%**	**%**	**mg/dL**	**mg/dL**
Argento 2016(Argento and Nakamura, 2016): retrospective case-control study of patients with T1DM ≥5 years with intensive insulin doses taking CANA x mean = 3.7 mo.	**CANA 100** (27)	**Controls:** (27): candidates for CANA but received only insulin adjustment (at most)	**CANA:** BL = 67.6 (13.1) Follow-up = 56.3 (10.7) **Δ = −11.30**	**Controls:** BL = 63.7 (13.0) Follow-up = 63.4 (11.8) **Δ = −0.3**	**CANA:** BL = 0.400 (0.044) Follow-up = 0.382 (0.053) **Δ = −0.018**	**Control:** BL = 0.381 (0.074) Follow-up = 0.382 (0.070) **Δ = −0.001**	**CANA:** BL = 168.3 (21.1) Follow-up = 146.9 (15.3) **Δ = −21.4**	**Control:** BL = 169.2 (24.1) Follow-up = 167.6 (22.4) **Δ = −1.6**
Phase 2 study*: parallel-group, treat-to-target, 18-wk study of patients with T1DM with inadequate control on basal-bolus insulin	**CANA 300** (117)	**Placebo** (118)	**CANA:** BL = 69.3 (12.74) 18 wk = 57.06 (12.60) **Δ = −12.24 (−13.90)**	**Placebo:** BL = 68.04 (12.85) 18 wk = 69.66 (15.82) **Δ = +1.62 (+14.04)**	Not available	Not available	**CANA:** BL = 164.70 (24.37) 18 wk = 152.46 (20.95) **Δ = −12.24 (−21.62)**	**Placebo:** BL = 162.00 (31.05) 18 wk = 172.26 (21.89) **Δ = +10.08 (+35.13)**
SITA trials								
Sakamoto 2012 (J-VICTORIA)(Sakamoto et al., 2012): actively controlled crossover study 4 wk of each treatment in T2DM patients with HbA1c = 6.5−9.5% w/o MET	**Vildagliptin (VILDA) 100 (20)**	**SITA 50 (20)**	**VILDA:** 35.5 (12.6)	**SITA:** 37.0 (13.9)	VILDA: Not reported	SITA: Not reported	**VILDA: 142.1 (14.0)**	**SITA: 153.2 (29.7)**
Guerci 2012 (Guerci et al., 2012): open-label actively controlled study of 2 DPP-4Is x 8 wk in T2DM patients with HbA1c = 6.5−8.0% on stable MET	**VILDA 100** (14)	**SITA 100** (16)	**VILDA:** BL = 29.3 (8.0) Follow-up = 24.2 (6.0) **Δ = −5.1** (p = 0.20)	**SITA:** BL = 29.1 (5.6) Follow-up = 23.1 (5.5) **Δ = −6.0**	VILDA: Not reported	SITA: Not reported	**VILDA:** BL = 29.3 (8.0) Follow-up = 24.2 (6.0) **Δ = −5.1** (p = 0.20)	**SITA:** BL = 29.1 (5.6) Follow-up = 23.1 (5.5) **Δ = −6.0**
Ellis 2011 (Ellis et al., 2011): Controlled crossover 8-wk study of adults with T1DM and HbA1c = 8.5%−12.0% on stable insulin doses	**SITA 100** (20) x 4 wk	**Placebo (20)** X 4 wk	Between-group difference: **Δ = −2.52 (−2.34; p = 0.29)**		Between-group difference: **Mean (SD) Δ = 1.1 (0.9; p = 0.27)**		Between-group difference: **Δ = −10.8 (−3.6)**	

*Janssen Protocol 28431754DIA2004.

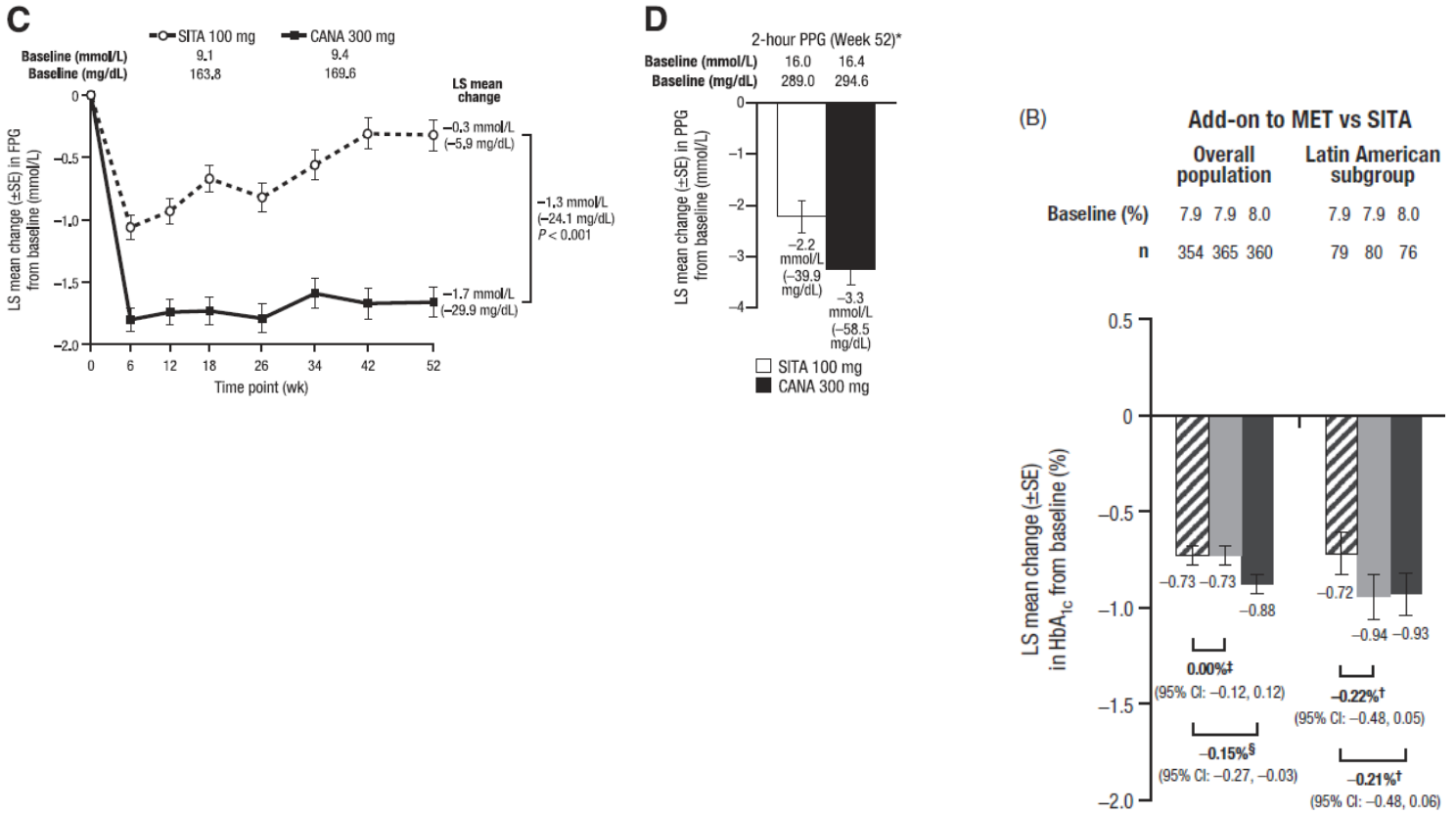

Figure 6. CANA vs. SITA (CANTATA-D). In this active-comparator study, including all (*left panels*) and Latin American (*right panel*) subjects, CANA 300 mg reduced hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG) compared to SITA 100 mg (Schernthaner et al., 2013; Lavalle-Gonzalez et al., 2016).

4.6.2.CANA CGM Trial Rationale

The impetus for the CANA CGM Trial in Mexican patients with T2DM derives in part from the recently reported Canagliflozin Treatment and Trial Analysis−DPP-4 Inhibitor Comparator Trial (CANTATA-D; Clinicaltrials.gov ID NCT01106677; Study DIA3015) in a Latin American subpopulation. This study, by Lavalle-González and co-workers in Brazil, Colombia, Costa Rica, and Mexico, showed that CANA 300 mg + MET (at stable doses) reduced HbA1c (net = −0.21%) and other clinical endpoints, including body weight (net = −3.7%) and systolic blood pressure (net = −4.0 mmHg), to a greater degree than SITA 100 mg + MET (Lavalle-Gonzalez et al., 2016).

Interpreting these differences, the authors pointed to the finding that Hispanic/Latino T2DM subpopulations experience reduced insulin sensitivity as their pivotal metabolic defect, and that CANA may hence be advantageous in these patients because it reduces PG through an insulin-independent mechanism (i.e. increased glucose excretion) (Cusi and Ocampo, 2011). On the other hand, SITA has minimal effects on measures of insulin sensitivity and resistance [assessed using the quantitative insulin sensitivity check index (QUICKI) and homeostasis model assessment insulin resistance (HOMA-IR)], consistent with the overall modest effects of the class of incretin mimetics on these parameters (Hansen and Corbett, 2005; Aschner et al., 2006).

A recent study evaluated model-based measures of β-cell function and insulin sensitivity using frequently sampled mixed-meal tolerance tests. Via this method, Polidori and European co-workers evaluated the effects of CANA 300 mg (vs. SITA 100 mg) when each was added to MET + SU in adults with T2DM and HbA1c 7.0%−10.5%, FPG < 300 mg/dL, and eGFR ≥ 55 mL/min $(1.73\ m^2)^{-1}$ in the CANTATA-D trial (Clinicaltrials.gov NCT01137812) (Schernthaner et al., 2013; Polidori et al., 2014). Treatment with CANA 300 mg resulted in least-squares mean increases of 30 to 50 mL min^{-1} m^{-2} on the oral glucose insulin sensitivity (OGIS) index as compared to a smaller increase of 12 mL min^{-1} m^{-2} with SITA 100 mg (each comparison $p \leq 0.02$). The range of values reflects raw data for OGIS and after adjustment for urinary glucose excretion.

Consequently, the CANA CGM Trial will, for the first time, compare the effects of CANA and SITA—which have divergent effects on insulin sensitivity—on glycemic variability using CGM in a Latin American population, which may serve as a parallel for other diabetic populations with reduced insulin sensitivity as their chief metabolic defect.

4.6.2.1. Potential Measures of Glycemic Variability

A number of measures have been proposed as indices of GV. **Table 3** summarizes their potential advantages and pitfalls in terms of methodology, associations with pathobiological and clinical outcomes, and other considerations.

Table 3. Measures of GV and Dispersion

Measure	Potential Advantages	Potential Pitfalls
Glucose CV %	Contributes the most to hypoglycemia (40%), vs. 10% for MAG and <5% for SD and MAGE (Qu et al., 2012).	Not reported in most CGM trials of SGLT-2 and DPP-4 inhibitors
SD	• Linear relationship with mean PG and other key indices of GV: GA/A1c ratio and FCPR index. • Linear relationship with PG interquartile range if not normally distributed • Associated with mortality in some studies(Meynaar et al., 2012)	SD is a measure of dispersion rather than variability. A patient can (in theory) have a high glycemic SD without oscillating PG pattern.
MAG	• Associated with ICU mortality in some studies(Hermanides et al., 2010)	Sometimes difficult to separate signal from noise given method = simple summation of all absolute changes in PG divided by the time over which measurements were taken.
MAGE	Captures mealtime-related glucose excursions.	• Postprandial glucose excursions can be more effective measured using CGM AUC. • Calculation is operator dependent/not standardized. • Outcome differs if computing is based on a postprandial increase or decrease (ascending or descending limb) • May not take into account relatively small, but still clinically meaningful changes.

A1c, hemoglobin A1c; CV, coefficient of variation; FCPR index, fasting C-peptide immunoreactivity to fasting plasma glucose (FPG) ratio; GA, glycated albumin; MAG, mean absolute glucose; MAGE, mean amplitude of glycemic excursions; PG, plasma glucose; Data from DeVries and Ogawa et al (Ogawa et al., 2012; DeVries, 2013).

5. STUDY PROCEDURES

Table 4 summarizes the time and events schedule for the study.

Table 4. Time and Events Schedule

	Phases (Visits), Timing (days), and Events											
Study assessment/ Procedure	**Prescreening (Optional)**	**Screening (Prescreening assessments can be performed here)**	**Selection**	**Randomization**	**Active treatment 1 (period 1)**	**CGM in**	**CGM out**	**Washout**	**Active treatment 2 (period 2)**	**CGM in**	**CGM out**	**End study**
Visit	**V1**	**V2**	**V3–V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V132**
Days	**Day −16 to −11**	**Day −10 to −8**	**Day −7 to −1 (see page below)**	**Day 0**	**Day 0**	**Day 22**	**Day 27**	**Day 28**	**Day 44**	**Day 66**	**Day 71**	**Days 72 to 80**
Screening/administrative	**X**	X										
Informed consent Form (ICF)[a]	**X**	X										
Demographics	**X**	X										
Review medical history requirements	**X**	X										
Inclusion/exclusion criteria[b]	**X**	X	**X**									
Non-study therapy (establish metformin at stable dose and continue it on trial)	**X**	X		**X (Ensure that subject continues metformin)**	**X (Ensure that subject continues metformin)**			**X (Ensure that subject continues metformin)**	**X (Ensure that subject continues metformin)**			**X (Ensure that subject continues metformin)**
Study drug administration												
Dispense/ administer drug					**X**				**X**			
Drug accountability (pill count)								**X**				**X**

Phases (Visits), Timing (Days), and Events

Study assessment/ Procedure	**Prescreening (Optional)**	**Screening (Prescreening assessments can be performed here)**	**Selection**	**Randomization**	**Active treatment 1 (period 1)**	**CGM in**	**CGM out**	**Washout**	**Active treatment 2 (period 2)**	**CGM in**	**CGM out**	**End study**
Visit	**V1**	**V2**	**V3–V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
Days	**Day −16 to −11**	**Day −10 to −8**	**Day −7 to −1**	**Day 0**	**Day 0**	**Day 22**	**Day 27**	**Day 28**	**Day 44**	**Day 66**	**Day 71**	**Days 72 to 80**
CGM device inserted for 6-day CGM glucose measurements (patient calibrates device using glucometer[d])			**X (Day −7)**			**X**				**X**		
CGM device removed and data downloaded from CGM device and Glucometer			**X (Day −1)**				**X**				**X**	
Patient Log Sheets distributed			**X (Day -7)**			**X**				**X**		
Data from patient log sheets entered manually into the system			**X (Day -1)**				**X**				**X**	
Glucometer (One Touch Ultra) and strips distributed			**X (Day -7)**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Data from Glucometer readings downloaded to system or entered manually			**X (Day -1)**				**X**				**X**	
Pedometer distribution			**X**			**X**	**X**			**X**	**X**	
Safety												
Physical examination		**X**										**X**
Lower limb examination	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Vital signs (pulse rate, blood pressure, respiration rate, body temperature)		**X**										**X**
Pulse rate and blood pressure (alone)	**X**	**(Measured as part of vital signs above)**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**(Measured as part of vital signs above)**
12-lead ECG		**X**										**X**
Clinical laboratory assessments												
Fasting serum[c] chemistries		**X**										**X**
Hematology		**X**										**X**

Study assessment/ Procedure	Prescreening (Optional)	Screening (Prescreening assessments can be performed here)	Selection	Randomization	Active treatment 1 (period 1)	CGM in	CGM out	Washout	Active treatment 2 (period 2)	CGM in	CGM out	End study
Urinalysis		X										X
HbA1C /C peptide		X										X
Fasting serum lipid profile		X										X
Fasting plasma glucose		X										X
Urine pregnancy testing in Central laboratory [e]		X										
Other assessments												
Body weight	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X

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

[b]Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 10.2.4, Source Documentation. Check clinical status again before first dose of study medication.
[c]For fasting laboratory assessments, if the subject has not fasted before the visit, the visit may proceed, but the subject must return within 24 hours in a fasted state to provide the necessary sample(s) for the assessments.

[d]CGM device calibration to be performed by the study subject using the One Touch UltraMini™ glucometer (Appendix 6).

[e] Urine pregnancy testing, unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations, for all women unless they are surgically sterile or unless there is a documented history of their postmenopausal status

ABBREVIATIONS

AE	Adverse event
AOC	Area over the curve
AUC	Area under the curve
BMI	Body mass index
CANA	Canagliflozin
CANA CGM	Canagliflozin Continuous Glucose Monitoring trial (present study's name)
CANTATA-D	Canagliflozin Treatment and Trial Analysis−DPP-4 Inhibitor Comparator Trial
CGM	Continuous glucose monitoring
CONGA	Continuous overlapping net glycemic action
COA	Clinical outcome assessment
CRF	Case report form
CV	Coefficient of variation (glycemic SD/mean; %)
DCF	Data clarification form
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DMC	Data Monitoring Committee
DPP-4	Dipeptidyl peptidase-4
eAG	Estimated average glucose
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
GLP-1RA	GLP-1 receptor agonist
GV	Glycemic variability
HbA1c	Hemoglobin A1c
ICF	Informed-consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IQR	Interquartile range
IRB	Institutional Review Board
ITT	Intent-to-treat (population)
IVRS	Interactive voice response system
MAGE	Mean amplitude of glucose excursions
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MET	Metformin
MODD	Mean of daily differences (in PG)
OGIS	Oral glucose insulin sensitivity
PG	Plasma glucose
PI	Prescribing information
PP	Per-protocol (population)
PPG	Postprandial glucose
PQC	Product Quality Complaint
QUICKI	Quantitative insulin sensitivity check index
SAP	Statistical Analysis Plan
SGLT1	Sodium-glucose co-transporter 1
SGLT-2	Sodium-glucose co-transporter 2
SAE	Serious AE
SD	Standard deviation
SITA	Sitagliptin
SUSAR	Suspected unexpected serious adverse reaction
SMBG	Self-Monitored Blood Glucose
TEAE	Treatment-emergent adverse event
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
USP	United States Pharmacopeia

5.1. Overview of Blinding, Control, Study Phases/Periods, and Treatment Groups

In this actively controlled crossover study, subjects will be randomized to treatment (e.g. A or B), period, and sequence (i.e. A/B or B/A), separated by a MET-only washout interval. Randomization will be used to minimize bias in the assignment of subjects to treatment and sequence groups, to increase the likelihood that known and unknown subject attributes (e.g. sociodemographic and other baseline characteristics) are evenly balanced and to enhance the validity of statistical comparisons. Double-blinded treatment will be used to reduce potential bias during data collection and evaluations of clinical (including surrogate CGM) endpoints.

5.2. Study Population

Screening for eligibility will be performed within 16 days before administration of study drugs. The inclusion and exclusion criteria for enrolling subjects in this study are described in the following two subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to the Statistical Analysis Plan.

5.2.1. Inclusion Criteria

Each potential subject must satisfy all of the following Inclusion Criteria to be enrolled in the study. If any of the Exclusion Criteria are met, the patient is not eligible to be enrolled.

1. Male or female.
2. Age >18 (or other legal age of consent in Mexico) and <55 years.
3. Type 2 diabetes mellitus.
4. Inadequate glucose control while using MET monotherapy for at least 8 weeks at stable daily doses of at least 1,500 mg before screening visit (Visit 1).
    a. Hemoglobin A1c (HbA1c) = 7.5% to 10.5% at Visit 1.
5. Adequate qualifying CGM reading during the prerandomization (selection) phase
6. Estimated glomerular filtration rate (eGFR) of at least 60 mL/min/1.73 m^2 at Visit 1.
7. Body mass index of 22 through 45 kg/m^2 at Visit 1.
8. Women of childbearing potential must agree to use a highly effective means of contraception (as defined according to local regulations) during the study (from Visits 1 through 6) and at least 4 weeks after the end-of-study visit.
9. Agree to sign an inform consent form (ICF) indicating that he/she understands the purpose of, and procedures required for, the study and is willing to participate in the study.
10. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

5.2.2. Exclusion Criteria

1. History of any of the following (at Visit 1):
    a. Diabetic ketoacidosis (DKA)
    b. Type 1 diabetes mellitus (T1DM)
    c. Pancreatic (e.g. β-islet cell) transplantation
    d. Diabetes secondary to pancreatitis or pancreatectomy
    e. Personal history of, or ongoing, pancreatitis
    f. One or more episodes of severe hypoglycemia (requiring assistance from others), as documented in the history obtained at Visit 1
    g. Hereditary glucose-galactose malabsorption or primary renal glucosuria.

2. Repeated FPG or fasting self-monitored blood glucose (SMBG) > 270 mg/dL during the pretreatment phase
3. Treatment with any other oral or parenteral antidiabetic medications different from metformin monotherapy, including but not limited to DPP-4 inhibitors, Sulphonylureas, thiazolidinediones, insulins and GLP-1RAs; SGLT-2 inhibitors and investigational agents.
4. Safety parameters out of range (according to local reference ranges).
    a. If, on the basis of the medical history, physical examination, vital signs, and 12-lead ECG performed at the prescreening visit (Visit 1), there are abnormalities, they must be consistent with the underlying illness in the study population (T2DM). This determination must be recorded in the subject's source documents and initialed by the investigator.
    b. If, on the basis of the serum chemistry panel (including liver enzymes) and other specific tests such as hematology or urinalysis) are outside of normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for5 the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator.
    c. History of significant cardiac, vascular, pulmonary, gastrointestinal, neurologic, hematologic, rheumatologic, and psychiatric disturbances documented during the medical history obtained at screening (Visit 1)
    d. History of malignancy except for squamous- and basal-cell carcinoma of the skin, cervical carcinoma, or malignancy considered cured and with minimal risk of recurrence
    e. Known allergies, hypersensitivity, or intolerance to CANA or SITA (or excipients).
    f. Contraindications to use of CANA or SITA according to local prescribing information.
    g. Using disallowed therapies (see 3 above)
5. Pregnancy: Urine pregnancy testing will be performed for all women according to local procedures unless they are surgically sterile or unless there is a documented history of their postmenopausal status. 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. Pregnancy test must be performed in Central Laboratory and the result reviewed prior to randomization.
6. Women of childbearing potential (or of uncertain potential or who becomes able to bear children during the study) must use a highly effective mode of contraception during the study and for 4 weeks after the end-of-study visit (Visit 13). The definition of "highly effective contraception" must be consistent with the criteria of local regulations.
7. Any condition for which any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g. compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
8. Potential subjects who have had major surgery (requiring general anesthesia) within 12 weeks before the screening visit or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 12 weeks after the last dose of study administration. (Subjects with planned surgical procedures to be conducted under local anesthesia may participate.)
9. Employee of the investigator or study site, with direct involvement in the proposed study or studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
10. Received an investigational drug or vaccine or used an invasive investigational medical device within 30 days before the planned first dose of study drug.
11. Current use of “Natural medicines” or natural medicinal products for diabetes (e.g. cactus-derived nutrients, celery).
12. 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.
13. Any proposed changes to the above eligibility criteria must be documented via an amendment.

5.3. Treatment

5.3.1. Procedures for Randomization, Stratification, Allocation, and Blinding

5.3.1.1. Randomization

Central randomization will be implemented in this study. Subjects will be randomly assigned to one of two treatments and one of two sequence groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor.

5.3.1.2. Stratification and Allocation

Randomized allocation of subjects will be balanced by using randomly permuted blocks and stratified by subject BMI tertiles at the screening visit (Visit 1), as follows:

For men, tertile 1 ranges from 22 to <28; 2, from 28 to <33; and 3 from 33 to <45, kg/m^2. For women, tertile 1 ranges from 22 to <30; 2, from 30 to <36; and 3, from 36 to <45 kg/m^2.

Stratified randomization will be performed by generating a separate block and assigning each subject to the appropriate block. A dynamic, permuted block randomization will be carried out to stratify subject allocation according to BMI tertile. For each block, a permutation (according to gender, gender-specific BMI tertile, and treatment sequence A/B or B/A) is chosen at random and subjects are allocated to treatment as they are enrolled according to that permutation. When the block is full, another permutation is chosen for the next group of patients. Block sizes will also be varied during the randomization. This procedure prevents potential selection bias, which can otherwise result because allocation of the last subject in a block is not random; it is completely determined by assignment of the prior subjects within the same block (Pond, 2011). This overall randomization procedure is compatible with the small projected sample population of the CANA CGM Trial (Suresh, 2011).

An interactive voice response system (IVRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. Based on this randomization code, the study drug will be packaged and labeled for each subject. Study drug code numbers will be preprinted on the study drug labels and assigned as subjects qualify for the study and are assigned to treatment. The requestor must use his or her own user identification and personal identification number when contacting the IVRS, and will then give the relevant subject details to uniquely identify the subject.

5.3.1.3. Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IVRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (e.g. treatment allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by exposing the concealed area of the label attached to the subject's source documents, opening the sealed code. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the appropriate section of the CRF and in the source document. The documentation received from the IVRS, indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded are not required to return for scheduled evaluations.

5.3.1.4. Dosage and Administration

Table 5. Description of Interventions

Treatment name	Canagliflozin (Invokana®)	Sitagliptin (Januvia®)
Test articles(s)	Study tablets formulated to have equal appearance and other characteristics.	Study tablets formulated to have equal appearance and other characteristics.
Dose per delivery	300 mg.	100 mg.
Frequency	Once-daily.	Once -daily.
Total daily dose	300 mg.	100 mg.
Delivery method	Oral (p.o.).	Oral (p.o.).
Delivery instructions	Blinded study drug will be taken orally and swallowed whole with liquid and not chewed, divided, dissolved, or crushed. One tablet will be taken daily, immediately before the first meal of the day (at approximately the same time of day).	Blinded study drug will be taken orally and swallowed whole with liquid and not chewed, divided, dissolved, or crushed. One tablet will be taken daily, immediately before the first meal of the day (at approximately the same time of day).

5.3.1.5. Treatment Compliance

A single dose of study drug will be administered orally, by designated study-site personnel at the study sites, who will check the subject's mouth to confirm that the dose was swallowed. Study-site personnel will maintain a log of all study drug administered. Drug supplies for each subject will be inventoried and accounted for.

When study drug is self-administered by subjects (i.e. between visits), the number of study drug dispensed will be recorded and compared with the number returned.

Subjects will receive instructions on compliance with study drug administration at the screening visit. During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to reeducate any subject who is not compliant with taking the study drug.

5.3.1.6. Prestudy and Concomitant Therapy

Prestudy therapies administered up to 30 days before the first dose of study drug must be recorded at screening. As mentioned above (Eligibility Criteria), patients must be taking MET monotherapy at stable daily doses of at least 1,500 mg at screening to be enrolled in this trial.

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study drug (Visit 6) to the end-of-study visit (Visit 13). Concomitant therapies should also be recorded beyond Visit 1 only in conjunction with new or worsening adverse events (AEs) or serious AEs (SAEs) that meet the criteria outlined below.

Allowed medications are the ones mentioned in the protocol (Canagliflozin, Sitagliptin during their respective periods and Metformin IR) and other medications unless among the prohibited concomitant medications.

Prohibited concomitant therapies include any other SGLT2 inhibitor, any other DPP-4 inhibitor, other oral or injectable antidiabetic agent (including colesevelam and bromocriptine, GLP1 analogs or insulin/inslulin analog) different from the medications specified in the protocol (Canagliflozin, Sitagliptin or Metformin IR during the respective periods). Subjects may not be in any other investigational drug during the study. Other prohibited concomitant medications are corticosteroids or immunosuppressive agents.

The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered.

Subjects must be on a stable blood pressure and lipid altering medication regimen for at least 4 weeks before baseline (Day 1). Adjustments to the blood pressure-lowering or lipid altering medication regimen that are considered to be

clinically appropriate should be made during the pretreatment phase to avoid the need to adjustment in these drugs during the double-blind treatment phase.

5.4. Study Procedures

5.4.1. Evaluations

5.4.1.1. Overview

The Time and Events Schedule (Table 4) summarizes the frequency and timing of efficacy, safety, and other measurements applicable to this study.

5.4.1.2. Study Procedures by Visit

The following events are summarized in Table 4.

5.4.1.2.1. Prerandomization Phase

Beginning 16 days before planned randomization, potential candidates for the study will be advised of the study's purposes and potential benefits and risks, and provided with an ICF, which must be signed before any study assessment or other procedure. There is no initial washout period, in part because patients must continue to use MET at stable doses of at least 1,500 mg during the study. Subjects will be instructed to continue using MET throughout the study. Medical history, physical examination, vital signs, and collection of other (e.g. sociodemographic and clinical) data will be conducted, in part to determine eligibility for enrollment. Venous blood and urine will be collected to perform clinical laboratory safety assessments. Body weight will be evaluated at each study visit (Visits 1 through 12).

Exceptional and limited retesting of abnormal screening values that lead to exclusion are allowed only once using an unscheduled visit during the screening period (to reassess eligibility).

At the screening visit, the results of clinical laboratory tests performed at the central laboratory must be within normal limits according to local guidelines and reference ranges. The investigator may consider a subject eligible if previously abnormal laboratory test results are within the reference range on a repeat testing by the central laboratory. Only one repeat test is allowed, at an unspecified time during the screening interval. No repeat testing for baseline CGM data (see below) is allowed.

Except for the tests specified above, if the results of other clinical laboratory tests are outside the normal reference ranges, the subject may be included only if the Investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the Investigator.

During the screening phase, each subject will be provided with the CGMS® Device: the Medtronic *i*Pro2 (Medtronic Minimed, Northridge, CA; **Figure 7**).

Figure 7. The CGMS® Device: Medtronic *i*Pro2 (Medtronic Minimed, Northridge, CA).

Study-site personnel will educate subjects in the use of the device, in part by reviewing the product manual with them. They will ask open-ended questions and attempt to anticipate any difficulties, in order to ensure that subjects are confident in using the device. Subjects will be provided with written instructions to obtain 24-hour technical support, if needed, to operate the device.

The *i*Pro2 measures interstitial-fluid glucose continuously, computing and storing PG readings every 5 min. for up to 6 days. The device is cordless and requires minimum patient interaction or training. A wire with a glucose oxidase tip is inserted subcutaneously into the abdominal wall using the Senserter. In the presence of glucose and oxygen (O_2), glucose oxidase catalyzes a biochemical reaction that transfers electrons to receiving molecule, creating electronic current measured by the device.

After 6 days, the device is removed, docked, and the data downloaded by the investigator into the system in a few simple steps (Appendix 7A). The docking station can be connected to a computer that contains dedicated software (Carelink *i*Pro Software) for use with the system. The computer can then generate a graph or a table of several days of glucose readings.

Subjects will be advised and instructed to maintain separate diet, activity, and symptom diaries during the 6 days of monitoring (from which 72 hours of continuous data for readings will be taken), in order to assist in interpreting CGM data. To measure daily physical activity, each subject will also be provided with a wearable pedometer. Study-site personnel will train subjects in the use of the device, including instructions to capture the data according to the study design. Subjects will be provided with written instructions on how to obtain 24-hour technical support, if needed, for operation of the device.

Glucometer readings data, the iPro2 device, completed diaries, and wearable pedometers will be returned by subjects and data collected/downloaded/stored by study-site personnel, within 3 days before the randomization visit (Visit 5).

Study-site personnel will instruct subjects that they will return to study sites to receive the CGM device and repeat the 6 day CGM procedure two more times during the study, at the end of: 1) active treatment phase 1 (days 22-27); and at the end of 2) active treatment phase 2 (days 66-71).

5.4.1.2.2. Randomization Phase

On Day 0 (Visit 5), subjects will be randomly allocated, to treatments and sequences, in a stratified manner based on gender-specific BMI tertiles, via permuted-block randomization. Physical examination and clinical laboratory evaluations will be conducted, vital signs assessed, and body weights measured.

5.4.1.2.3. Double-Blind Active Treatment Phase 1

On Day 1 (Visit 6) subjects will report to study sites before their first meal to receive their blinded medication and take the first dose under supervision by study-site personnel. Study-site personnel will also remind each subject to return on Day 22 to receive their CGM *i*Pro2 device and nutrition/activity/symptom diaries. Telephone reminders will also be done to subjects a few days prior to remind them to return to study sites on Day 22.

On Day 22, study-site personnel will reacquaint subjects in the use of the CGM *i*Pro2 device and distribute / insert it for use on Days 22-27. Study-site personnel will ask subjects about their first experiences with the device, attempt to address any difficulties from that initial experience, and ask open-ended questions to anticipate any difficulties, in order to ensure that subjects are confident in using the device. Subjects will be provided with written instructions to obtain 24-hour technical support, if needed, to operate the device. Subjects will be advised and instructed to maintain separate diet, activity, and symptom diaries and to perform and record Capillary Blood glucose readings with the Glucometer during the 6 days of monitoring, in order to assist in interpreting CGM data.

To measure daily physical activity, each subject will also be provided with a wearable pedometer for concurrent use with the CGM *i*Pro2 device (Days 22-27). Study-site personnel will train subjects in the use of the device, including instructions to capture the data according to the study design. Subjects will be reminded how to obtain 24-hour technical support, if needed, for operation of the device.

The *i*Pro2 device, the glucometer One Touch Ultra mini ™, completed diaries, and wearable pedometers will be returned by subjects, and data collected/downloaded/stored by study-site personnel, on Day 27, immediately before

the MET washout visit (Visit 9). On Day 27, body weight will be measured, and study-site personnel will elicit any reports of AEs from subjects via open-ended questioning and record the data in CRFs. Tablet vials will be collected and pills counted to assess compliance.

5.4.1.2.4. Metformin Washout Phase

On Day 28 (Visit 9), subjects will be instructed to continue taking MET and to return to study sites on Day 44.

5.4.1.2.5. Double-Blind Active Treatment Phase 2

On Day 44 (Visit 10) subjects will report to study sites before their first meal to receive their blinded medication and take the first dose under supervision by study-site personnel. Study-site personnel will also remind each subject to return on Day 66 to receive their CGM *i*Pro2 device and nutrition/activity/symptom diaries (patient log sheet). Telephone reminders will also be done to subjects a few days prior to remind them to return to study sites on Day 66.

On Day 66, study-site personnel will reacquaint subjects in the use of the CGMS *i*Pro2 device and distribute it for use on Days 66-71. Study-site personnel will ask subjects about their previous experiences with the device, attempt to address any difficulties from these experiences, and ask open-ended questions to anticipate any difficulties, in order to ensure that subjects are confident in using the device. Subjects will be reminded of instructions to obtain 24-hour technical support, if needed, to operate the device. Subjects will be advised and instructed to maintain separate diet, activity, and symptom diaries during the 6 days of monitoring, in order to assist in interpreting CGM data.

To measure daily physical activity, each subject will also be provided with a wearable pedometer for concurrent use with the CGMS *i*Pro2 device (Days 66-71). Study-site personnel will reacquaint subjects in the use of the device, including instructions to capture the data according to the study design.

The *i*Pro2 device, the OneTouch Ultra Mini ™ Glucometer, completed diaries, and wearable pedometers will be returned by subjects, and data collected/downloaded/stored by study-site personnel, on Day 71 (Visit 12). On Day 71, body weight will be measured, and study-site personnel will elicit any reports of AEs from subjects via open-ended questioning and record the data in CRFs. Bottles will be collected and pills counted to assess compliance.

5.4.1.2.6. End-of-Study Phase/Early Withdrawal/Completion

A subject will be considered to have completed the study if he or she has completed all study assessments (i.e. Visits 1 through 12) or has experienced a clinical endpoint that precludes further continuation in the study (e.g. hospitalization for severe hypoglycemia). Venous blood and urine will be collected to perform end-of-study clinical laboratory safety assessments.

Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind phase will not be considered to have completed the study.

5.4.1.2.6.1. Withdrawal from the Study

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

- Lost to follow-up
- Withdrawal of consent
- Death
- Noncompliance defined as returned pill counts with >20% (6 pills) of dispensed tablets remaining after 28 days of active treatment of subject
- Disease-related events (e.g. hypoglycemia, microvascular events, macrovascular events)
- Discontinuation of study treatment for any reason. A subject's study treatment will be automatically discontinued if the investigator or sponsor believes (e.g. that for safety or tolerability reasons (e.g. adverse event) it is in the best interest of the subject to discontinue treatment.

- The subject becomes pregnant (study therapy should be immediately interrupted based upon a positive [hCG], test).
- The subject requires chronic dialysis or renal transplantation
- The subject requires disallowed therapy, including need for rescue therapy due to poor glucose control:
  - After Day 1 through the end of the study, the investigator will withdraw the patient from the study in order to start the rescue therapy considered appropriate in patients that present with FPG measured by SMBG in repeated occasions over the course of 7 days, with a mean value equal or greater than 280 mg/dl and confirmed by the investigator with Laboratory FPG of equal or greater than 280 mg/dl. Subjects should have reinforcement of diet and exercise recommendations before obtaining the repeat FPG value. Subjects should be counseled to contact the site if their fasting self-monitored blood glucose (SMBG) consistently exceeds these values, and an FPG measurement to determine eligibility for glycemic rescue therapy should be obtained and therefore study withdrawal should be done. At the investigator's discretion, based upon recent fasting SMBG values that are consistent with the initial FPG result meeting glycemic rescue criteria, this single FPG (ie, without a repeat FPG value) may be used to demonstrate eligibility for withdrawal from the study.
- The subject experiences a serious adverse event of biochemically-confirmed (eg, pH, serum ketones, anion gap) DKA.
- The subject requires or has a programmed surgery or surgical procedure or presents with an infection which may transitorily alter glycemic control or which treatment may transitorily alter glycemic control.

If a subject withdraws from the study for any reason before the end of any post-randomization study phase (i.e. Visits 2-5), end-of-treatment and/or post-treatment assessments should be obtained.

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study before the end of any post-randomization study phase (i.e. Visits 2-5), end-of-treatment and post-treatment assessments should be obtained.

5.4.1.2.7. Post-treatment Phase (Follow-Up)

Visit 13 will be made to determine any resolution or other outcome of SAEs for up to 7 days after the last dose of study drug (days 72-80), unless the subject has died, is lost to follow-up, or has withdrawn consent. If the information on patient safety is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented on the CRF.

Investigators may recontact the subject to obtain long-term follow-up information regarding the subject's safety or survival status as noted in the ICF (refer to Section 10.2.3, Informed Consent).

Subjects will be instructed that study drug will not be made available to them after they have completed/discontinued study drug, that they should continue to take MET as they have done throughout the study, and that they should return to their primary physician to determine standard of care.

5.5. Efficacy Evaluations

CGM parameters will be measured using the CGM® Device: Medtronic *i*Pro2 (Medtronic Minimed, Northridge, CA; Figure 7). Study-site personnel, including Investigators, will be centrally trained to calibrate and operate the device, instruct subjects in its use, and download and analyze data, according to the device's product manual.

The following efficacy parameters will be evaluated:

Primary efficacy endpoint: Mean (SD) change from baseline in intrapatient coefficient of variation of glucose profiles (CV %; SD/mean glucose), as assessed using CGM over a 6-day period at baseline and after each active treatment.

Secondary efficacy endpoints. Mean (SD) changes from baseline in:

- Glycemic SD for 24-hour glucose (mg/dL).
- Mean 24-hour glucose (mg/dL).
- Preprandial glucose (mg/dL).
- 2-hour PPG (mg/dL).
- Time (minutes), percent of 24 hours, or area under the Glucose time curve for 24 hours (AUC_{24h}) with glucose = 70−139 mg/dL (time spent with PG within reference range).
- Time (minutes), percent of 24 hours, or AUC_{24h} (mg/dL/hr) with glucose > 140 mg/dL (time spent with PG above reference range).
- Time (minutes), percent of 24 hours, or AUC_{24h} (mg/dL/hr) with glucose > 180 mg/dL (time spent with PG markedly above reference range).
- Time (minutes), percent of 24 hours, or area over the PG time curve for 24 hours (AOC_{24h}; mg/dL/hr) with glucose < 70 mg/dL.
- Frequency (%) of 2+ consecutive glucose readings < 70 mg/dL (and/or of hypoglycemic symptoms requiring personal support).

Exploratory efficacy endpoints. Mean (SD) changes from baseline in:

- AUC for glycemic variability (mg/dL/hr) throughout the day (0−24 hours), after breakfast (0−5 hours), after lunch (5−11 hours), after dinner (11−15 hours), and during sleep (15−24 hours).
- Peak glucose (mg/dL) throughout the day (0−24 hours), after breakfast (0−5 hours), after lunch (5−11 hours), after dinner (11−15 hours), and during sleep (15−24 hours).
- Overall hyperglycemia: AUC_{total} (mg/dL/hr).
- Nadir glucose (mg/dL): lowest glucose level over 72 hours.
- Continuous overlapping net glycemic action (CONGA): the SD of summed differences between observations separated by *n* hours.
- Mean of daily differences in PG (MODD).

5.6. Safety/Tolerability Evaluations

5.6.1. Safety

5.6.1.1. Physical Examination

A medical history will be taken and physical examination conducted at the screening and end-of-study visits (Visits 1 and 12), according to each investigator's usual practice and/or local/regional/global practice guidelines.

At minimum, Investigators will collect the following information and conduct the following assessments.

History:

- Sociodemographic data: age, race/ethnicity, gender, height, and weight. Weight will also be measured at each study visit to assess and record any changes.

- History of T2DM: diagnosis date and time from this date to the screening visit (screening assessment only)
- Past medical history: other major illnesses other than T2DM (history or ongoing), and previous surgeries
- Family history (including of T2DM)
- History of (and ongoing) medication use, including MET at stable dosages
- Social history: marital or cohabitating status, number of children, employment status
- Lifestyle history: behavioral risk factors, including physical activity, nutrition, tobacco/alcohol/substance use or abuse
- Allergies
- Sexual history

Assessments of organ-systems:

- Cardiovascular
- Cranial-nerve
- Cutaneous
- Endocrine
- Gastrointestinal
- Genitourinary
- Musculoskeletal
- Nervous-system
- Respiratory

5.6.1.2. Vital Signs

Vital signs will be measured at the screening and end-of-study visits (Visits 1 and 12), according to each Investigator's usual practice and/or local/regional/global practice guidelines. Oral temperature, pulse/heart rate, respiratory rate, and blood pressure will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. Pulse rate and blood pressure will be measured at every clinic visit during the study.

Blood pressure and pulse/heart rate measurements will be performed at every visit and should be preceded by at least 5 minutes of rest in a quiet setting without distractions (e.g. television, cell phones) according to instructions (APPENDIX 5)

5.6.1.3. Electrocardiogram (ECG)

Twelve-lead ECGs will be conducted at the screening and end-of-study visits (Visits 1 and 12), according to each Investigator's usual practice and/or local/regional/global practice guidelines. During the collection of ECGs, subjects should be in a quiet setting without distractions (e.g. television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. When performing safety evaluations, the investigator should adhere to the following sequences: ECG, vital signs, blood draw, and urine collection.

5.6.1.4. Clinical Laboratory Assessments

Venous blood samples of approximately ≥5 mL will be collected for measurement of serum chemistries and complete blood count/hematology (APPENDIX 10). Estimated glomerular filtration rate (eGFR) will be computed using serum creatinine and other clinical data according to the abbreviated Modification of Diet in Renal Disease (MDRD) equation:

$$eGFR = 186 \times (Creat/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$$

Blood samples for serum chemistry and hematology, and a random urine sample for urinalysis, will be collected at the screening and end-of-study visits for evaluation by a central laboratory. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. Laboratory reports must be filed with the source documents. Subject confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

Safety assessments will be based on medical review of adverse event reports and the results of vital-sign measurements, 12-lead ECGs, physical examinations, clinical laboratory tests, and other safety evaluations at specified time points as described in the Time and Events Schedule (Table 4).

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF and laboratory requisition form. Refer to the Time and Events Schedule (Table 4) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the central laboratory manual.

5.6.2. Tolerability: Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 7, Adverse Event Reporting.

5.6.3. Other Evaluations

At each study visit, body weight will be measured.

6. STATISTICAL ANALYSIS PLAN

6.1. Sample Size Determination

Crossover trials yield more statistically efficient comparisons of treatments than parallel-group designs. (Shen, 2006; Wellek and Blettner, 2012) Because of these considerations, crossover studies achieve the same level of statistical power and precision while using smaller sample sizes than parallel-group studies. Because each subject serves as his or her own control, data are paired rather than independent.

To compute sample sizes in the CANA CGM Trial, the following software package was utilized: P/S (Power and Sample Size Calculation) version 3.1.2 (Biostatistics Department of Vanderbilt University (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize). Raw data outputs on sample size computations using this software are presented in the **Appendices**.

In the present Statistical Analysis Plan, sample size calculations are conducted using more than one set of assumptions because: 1) CANA 300 mg and SITA 100 mg have never been compared directly in a CGM study and 2) there are no available comparative data on the effects of CANA 300 mg versus SITA 100 mg on mean intrapatient glucose CV % (the primary outcome measure as specified by Janssen and principal investigator Dr. Fernando Javier Lavalle-González).

Although the effects of CANA 300 mg and SITA 100 mg on GV have never been directly compared in a clinical trial employing CGM, each active therapy has been compared with placebo using this methodology. The effects of the two therapies have been compared directly in non−CGM studies.

In a Phase 2 trial (Janssen Study 28431754DIA2004), 18 weeks of treatment with CANA 300 mg were associated with a mean decrease in glycemic SD of 12.24 (SD: 13.90) mg/dL compared to placebo (**Table 2**). In the same study,

the change with placebo was a mean increase in glycemic SD of 1.62 (SD: 14.04) mg/dL. Hence, the mean treatment difference between CANA 300 mg and placebo in glycemic SD was 13.86 mg/dL.

In a similar population, subjects received either SITA 100 or placebo. Compared to placebo, SITA 100 mg was associated with a mean decrease in glycemic SD of 2.52 (SD: 2.34) mg/dL (Ellis et al., 2011). Comparing the effects of CANA 300 mg and SITA 100 mg with placebo across these studies, the net decrease in glycemic SD (vs. placebo) between CANA 300 mg and SITA 100 mg is hence 13.86 – 2.52 = 11.36.

Using a two-sided $\alpha = 0.05$ and a power of 80%, a total of **12 subjects** are needed to detect a mean difference of 11.36 mg/dL in glycemic SD between CANA 300 mg and SITA 100 mg, assuming a common SD of 13.00 mg/dL (Appendix 1).

Because the above sample size calculation on mean glycemic SD involves indirect comparisons between CANA 300 mg (and SITA 100 mg) and placebo, a second sample size calculation is conducted using data from a direct-comparator (CANA 300 mg vs. SITA 100 mg) trial that did not employ CGM but did involve a Latin American population (CANTATA-D) (**Table 1**) (Lavalle-Gonzalez et al., 2013b).

To compute sample size using studies that directly compared the effects of CANA 300 mg or SITA 100 mg on glucose profiles, we translated HbA1c to estimated average glucose (eAG) using the formula of formula of Nathan et al (Nathan et al., 2008) Values computed in this way are normally distributed. Using least–squares regression analysis with HbA1c as the independent variable and mean eAG as the dependent variable, there was no deviation from linearity when fitting higher-order polynomial terms (Wilson et al., 2011). When examining residual values, no outliers or other overly consequential values were identified that modified the normal distribution. There was no meaningful divergence from the assumption of homoscedasticity when plotting residuals versus predicted values (Wilson et al., 2011).

In the Latin American subpopulation of the CANTATA-D trial, the mean (SD) difference between the two treatments in eAG was −41.00 (−38.55) mg/dL (Lavalle-Gonzalez et al., 2016). According to a two-sided $\alpha = 0.05$ and power of 80%, a total of **9 subjects** with paired data are needed to detect a mean (SD) difference of 41.00 (38.55) mg/dL between CANA 300 mg and SITA 300 mg with a power of 80% (Appendix 2).

Finally, effects of CANA 300 mg and SITA 100 mg were directly compared in the overall CANTATA-D trial (all patients). The mean (SD) difference in eAG between groups was 11.11 (26.28) mg/dL. According to a two-sided $\alpha = 0.05$ and power of 80%, a total of **46 subjects** with paired data are needed to detect a mean (SD) difference of 11.11 (16.28) mg/dL between CANA 300 mg and SITA 300 mg with a power of 80% (Appendix 3).

Using this, most conservative sample size (N = 46) and a conservative subject attrition rate of 20% for an approximately 12-week study, the required sample size for this crossover trial is 46 + 13.8 = 60subjects, each randomly allocated in a double-blind manner to two treatments, two periods, and two sequences involving CANA 300 mg compared with SITA 100 mg as add-ons to MET in T2DM subjects with glucose inadequately controlled on the biguanide as monotherapy who meet all eligibility criteria.

6.2. Overall Statistical Methods

Subjects will be randomized 1:1 to each treatment sequence. The CANTATA-D study found that treatment with CANA 300 mg was associated with a 2.1% to 2.9% reduction in body weight compared to SITA 100 mg when each was added to ongoing MET over 52 weeks (Lavalle-Gonzalez et al., 2013; Lavalle-Gonzalez et al., 2016). It is also possible that, once subjects lose weight while randomized to CANA 300 mg, they will become more physically active. To minimize the effects of this potentially important covariate with relation to GV, randomization will be stratified according to gender-specific tertiles of body mass index (BMI) (Kriska et al., 2003). For men, tertile 1 ranges from 17 to <28; 2, from 28 to <33; and 3 from 33 to <66, kg/m^2. For women, tertile 1 ranges from 16 to <30; 2, from 30 to <36; and 3, from 36 to <69 kg/m^2. Because the eligibility criteria in this trial require a range of BMI = 22 to 45 kg/m^2 for study entry, the tertiles are redefined as follows. For men, tertile 1 ranges from 22 to <28; 2, from 28 to <33; and 3 from 33 to <45, kg/m^2. For women, tertile 1 ranges from 22 to <30; 2, from 30 to <36; and 3, from 36 to <45 kg/m^2.

This stratified randomization method will control for any influence of the covariate of baseline BMI (surrogate for body weight). One potential limitation of stratified randomization is that the covariate must be measured (and known)

at baseline. If it is not feasible to determine all subjects' BMI (or body weight) values at baseline, an analysis of covariance (ANCOVA) model controlling for the covariate of baseline BMI (and/or body weight) can be constructed.

6.2.1. Efficacy Outcome Measures and Hypothesis Testing

Three null hypotheses (NH) will be tested:

H_{0A}: There is no statistically significant difference between CANA 300 mg and SITA 100 mg in terms of their effects on mean intrapatient glucose CV % from baseline as measured by CGM over a continuous 72 hour period at baseline and after each active treatment.

H_{1A} [Alternative hypothesis (AH)]: There is a statistically significant difference between CANA 300 mg and SITA 100 mg in terms of their effects on mean intrapatient glucose CV % from baseline as measured by CGM over a continuous 72 hour period at baseline and after each active treatment.

H_{0B}: There is no statistically significant difference between CANA 300 mg and SITA 100 mg in terms of their effects on mean intrapatient glycemic SD for 24-hour PG from baseline as measured by CGM over a continuous 72 hour period at baseline and after each active treatment.

H_{1B}: There is a statistically significant difference between CANA 300 mg and SITA 100 mg in terms of their effects on mean intrapatient glycemic SD for 24-hour PG from baseline as measured by CGM over a continuous 72 hour period at baseline and after each active treatment.

H_{0C}: There is no statistically significant difference between CANA 300 mg and SITA 100 mg in terms of their effects on mean 24-hour PG from baseline as measured by CGM over a continuous 72 hour period at baseline and after each active treatment.

H_{1C}: There is no statistically significant difference between CANA 300 mg and SITA 100 mg in terms of their effects on mean 24-hour PG from baseline as measured by CGM over a continuous 72 hour period at baseline and after each active treatment.

Descriptive statistics will be presented as mean (SD) for normally distributed continuous variables, median [interquartile range (IQR)] for non-normally distributed continuous variables, and numbers (%) for categorical variables. Baseline sociodemographic and other characteristics will be compared using Fisher's Exact test for categorical variables and Student's t-test for normally distributed continuous variables.
Efficacy analyses will be conducted using intent-to-treat and per-protocol populations. Although a previous randomized controlled trial compared effects of another SGLT2 inhibitor (and also open-label SITA 100 mg) using a modified last observation carried forward approach (with linear interpolation) to missing data,(Rosenstock et al., 2013) no data imputation will be performed in the present study, which has a limited number of visits (six).

As in a previous CGM study, the distribution of each glycemic indicator (except for SD; see below), as well as body weight will be assessed for normality via the Shapiro-Wilk test (Nomura et al., 2011). For normally distributed data, the mean (SD) value will be presented and, for non-normally distributed data, the median and IQR. Most between-treatment differences will be assessed using a paired Fisher's Exact test for baseline categorical variables and paired t-tests or Wilcoxon signed rank sum tests for normally and non-normally distributed continuous efficacy endpoints (respectively), according to the Shapiro-Wilk test results.

Also paralleling a previous CGM study involving SITA 100 mg, data for analyses of the CANA CGM Trial's secondary endpoints related to AUC_{24hr} (and AOC_{24hr} for hypoglycemia) will be included per subject only if >70% of his or her CGM readings are available during each assessment period (3-day CGM at the end of the baseline and each of two treatment intervals); and AUC values will be adjusted for preprandial PG (FPB) readings (Ellis et al., 2011). Some of these variables (e.g. percentage of time with PG in different ranges) are known to be non-normally distributed and, as in previous CGM studies, will be evaluated using paired Wilcoxon rank sum tests on median and IQR values (Nomura et al., 2011; Nishimura et al., 2015).

Body weight will be assessed at each visit. In the event of a significant mean (SD) [or median (IQR)] difference in change from baseline in body weight or physical activity between CANA 300 mg and SITA 100 mg (according to a statistical assessment informed by the Shapiro-Wilk test) a statistical approach similar to a prior SGLT2 (vs. SITA) trial will be taken (Rosenstock et al., 2013). A sensitivity analysis using either: 1) a repeated-measures mixed-effect

model with baseline CGM values as fixed effects and on-treatment body weight, and subject as random effects; or 2) an ANCOVA with visit-wise body weights and physical activity as covariates.

The primary efficacy analysis will be conducted on the intent-to-treat population, which comprises all subjects who received at least one dose of medication and in whom CGM recordings at baseline and after each active treatment were successful. A secondary efficacy analysis will be conducted on the per-protocol population, which will include all intent-to-treat subjects without a major protocol violation.

To evaluate carry-over effects, Grizzle's two-stage model will be employed to statistically test for treatment x period interactions (Shen, 2006) (Appendix 4). In the event of a significant carryover effect, the methodology enables comparison of the effects of CANA 300 mg versus SITA 100 mg on parameters of GV in one of the two treatment periods.

All tests will be conducted at a two-sided $\alpha = 0.05$ (i.e. *a priori* significance level of $p < 0.05$).

6.2.2. Safety/Tolerability Measures

Subjects receiving at least one dose of active treatment will comprise the safety population. Safety will be assessed according to mean values for vital signs, 12-lead ECGs, and laboratory examinations at screening and the end of each active treatment period. Adverse events will be elicited by open-ended questioning at each visit and coded as to system-organ class and preferred term using the Medical Dictionary of Regulatory Activities (MedDRA) version 14 or higher. Safety and tolerability parameters will be summarized by descriptive statistics only; no hypotheses will be tested. Continuous variables will be expressed as mean (SD; for normally distributed) or median (IQR; for non-normally distributed) and categorical variables as numbers (%).

7. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Care will be taken not to introduce bias when detecting adverse events (AEs) or serious AEs (SAEs). Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE event occurrence.

7.1 Definitions

7.1.1 Adverse Event Definitions and Classifications

7.1.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (noninvestigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or noninvestigational) product, whether or not related to that medicinal (investigational or noninvestigational) product (definition per International Conference on Harmonization [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF.

7.1.1.2. Serious Adverse Events

An SAE based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death.
- Is life threatening.
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is a suspected transmission of any infectious agent via a medicinal product.
- Is medically important.* (*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.)

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event, the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint. In the CANA CGM Trial, the chief SAE that may also be a study endpoint is an event of hypoglycemia (according to both symptoms and signs of PG < 70 mg/dL) that requires medical attention or other assistance from a caregiver.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event, the event must be reported under § 312.32(c)(1)(i) as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint unless contradicted by local regulations. Refer to 21 CFR 312.32(c)(5) for further guidance as appropriate.

7.1.1.3. Unlisted (Unexpected) Adverse Events/Reference Safety Information

An AE is considered unlisted if its nature or severity is not consistent with the applicable product reference safety information. For CANA, the expectedness of an AE event will be determined by whether or not it is listed in the full prescribing information [package insert (PI)]. For SITA and MET, with marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in each product's PI.

7.1.1.4. Adverse Events Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is [possible, probable, or very likely by the definitions listed in the following section (Attribution Definitions).

7.1.1.5. Attribution Definitions

7.1.1.5.1. Not Related

An AE that is not related to the use of the drug.

7.1.1.5.2. Doubtful

An AE for which an alternative explanation is more likely, such as concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

7.1.1.5.3. Possible

An AE that might be due to the use of the drug. An alternative explanation, such as concomitant drug(s) or concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

7.1.1.5.4. Probable

An AE that might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation, such as concomitant drug(s) or concomitant disease(s), is less likely.

7.1.1.5.5. Very Likely

An AE event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, such as concomitant drug(s) or concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

7.2. Severity Criteria

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

- **Mild**: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: Sufficient discomfort is present to cause interference with normal activity.
- **Severe**: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal, everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (e.g. laboratory abnormalities).

7.3 Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor or other study drug (overdose being the ingestion of one or more tablet from the dose indicated in the protocol. Investigators should take the actions considered appropriate for the situation, ensuring the patient's best interest and wellbeing.
- Suspected abuse/misuse of a sponsor or other study drug
- Accidental or occupational exposure to a sponsor or other study drug
- Any failure of expected pharmacologic action (i.e. lack of effect) of a sponsor or other study drug
- Unexpected therapeutic or clinical benefit from use of a sponsor study drug
- Medication error involving a sponsor product (with or without subject exposure to the sponsor study drug, such as name confusion)
- Exposure to a sponsor study drug from breastfeeding
- Amputation

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the CRF.

7.3.1.Procedures

7.3.1.1. All Adverse Events

All AEs and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected SAEs (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and the IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study, indicating the following:

- Study number
- Statement, in Spanish or English, that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

Consistent with standard diabetes treatment guidelines, all study subjects should be provided with routine preventative foot care and early intervention for foot problems. Specifically:

- Provide or ensure that all subjects have had general foot self-care education.
- Perform a comprehensive foot evaluation at each visit to identify risk factors for ulcers and amputations. The examination should include inspection of the skin, assessment of foot deformities, neurological assessment including pinprick or vibration testing or assessment of ankle reflexes, and vascular assessment including pulses in the legs and feet.
- Subjects who have a history of prior lower extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease should be referred to foot care specialists for ongoing preventive care.

Study research staff should make study subjects aware of potential signs and symptoms of DKA such as difficulty breathing, nausea, vomiting, abdominal pain, feeling confused, fruity-smelling breath, and unusual fatigue or sleepiness. Study subjects should be instructed to contact the site if they experience such symptoms. If the investigator suspects these symptoms may be related to DKA (even if the subject’s blood glucose levels are less than 250 mg/dL (13.9 mmol/L), testing for urine or blood ketones should be considered.

For all study subjects, there should be a clinical evaluation at every visit to assess the presence of any sign or symptom suggestive of volume depletion (eg, hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), which if present should be adequately treated either by decreasing dose or eliminating use of diuretics or other antihypertensive medications or interrupting study drug until the condition resolves. However, consider withdrawal of other antihypertensive agents prior to adjusting dose of ACE inhibitors or ARBs.

7.3.1.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g. social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). [Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in prolongation of the originally planned hospitalization is to be reported as a new SAE.]
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

The cause of death of a subject in a study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered an SAE.

7.3.1.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. If a subject becomes pregnant during the study, a determination regarding study drug discontinuation must be made by the investigator in consultation with the sponsor.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

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

7.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

7.5. Product Quality Complaint Handling

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging (i.e. any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity). A PQC may have an impact on the safety and efficacy of the product. Timely,

accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

7.5.1. PQC Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to 6.1.1.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

7.5.1.1. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

8. STUDY DRUG INFORMATION

8.1. Physical Description of Study Drugs

CANA is formulated as 300-mg tablets and SITA as matched 100-mg tablets. Subjects will continue to use their own MET (at stable entry doses) throughout the study. CANA will be manufactured and provided under the responsibility of the sponsor.

8.2. Packaging

The study drug will be packaged in individual subject kits. Each kit will consist of study drug for the first phase; diaries to record daily nutrition, physical activity, and any clinical symptoms (e.g. suggestive of hypoglycemia). Subjects will return to study sites 4 days before the end of their active-treatment and washout phases to receive their CGM and then return to these sites 3 to 4 days later to return the devices (and to allow study-site personnel to download the data). All study drug will be dispensed in child-resistant packaging.

8.3. Labelling

Study drug labels will contain information to meet the applicable regulatory requirements.

8.4. Preparation, Handling, and Storage

Subjects will be instructed to store CANA at an approximate temperature of 25°C (77°F). Excursions from 15°C to 30°C (59°F to 86°F) are allowed.

Subjects will be instructed to store SITA at an approximate temperature of at 20°C to 25°C (68°F to 77°F). Excursions from 15°C to 30°C (59°F to 86°F) are allowed.

Subjects will store and use MET (at stable doses) in the same manner as at the screening visit.

8.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject, must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study site monitor

during on-site monitoring visits. The return to the sponsor of unused study drug will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Initial dispensing of study drugs (CANA and SITA) will be under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Whenever a subject brings his or her study drug to the study site for pill count, this is not seen as a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

9. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Package inserts for CANA, SITA, and MET.
- Approved study protocol
- User's manual (with technical support contact information) for the CGMS® Device: the Medtronic *i*Pro2 (Medtronic Minimed, Northridge, CA [Laboratory manual]
- Example subject Patient Log Sheet used to record nutrition, physical activity, and any important clinical symptoms (e.g. of hypoglycemia)
- IVRS Manual, including contact information
- DMC and other central-study administrative contact information
- Sample ICF
- Health care related materials for the randomized subjects, distributed within the protocol visits, with the aim to encourage subject retention in the protocol will be provided. These materials are non-returnable to the site.

10. ETHICAL ASPECTS

10.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily, will be enrolled.

10.2. Regulatory Ethics Compliance

10.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

10.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments

- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Full prescribing information (PIs) of study drugs
- Sponsor-approved subject recruiting materials
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

10.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. Because the total duration of this study is 80 days (and of active treatment 56 days), the potential benefits and risks are of a short-term nature. The potential clinical benefits include enhanced glucose control (and overall care in the setting of a clinical study) using either active treatment in conjunction with MET (compared to MET monotherapy). A potential (but very small) risk of the study is hypoglycemia. In part because time with hypoglycemia represents a secondary efficacy endpoint, subjects will receive diaries to record any signs or symptoms of hypoglycemia, as well their nutrition and physical activity.

The ICF must be signed before performance of any study-related activity. The ICF that is used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The

informed consent will be in accordance with ethical tenets originating in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before any assessment or other procedure, including enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations.

By signing the ICF, the subject is authorizing such access. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject is unable to read or write, an impartial witness/legally acceptable representative should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained.

The blood volume taken for safety testing, at the screening and end-of-study visits, is necessary to assess and ensure the safety of each subject. This volume is much less than would be required for standard blood donation (500 mL over 60 days).

10.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to data necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to others.

11. ADMINISTRATIVE REQUIREMENTS

11.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

11.2. Regulatory Documentation

11.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

11.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (e.g. Form FDA 1572), if applicable
- Documentation of investigator qualifications (e.g. curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (e.g. curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (e.g. accreditation/license), if applicable

11.2.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the

study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

11.2.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following individual subject-level data will be recorded directly into the CRF and will be considered source data:

- Age
- Gender
- Race/ethnicity
- Body weight/height/BMI
- Date of diabetes diagnosis (i.e. to compute duration of diabetes)
- History of smoking
- Blood pressure and pulse rate
- Details of physical examination
- Concomitant medications (apart from MET)
- Relevant data from clinical laboratory assessments

The minimum source documentation requirements for Inclusion Criteria and Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician
- Complete history of medical notes at the site

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (e.g. physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (e.g. electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. These data are electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system, but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

11.2.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in printed or electronic format. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

All printed forms must be filled out legibly in black ballpoint pen or typed. The appropriate pages of the CRF must be signed and dated by the investigator.

In the event that electronic CRFs (eCRFs) are used, study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into the CRF in Spanish or English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

Corrections to paper CRFs must be made in such a way that the original entry is not obscured. Correction fluid or tape must NOT be used. The correct data must be inserted, dated, and initialed. If multi-part pressure-sensitive CRF are used, the separated parts of the CRF left at the study site must not be written on once the original has been sent to the sponsor. Completed CRF will be continuously submitted according to the sponsor's instructions and reviewed by the sponsor to determine their acceptability. If corrections to a CRF are needed after removal of the original CRF copy from the study site, Data Correction/Clarification Forms (DCF) will be generated and transmitted to the study site. The CRF must be adjusted (if applicable) and a response provided to the query (complete, sign, and date the DCF).]

In the event that eCRFs are utilized, the following conditions must be met. If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- The sponsor or a sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

An electronic audit trail will be established to document all changes to the data after they leave the eCRF collection device.

11.2.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and direct transmission of clinical laboratory data from a central laboratory (or other data source) into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. In the event of paper CRF use, the sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after their return to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. The data will be entered into the study database and verified for accuracy and consistency with the data sources.

In the event of eCRF use, the sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After download of the data into the study database they will be verified for accuracy and consistency with the data sources.

11.2.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

For CRF completed on pressure-sensitive paper, a copy is to be retained in the archives of the sponsor. A second copy must be archived by the investigator.

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

11.2.8. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (e.g. medical records; a sample may be reviewed). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that, during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

11.2.9. Study Completion/Termination

11.2.9.1. Study Completion/End of Study

The study is considered completed with the last visit (Visit 13; scheduled study assessment as shown in the Time and Events Schedule) for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

11.2.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

11.2.9.3. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

11.3. Use of Information and Publication

All information, including but not limited to information regarding CANA or the sponsor's operations (e.g. patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of CANA, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of exploratory analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for

abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

11.4. Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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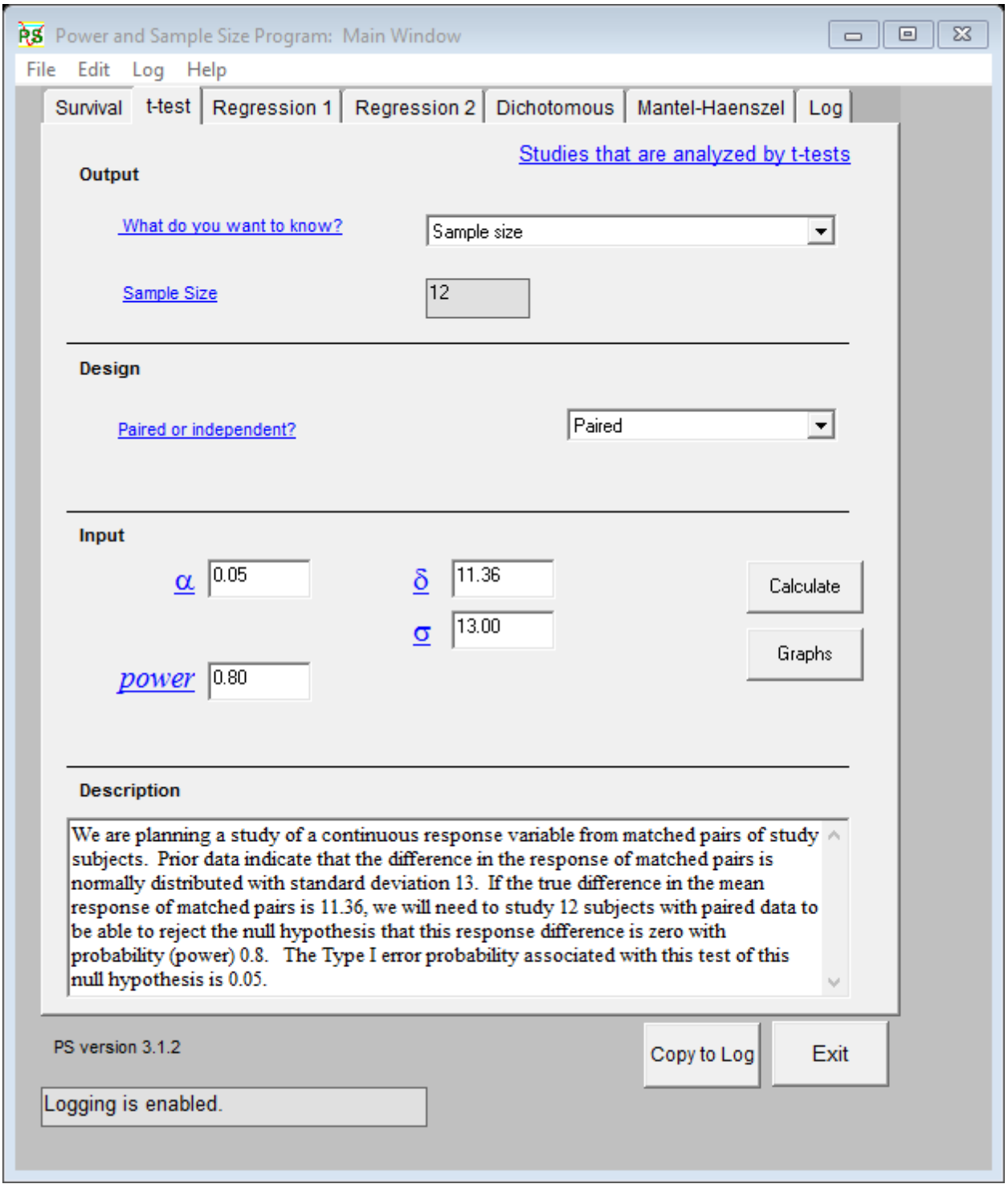
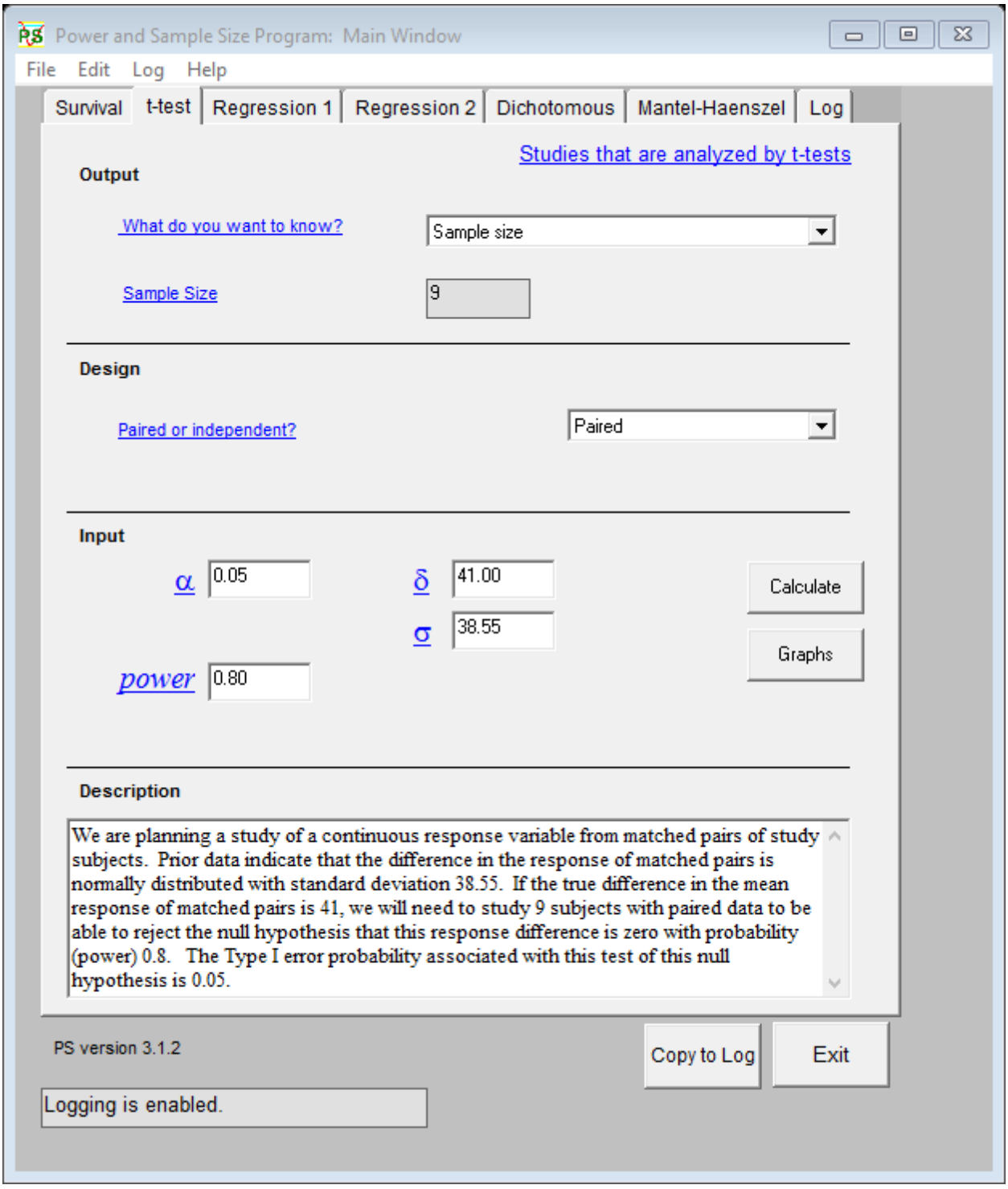
APPENDICES: SAMPLE SIZE CALCULATIONS. RAW DATA FROM PS (POWER AND SAMPLE SIZE CALCULATION) VERSION 3.1.2

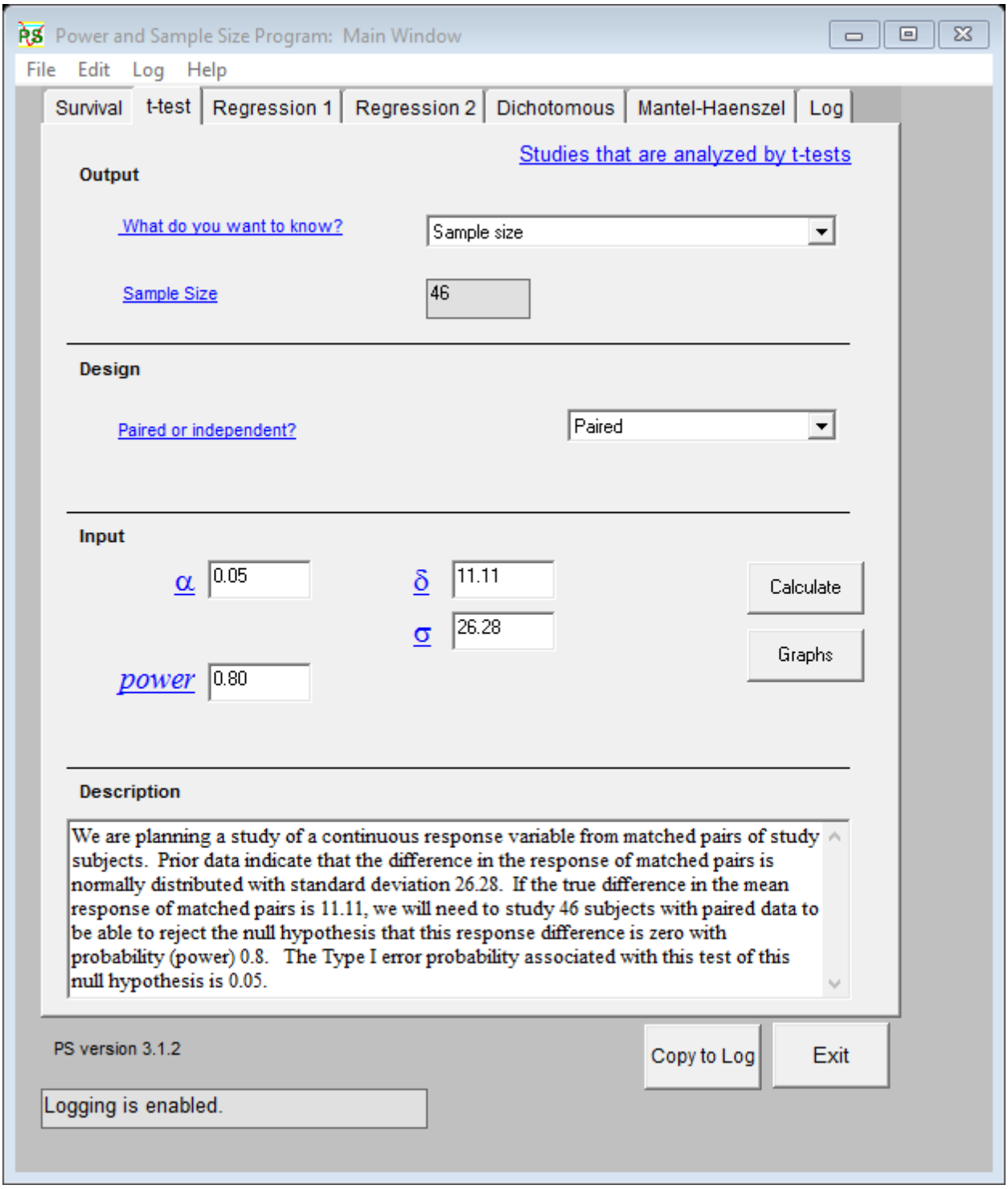
APPENDIX 1. SAMPLE SIZE CALCULATION BASED ON MEAN (SD) DIFFERENCE IN GLYCEMIC SD (SD OF 24-HOUR GLUCOSE PROFILE) IN PATIENTS RECEIVING CANAGLIFLOZIN 300 MG/SITAGLIPTIN 100 MG, EACH AS RELATED TO PLACEBO, ON CGM



APPENDIX 2. SAMPLE SIZE CALCULATION BASED ON MEAN (SD) DIFFERENCE IN ESTIMATED AVERAGE GLUCOSE BETWEEN CANAGLIFLOZIN 300 MG/SITAGLIPTIN 100 MG IN MEAN (SD) ESTIMATED AVERAGE GLUCOSE (EAG) IN DIRECT COMPARATIVE TRIALS WITHOUT CGM (CANTATA-D TRIAL, LATIN AMERICAN POPULATION)

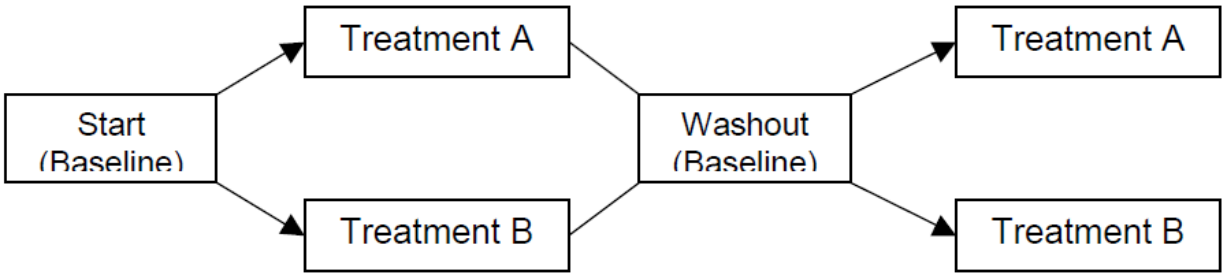


APPENDIX 3. SAMPLE SIZE CALCULATION BASED ON MEAN (SD) DIFFERENCE IN ESTIMATED AVERAGE GLUCOSE BETWEEN CANAGLIFLIZIN 300 MG AND SITAGLIPTIN 100 MG IN MEAN (SD) ESTIMATED AVERAGE GLUCOSE (EAG) IN DIRECT COMPARATIVE TRIALS WTIHOUT CGM CANTATA-D TRIAL, TOTAL POPULATION)



APPENDIX 4. GRIZZLE'S TWO-STAGE MODEL TEST OF CARRYOVER: FORMULAS (Shen, 2006)

The order of drug treatment in a crossover study is called a sequence and the time of a treatment is called a period. The treatment are represented with capital letters, such as A, B, etc. The most common crossover design is AB/BA.



$Y_{ijk} = \mu + b_{ij} + \pi_k + \phi_m + \lambda_m + \varepsilon_{ijk}$

where i = sequence, j = patient, k = period and m = treatment

μ : overall mean

b_{ij} : effect of j^{th} patient with i^{th} sequence and is ~$N(0, \sigma_b^2)$

π_k : effect of k^{th} period

ϕ_m : direct effect of m^{th} drug treatment

λ_m : residual effect of m^{th} drug treatment

ε_{ijk} : random error and is ~$N(0, \sigma_b^2)$

The table 1 lists al the effects in period 1 and period 2. Note this is no carryover effect in period 1.

Table 1. Effects of AB| in both Period BA

	Period 1	Period 2	Sum	Difference
Sequence AB	$\mu + \pi_1 + \phi_1$ ($Y_{1.1}$)	$\mu + \pi_2 + \phi_2 + \lambda_1$ ($Y_{2.1}$)	$Y_{1.1} + Y_{2.1}$	$Y_{1.1} - Y_{2.1}$
Sequence BA	$\mu + \pi_1 + \phi_2$ ($Y_{1.2}$)	$\mu + \pi_2 + \phi_1 + \lambda_2$ ($Y_{2.2}$)	$Y_{1.2} + Y_{2.2}$	$Y_{1.2} - Y_{2.2}$

Step 1. Estimate the carryover effect

H_0: $\lambda_1 = \lambda_2$

The effect sum for each sequence can be used for the hypothesis test.

H_0 $Y_{1.1} + Y_{2.1} = Y_{1.2} + Y_{2.2}$

that is $\mu + \pi_1 + \phi_1 + \mu + \pi_2 + \phi_2 + \lambda_1 = \mu + \pi_1 + \phi_2 + \mu + \pi_2 + \phi_1 + \lambda_2$

finally $\lambda_1 = \lambda_2$

If the null hypothesis can not be rejected, then go to step 2, otherwise go to step 3.

Step 2. Estimate the treatment effect of 2 periods

H_0: $\phi_1 = \phi_2$

The effect crossover difference for each sequence can be used for the hypothesis test.

H_0 $\frac{1}{2}(Y_{1.1} - Y_{2.1}) = \frac{1}{2}(Y_{1.2} - Y_{2.2})$

that is $\frac{1}{2}(\mu + \pi_1 + \phi_1 - \mu - \pi_2 - \phi_2 - \lambda_1) = \frac{1}{2}(\mu + \pi_1 + \phi_2 - \mu - \pi_2 - \phi_1 - \lambda_2)$

$\phi_1 - \frac{1}{2}\lambda_1 = \phi_2 - \frac{1}{2}\lambda_2$

assume $\lambda_1 = \lambda_2$

then $\phi_1 = \phi_2$

Step 3. Estimate the treatment effect of period 1

H_0: $\phi_1 = \phi_2$

If carryover effect is significant, then data from period 1 only is used.

H_0: $Y_{1.1} = Y_{2.1}$

$\mu + \pi_1 + \phi_1 = \mu + \pi_1 + \phi_2$

that is $\phi_1 = \phi_2$

APPENDIX 5. METHOD OF BLOOD PRESSURE MEASUREMENT

Subject Preparation
The subject should remove all clothing that covers the location of cuff placement. (The sleeve should not be rolled up so that it has a tourniquet effect.) The subject should be comfortably seated with legs uncrossed, and back and arm supported, so that the upper arm is at the level of the right atrium (midpoint of the sternum). The subject should be instructed to relax and not talk; approximately 5 minutes should pass before the reading is taken.

Blood Pressure Measurement

Device
Blood pressure readings should be taken manually with a mercury sphygmomanometer or an automated blood pressure monitor.

Cuff Size
A cuff should be chosen that is appropriate for the individual, based upon the upper arm circumference in centimeters. The bladder of the cuff should encircle ≥ 80% of the arm circumference.

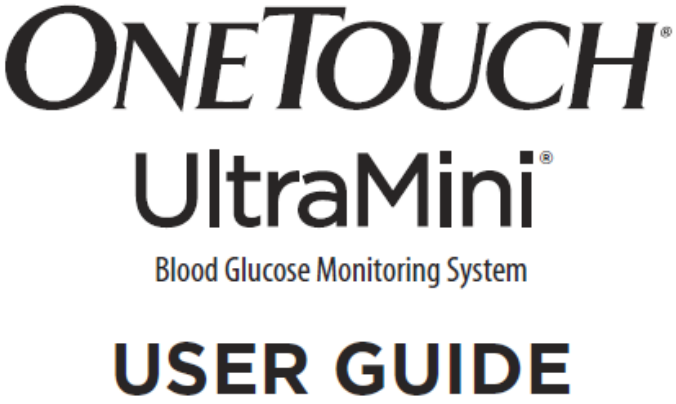
Arm circumference (cm)
Arm Circumference (cm) Size 22-26 Small Adult 27-34 Adult 35-44 Large Adult 45-52 Adult Thigh For the subject with an arm circumference >52 cm when the thigh cuff cannot be fitted over the arm, an appropriately sized cuff should be placed on the subject's forearm, the forearm should be supported at heart level, and the radial pulse at the wrist should be used.

Cuff Placement
Palpate the brachial artery in the antecubital fossa. Place the midline of the bladder of the cuff so that it is over the arterial pulsation on the subject's bare upper arm. The lower end of the cuff should be 2 to 3 cm above the antecubital fossa to allow space for the stethoscope. Pull the cuff snugly around the bare upper arm. Neither the observer nor the subject should talk.

Inflation/Deflation
Inflate the cuff to ≥30 mmHg above the point at which the radial pulse disappears. Deflate the mercury column at 2 to 3 mmHg per second. The first and last audible sounds should be taken as systolic and diastolic blood pressure.

Number of Measurements
One reading should be taken, and the results recorded on the CRF. Blood pressure should be measured at the screening visit in both arms. If there is an interim difference of >10 mmHg in either the systolic or diastolic blood pressure, the arm with the higher pressure should be used for all subsequent blood pressure measurement during the study. If possible, if the blood pressure is measured manually, it should be taken by the same individual, using the same equipment, at each visit so as to reduce interobserver variability (American Heart Assoc Council on High Blood Pressure 2005).

Appendix 6. ONE-TOUCH ULTRA MINI USER GUIDE



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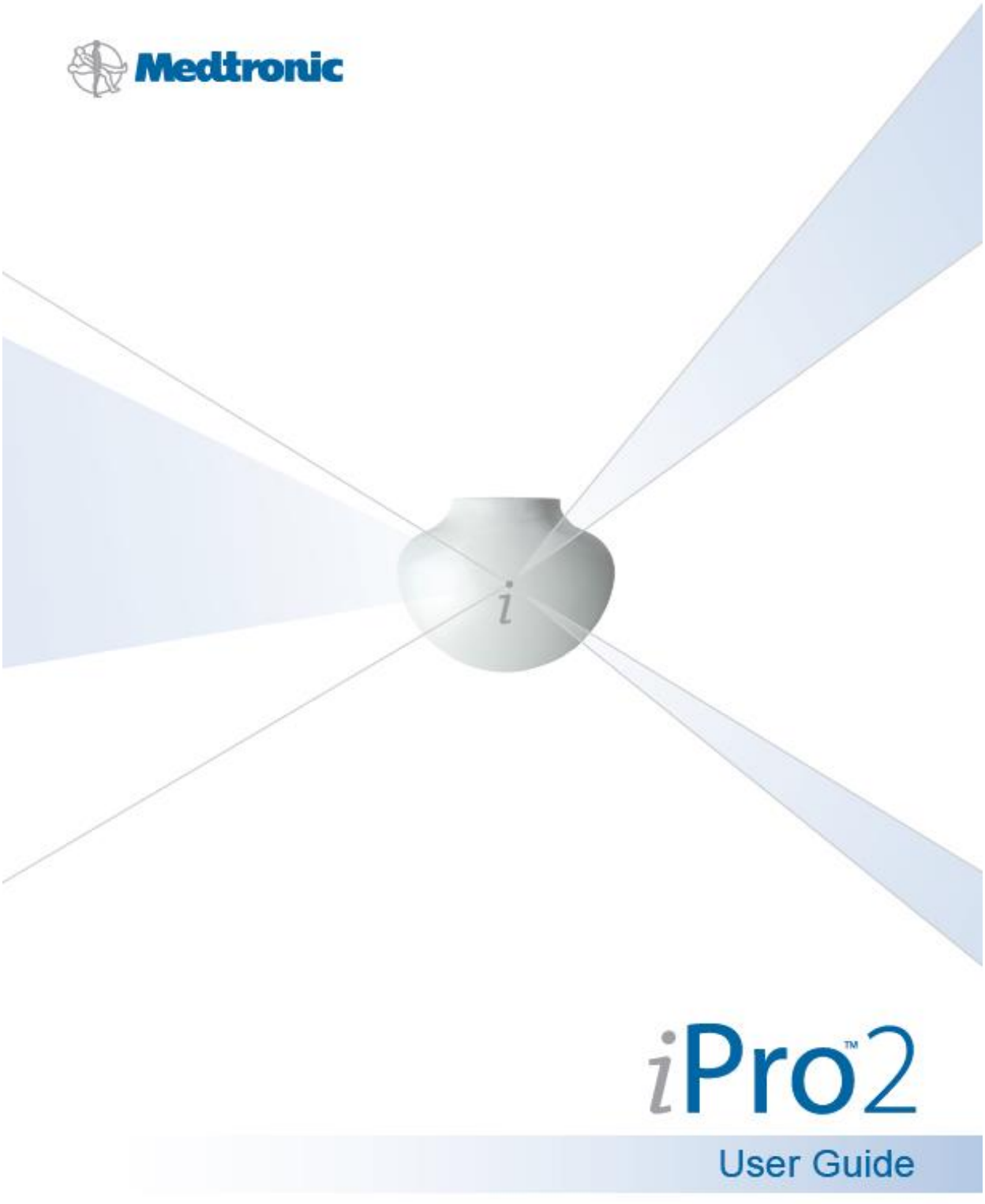
Rev. date: 07/2009

(This is the cover of the document which will be available in the investigator regulatory binder)

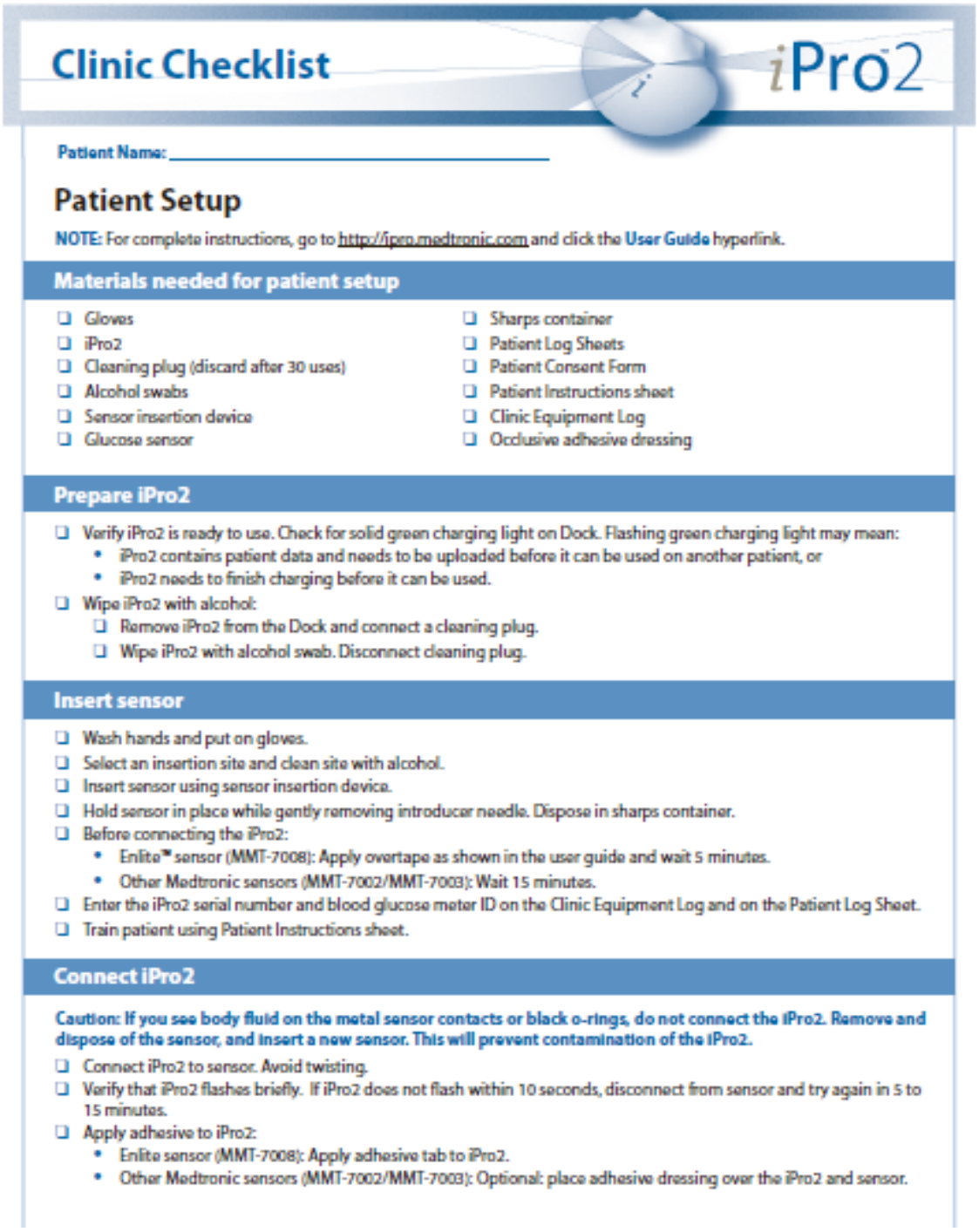
APPENDIX 7.

APPENDIX 7.A. I PRO 2 USER GUIDE



(This is the cover of the document which will be available in the investigator regulatory binder)

APPENDIX 7.B. CLINIC (SITE) CHECKLIST



Clinic Checklist

iPro2

Patient Name: _____

Patient Setup

NOTE: For complete instructions, go to http://ipro.medtronic.com and click the **User Guide** hyperlink.

Materials needed for patient setup

- ❑ Gloves
- ❑ iPro2
- ❑ Cleaning plug (discard after 30 uses)
- ❑ Alcohol swabs
- ❑ Sensor insertion device
- ❑ Glucose sensor
- ❑ Sharps container
- ❑ Patient Log Sheets
- ❑ Patient Consent Form
- ❑ Patient Instructions sheet
- ❑ Clinic Equipment Log
- ❑ Occlusive adhesive dressing

Prepare iPro2

- ❑ Verify iPro2 is ready to use. Check for solid green charging light on Dock. Flashing green charging light may mean:
  - iPro2 contains patient data and needs to be uploaded before it can be used on another patient, or
  - iPro2 needs to finish charging before it can be used.
- ❑ Wipe iPro2 with alcohol:
  - ❑ Remove iPro2 from the Dock and connect a cleaning plug.
  - ❑ Wipe iPro2 with alcohol swab. Disconnect cleaning plug.

Insert sensor

- ❑ Wash hands and put on gloves.
- ❑ Select an insertion site and clean site with alcohol.
- ❑ Insert sensor using sensor insertion device.
- ❑ Hold sensor in place while gently removing introducer needle. Dispose in sharps container.
- ❑ Before connecting the iPro2:
  - Enlite™ sensor (MMT-7008): Apply overtape as shown in the user guide and wait 5 minutes.
  - Other Medtronic sensors (MMT-7002/MMT-7003): Wait 15 minutes.
- ❑ Enter the iPro2 serial number and blood glucose meter ID on the Clinic Equipment Log and on the Patient Log Sheet.
- ❑ Train patient using Patient Instructions sheet.

Connect iPro2

Caution: If you see body fluid on the metal sensor contacts or black o-rings, do not connect the iPro2. Remove and dispose of the sensor, and insert a new sensor. This will prevent contamination of the iPro2.

- ❑ Connect iPro2 to sensor. Avoid twisting.
- ❑ Verify that iPro2 flashes briefly. If iPro2 does not flash within 10 seconds, disconnect from sensor and try again in 5 to 15 minutes.
- ❑ Apply adhesive to iPro2:
  - Enlite sensor (MMT-7008): Apply adhesive tab to iPro2.
  - Other Medtronic sensors (MMT-7002/MMT-7003): Optional: place adhesive dressing over the iPro2 and sensor.

Patient Name: _____

Uploading to CareLink® iPro

NOTE: For complete instructions, go to http://ipro.medtronic.com and click the **User Guide** hyperlink.

Materials needed for cleaning and uploading

- ❑ Gloves
- ❑ iPro2 (which has been worn by the patient)
- ❑ Cleaning plug (discard after 30 uses)
- ❑ Optional: adhesive remover, such as Detachol*
- ❑ Mild liquid soap
- ❑ Quaternary ammonium compound, such as Cavicide*
- ❑ 70% isopropyl alcohol
- ❑ Bio-waste container
- ❑ Clinic Equipment Log
- ❑ Dock, connected to a computer
- ❑ Patient's blood glucose (BG) meter
- ❑ Patient Log Sheet
- ❑ Meter manufacturer's cable

Reminders: To avoid erasing data on your iPro2

- ✔ Make sure that the white Dock power light is on before connecting iPro2 to the Dock.
- ✔ Do not connect or disconnect the Dock from its power source while the iPro2 is connected.
- ✔ Never connect the iPro2 to a blue charger.
- ✔ Upload data within 17 days of starting the study.
- ✔ Do not push the reset button on the Dock while an iPro2 containing data is connected.

Remove and clean iPro2

- ❑ Wash hands and put on gloves.
- ❑ Remove iPro2 from sensor. Avoid twisting.
- ❑ Remove sensor from patient's body and dispose in bio-waste container.

Always clean and disinfect the iPro2 before connecting it to the Dock.

- ❑ Connect a cleaning plug to the iPro2. Never connect an iPro2 to a blue test plug.
- ❑ Remove adhesive residue using adhesive remover (Detachol).
- ❑ Wipe with mild liquid soap solution and rinse with water.
- ❑ Apply quaternary ammonium compound disinfectant (Cavicide).
- ❑ Wipe with 70% isopropyl alcohol.
- ❑ Disconnect cleaning plug and allow iPro2 to air dry.

Warning: If body fluid enters the iPro2's connector, you must dispose of the iPro2. Do not connect it to the Dock.

Upload data and generate reports

On computer:

- ❑ Find the patient's record in CareLink iPro (http://ipro.medtronic.com) or create a new patient record if needed.
- ❑ Use the Clinic Equipment Log or Patient Log Sheet to identify the correct iPro2 and BG meter for the patient.
- ❑ Click **Upload iPro2**. Follow on-screen instructions for uploading data from iPro2 and BG meter.
- ❑ Click **Open Logbook** to add event markers or BG meter readings from Patient Log Sheets.
- ❑ Click individual reports to view them, or click **Print all** to print them.

APPENDIX 7.C. PATIENT INSTRUCTIONS:

Simple tips, instructions and guidelines for iPro2 use

Blood glucose (BG) testing

- On the first day:
  - Take your first BG meter reading at least 1 hour after you leave the physician's office.
  - Take a second BG meter reading at least 3 hours after you leave the physician's office.
  - Collect at least one more meter reading before going to bed.
- Collect at least 4 BG meter readings each day, such as before breakfast, lunch, dinner, and bedtime.
- Do not change any settings on your meter during the study, even if a daylight savings time change occurs.
- Use the same blood glucose meter for all BG meter readings.
- Do not let anyone else use your meter during the study.
- Do not use control solution during the study.

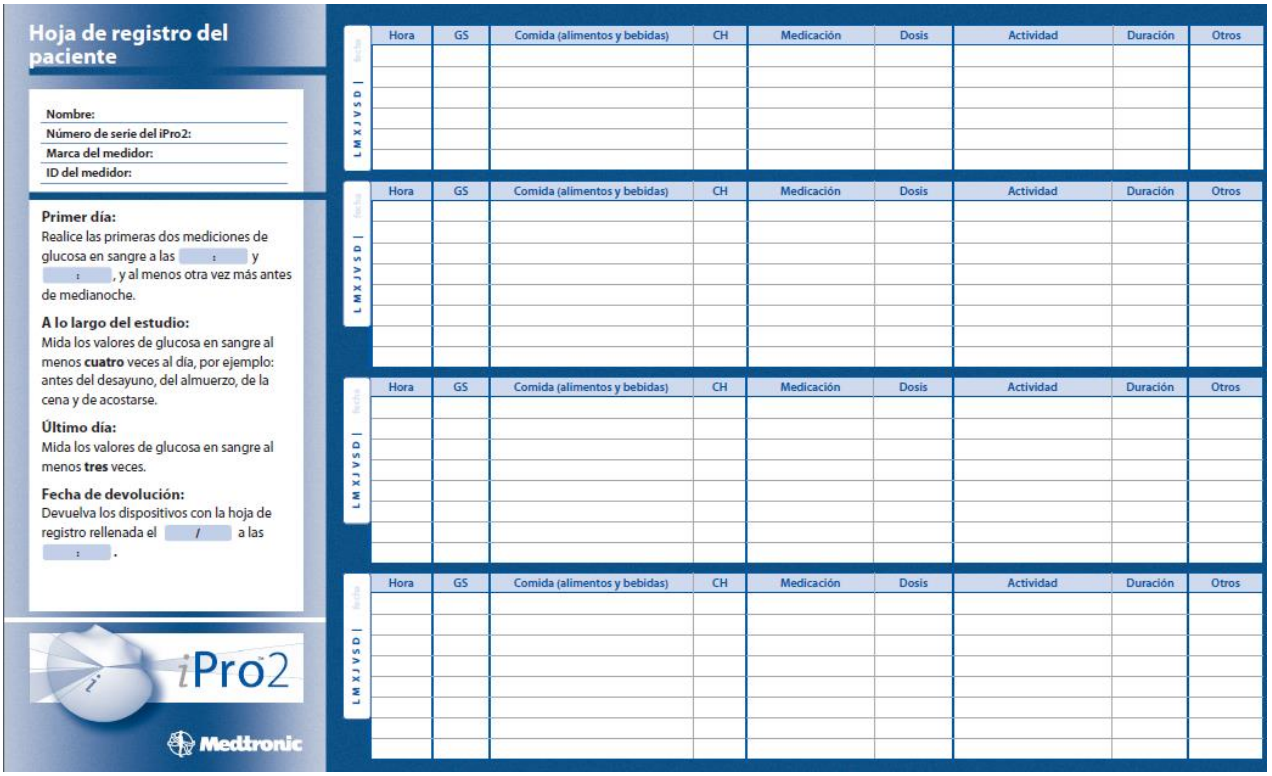
Log sheet entries

- Write down your BG meter readings, food or drink and number of carbohydrates, physical activity and duration, medications and dosages, and other events (such as feeling hypoglycemic, stress, or illness).
- Keep the log sheet with you at all times so you can write down the information immediately after each event. Record the time and date within 5 minutes of each BG meter reading.

Care and wearing

- Live your life with your normal behaviors. If you normally exercise, then exercise.
- Keep tape over the sensor and iPro2 to prevent accidental removal or sensor movement. If the sensor comes out even a small amount, it may stop working. If new tape is needed, just put it over the existing tape. If the sensor comes out, place the sensor and iPro2 into a plastic resealable bag and notify your physician's office.
- Check the site 4 times a day to ensure that the sensor and iPro2 are firmly connected, the sensor is still fully inserted, and there is no bleeding or irritation.
- If the sensor is partly pulled out, attempt to gently push it back into place.
- Remove the sensor if you have redness, pain, tenderness, or swelling at the site, and notify your physician's office.
- You may shower and swim while wearing the iPro2 and sensor. The iPro2 is watertight at a depth of up to 2.4 meters (8 feet) for 30 minutes. There is no time limit if you are swimming on the surface of a pool or showering.
- Insulin should be injected at least 7.5 centimeters (3 inches) away from the sensor insertion site, and insulin pump infusion should be at least 5 centimeters (2 inches) from the sensor insertion site.
- The iPro2 and sensor must be removed prior to an x-ray, CT scan or MRI.

APPENDIX 8. PATIENT LOG SHEET



Hoja de registro del paciente

Nombre:
Número de serie del iPro2:
Marca del medidor:
ID del medidor:

Primer día:
Realice las primeras dos mediciones de glucosa en sangre a las : y : , y al menos otra vez más antes de medianoche.

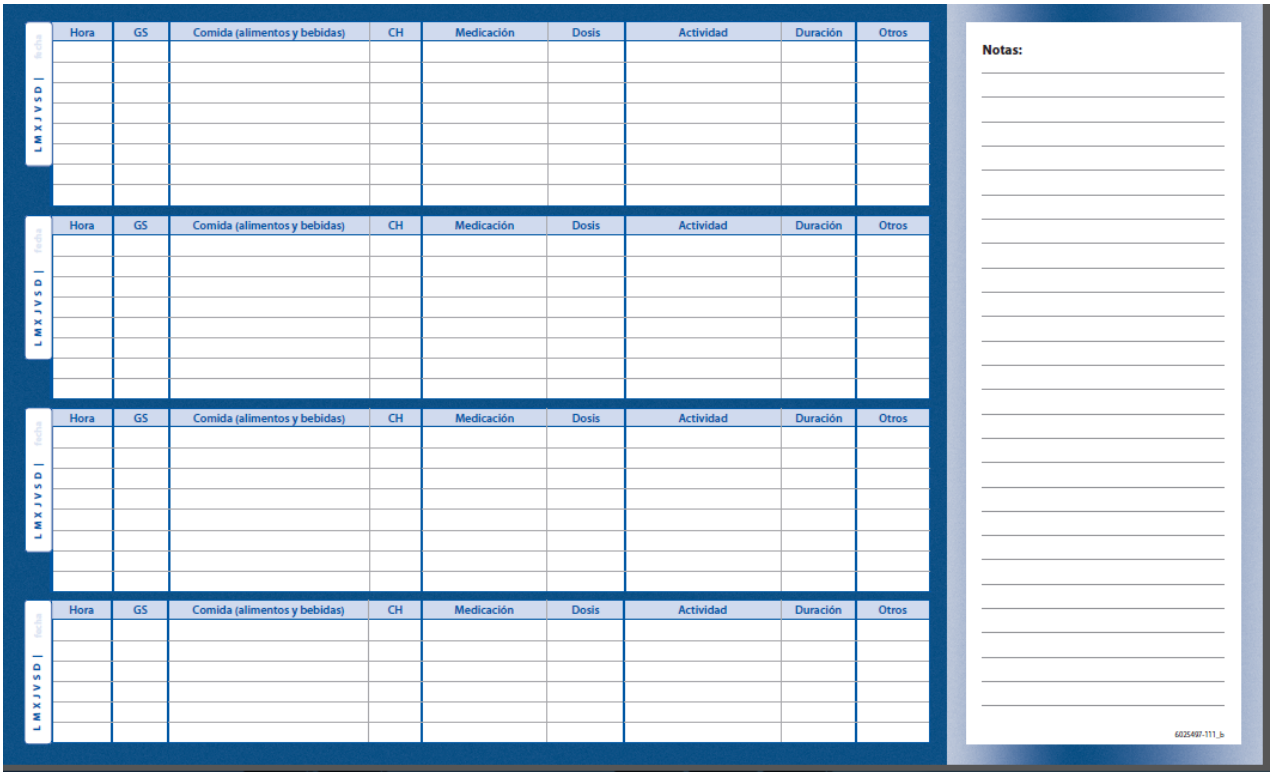
A lo largo del estudio:
Mida los valores de glucosa en sangre al menos **cuatro** veces al día, por ejemplo: antes del desayuno, del almuerzo, de la cena y de acostarse.

Último día:
Mida los valores de glucosa en sangre al menos **tres** veces.

Fecha de devolución:
Devuelva los dispositivos con la hoja de registro rellenada el / a las : .

iPro2
Medtronic

Fecha L M X J V S D	Hora	GS	Comida (alimentos y bebidas)	CH	Medicación	Dosis	Actividad	Duración	Otros



Fecha L M X J V S D	Hora	GS	Comida (alimentos y bebidas)	CH	Medicación	Dosis	Actividad	Duración	Otros

Notas:

APPENDIX 9. INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): Fernando Javier Lavalle-González, MD

Institution and Address: Facultad de Medicina de la Universidad Autónoma de Nuevo León
Madero y Dr. Aguirre Pequeño, Col. Mitras Centro sin número
[redacted] Mexico [redacted]

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Patricia Cabrera, MD, Regional Therapeutics Area Manager, Metabolics

Institution: Janssen Research & Development/Janssen Latin America

Signature: _____ Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

APPENDIX 10: CLINICAL LABORATORY TESTS

Blood samples for serum chemistry and hematology, and a random urine sample for urinalysis will be collected. The following tests will be performed by the central laboratory:

- **Hematology Panel**
  - -hemoglobin
  - -platelet count
  - -hematocrit
  - -red blood cell (RBC) count
  - -white blood cell (WBC) count with differential

- **Serum Chemistry Panel**

-sodium
-potassium
-chloride
-bicarbonate
- blood urea nitrogen (BUN)
-creatinine
-aspartate aminotransferase (AST)
-alanine aminotransferase (ALT)
-gamma-glutamyltransferase (GGT)
-total bilirubin
-alkaline phosphatase
-creatine phosphokinase (CPK)
-lactic acid dehydrogenase (LDH)
-uric acid
-calcium
-phosphate
-albumin
-total protein
-magnesium

- Follicle-stimulating hormone only for women >45 years of age who have had amenorrhea for at least 6 months and <18 months before screening.
- Fasting serum lipid profile (triglycerides, LDL-C, HDL-C, total cholesterol). LDL-C will not be measured but will be calculated using the Friedewald equation
- HbA1c
- Fasting plasma glucose
- C-peptide
- Urinalysis. Dipstick done at central laboratory
  - -specific gravity
  - -pH
  - -protein
  - -blood
  - -ketones
  - -bilirubin
  - -urobilinogen
  - -nitrite
  - -leukocyte esterase

If dipstick result is abnormal, microscopic examination will be performed.

- Urine pregnancy testing, unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations, for all women unless they are surgically sterile or unless there is a documented history of their postmenopausal status.

Subjects must be fasting for at least 8 hours before blood sample collections, except for the screening visit when nonfasting blood samples may be collected.

Central laboratory will report the eGFR according to the Modification of Diet in Renal Disease Study (MDRD) equation (Levey 1995; Myers 2005; Stevens 2006) at study visits when serum creatinine is measured.

The 4-variable MDRD eGFR includes serum creatinine, age, race, and sex according to the equation below:
For creatinine in mg/dL:
eGFR (mL/min/1.73 m2) = 175 x (serum creatinine)-1.154 x (age)-0.203 x (0.742 if female) x (1.21 if black)