PROTOCOL: DPO-203

Study Title:	A Phase 2, Double-blind, Dose Escalation Regimen of Once-weekly OPK-88003 in Subjects with Type 2 Diabetes
Study Number:	DPO-203
Study Phase:	Phase 2
Product Name:	OPK-88003
IND Number:	IND 113480
Indication:	Type 2 Diabetes Mellitus
Investigators:	Multicenter
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1	24 Jan 2018
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SYNOPSIS

Sponsor:
OPKO Ireland Global Holdings Ltd., a subsidiary of OPKO Health, Inc.

Name of Finished Product:

OPK-88003

Name of Active Ingredient:
OPK-88003

Study Title:
A Phase 2, Double-blind, Dose Escalation Regimen of Once-weekly OPK-88003 in Subjects with Type 2 Diabetes

Study Number:

DPO-203

Study Phase:

Phase 2

Primary Objective:
To evaluate the effect of dose escalation of once-weekly (QW) subcutaneous (SC) OPK-88003 vs placebo injections on HbA1c absolute change from baseline to after 30 weeks treatment in subjects with type 2 diabetes mellitus (T2DM) inadequately controlled with diet and exercise alone, or treated with a stable dose of metformin.

Secondary Objectives:
1. Mean percent (%) body weight change from baseline to after 30 weeks treatment
2. Percent (%) of subjects with 5% or greater body weight loss after 30 weeks treatment
3. Change of fasting plasma glucose (FPG) from baseline to after 30 weeks treatment
4. Number and percent (%) of subjects achieving HbA1c ≤6.5

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3. Percent (%) of subjects permanently discontinued from the study due to hyperglycemia
4. Incidence and rate of gastrointestinal (GI) events, major cardiovascular (CV) events, hypoglycemia, injection site reactions, hypersensitivity reactions and pancreatic events.
5. To evaluate immunogenicity of OPK-88003

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Study Design:
Study DPO-203 is a randomized, double-blind, dose escalation, placebo-controlled, phase 2 multicenter trial in subjects with T2DM. There will be up to approximately 30 investigational sites. The trial consists of four phases: a screening/baseline phase (up to 2 weeks prior to first dose), a 30-week treatment period consisting of a dose escalation phase (8 weeks) and a target dose phase (22 weeks), and a follow-up period (4 weeks). Subjects will be randomly assigned to OPK-88003 or placebo administered QW. CCI [redacted]

Study Population:
Approximately 200 subjects are expected to be screened, and 110 subjects will be randomized to treatment (70 subjects) and placebo (40 subjects) at a ratio 1.75:1, respectively.

Inclusion criteria:
Subjects are eligible to be included in the study only if they meet all of the following criteria at the indicated visit:

1. Have T2DM for at least 6 months before entering the trial based on the disease diagnostic criteria (AmDA 2018), controlled with diet and exercise alone or with a stable dose of metformin (≥1000 mg/day) for at least 3 months prior to visit 1.
2. Males or females 18 to 80 years of age inclusive.
3. Females must be not of childbearing potential due to surgical sterilization. (hysterectomy or bilateral oophorectomy or tubal ligation) or menopause. Women with an intact uterus are deemed postmenopausal if they are ≥45 years old, and
   - have not taken hormones or oral contraceptives within the last year and had cessation of menses for at least 1 year
     OR
   - have had at least 6 months of amenorrhea with follicle-stimulating hormone (FSH) levels consistent with a postmenopausal state (FSH ≥40 mIU/mL).
4. Have an HbA1c value at screening of ≥7.0% and ≤10.5%.
5. Have a Body Mass Index (BMI) ≥27and ≤45 kg/m^2 at screening.
6. In the investigator's opinion, are capable and willing to:
   - administer weekly study medication injection (with assistance if necessary)
   - complete study diaries
   - follow lifestyle counseling advice
   - perform self-monitored blood glucose (SMBG)
7. Are willing to be available for the duration of the trial, comply with the required study procedures and visits, and abide by the clinical research site policy.
8. Have given written informed consent.

Exclusion criteria:
Subjects will be excluded if they meet any of the following criteria at visit 1, unless otherwise specified:

1. Participation in any other interventional trial within 30 days.
2. Have type 1 diabetes mellitus.
3. Previous exposure or known allergies to OPK-88003 or its components.

4. Previous treatment with incretin mimetic drugs (GLP-1 agonists), excluding DPP-IV inhibitors.
5. Have used insulin for diabetic control for more than 6 consecutive days within the prior year.
6. Use of thiazolidinedione, or any other drugs, including investigational drugs, for treatment of hyperglycemia (except metformin), within the prior 3 months.
7. Use of systemic (including nasal and inhaled) glucocorticoids within the prior month, or subjects likely to require systemic doses of glucocorticoids during study participation are also excluded. Topical applications are permitted.
8. Evidence of hepatitis B and/or positive hepatitis B surface antigen. Evidence of hepatitis C.
9. Evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies.
10. Have cardiac disease with functional status that is NYHA Class III, or IV or in the last 6 months have had any of the following: myocardial infarction (MI), unstable angina, acute coronary syndrome, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI; diagnostic angiograms are permitted), transient ischemic attack (TIA), cerebrovascular accident (for example, stroke) or decompensated congestive heart failure.
11. Have hypertension (mean systolic blood pressure >160 mm Hg or mean diastolic blood pressure >100 mm Hg), malignant hypertension, renal artery stenosis, and/or evidence of labile blood pressure including symptomatic postural hypotension at visit 1. If on treatment for hypertension, doses of antihypertensive medications must be stable for the prior 30 days.
12. Have obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or an alanine transaminase (ALT) or aspartate aminotransferase (AST) levels >2.5 x upper limit of normal (ULN) or serum total bilirubin >2.0 mg/dL.
13. Evidence of hypothyroidism or hyperthyroidism based on clinical evaluation and/or an abnormal thyroid-stimulating hormone (TSH). Subjects on a stable dose of thyroid replacement therapy for at least the prior two months may be eligible if they meet the other criteria.
14. Evidence of obesity induced by other endocrinologic disorders (eg. Cushing Syndrome).
15. Clinically significant peripheral vascular disease in the opinion of the investigator.
16. Active proliferative diabetic retinopathy.
17. Known significant autonomic neuropathy as evidenced by urinary retention, resting tachycardia, orthostatic hypotension or diabetic diarrhea.
18. Have an active or untreated malignancy or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix or in situ prostate cancer) for less than five years. Have a personal or family history of medullary C-cell thyroid hyperplasia, focal hyperplasia, carcinoma (including sporadic, familial or part of Multiple Endocrine Neoplasia syndrome type 2A or 2B); or a serum calcitonin ≥20 pg/mL.
19. Impaired renal function (eGFR <60 mL/min/1.73 m^2).
20. Triglycerides >600 mg/dL (6.84 mmol/L) at screening. If subject is on lipid lowering therapies, doses must be stable for 30 days prior to screening.

21. Any subject having experienced a keto-acidotic episode requiring hospitalization in the prior 6 months.
22. Have an ECG considered by the investigator indicative of active cardiac disease or with abnormalities that may interfere with the interpretation of changes in ECG intervals. A QTcB interval greater than 450 msec in men and greater than 470 msec in women at visit 1 or visit 2 is specifically excluded.
23. Personal or family history of long QT syndrome, family history of sudden death in a first-degree relative (parents, sibling, or children) before age 40 or personal history of unexplained syncope within the last year. Use of prescription or over-the-counter medications known to prolong the QT or QTc interval.
24. History or presence of CV, respiratory, hepatic, renal, GI, endocrine (other than diabetes), hematological, or neurological disorders capable of significantly altering the absorption, or metabolism or elimination of drugs or of constituting a risk when taking the study medication or interfering with the interpretation of data.
25. Diagnosis of gastroparesis or bariatric surgery prior to screening, or planned bariatric surgery for the trial duration period.
26. Have had more than one episode of severe hypoglycemia within 6 months prior to visit 1, as defined by hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery, or has a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms. Any subject that the investigator feels will not be able to communicate an understanding of hypoglycemic symptoms and the appropriate treatment of hypoglycemia should also be excluded.
27. Have had two or more emergency room visits or hospitalizations due to poor glucose control within the prior 6 months.
28. Have taken prescription or over-the-counter medications to promote weight loss within the prior 3 months.
29. Have had a significant change in weight, defined as a gain or loss of more than 5% in the prior 3 months.
30. Are currently taking CNS stimulants (eg, Ritalin-SR®) with the exception of caffeinated beverages.
31. Have had a blood transfusion or severe blood loss within the prior 3 months or have known hemoglobinopathy, hemolytic anemia, sickle cell anemia, or have a hemoglobin value <11 g/dL (males) or <10 g/dL (females), or any other condition known to interfere with HbA1c methodology.
32. Blood donation of 450 mL or more in the prior 3 months or any blood donation within the prior month.
33. Have a history of alcohol or drug dependence or abuse within the last 2 years and/or have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females) [1 unit = 12 oz. or 360 mL of beer; 5 oz. or 150 mL of wine; 1.5 oz. or 45 mL of distilled spirits].
34. Have a history of atopy (severe or multiple allergic manifestations) or clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, anaphylaxis, angioedema, or exfoliative dermatitis).

35. Have a history of acute or chronic pancreatitis or confirmed elevation in serum lipase/amylase (>2 x ULN).
36. Have any other condition or psychiatric disorder that, in the opinion of the investigator, may preclude the subject from following and completing the protocol related procedures.
37. Are unsuitable for inclusion in the study in the opinion of the investigator or sponsor.
38. Are unable to undergo MRI procedures for any reason CCI [redacted]

Test Product, Dose, and Mode of Administration:
OPK-88003 and placebo are supplied for once-weekly SC injection. OPK-88003 or placebo will be initially administered for 4 weeks at 20 mg QW followed by 4 weeks at 40 mg QW followed by 70 mg QW for 22 weeks. There are no restrictions on the time of day each dose is given but it is advisable to administer SC injections on the same day and time of the week for the full 30-week treatment period. Study drug should not be administered within four days of the previous injection.

Duration of Treatment:
OPK-88003 or placebo will be administered for 30 weeks. Each subject may participate in the study for up to 36 weeks (including screening phase and follow-up).

Efficacy Assessments:
The primary efficacy measure is HbA1c (absolute change from baseline). Secondary efficacy measures include: body weight (mean change from baseline and % of subjects with > 5% loss from baseline to endpoint), FPG, number and % subjects achieving HbA1c ≤6.5.

Safety Assessments:
Safety assessments include all AEs, vital signs, ECG monitoring, and development of anti-drug antibodies (ADA).

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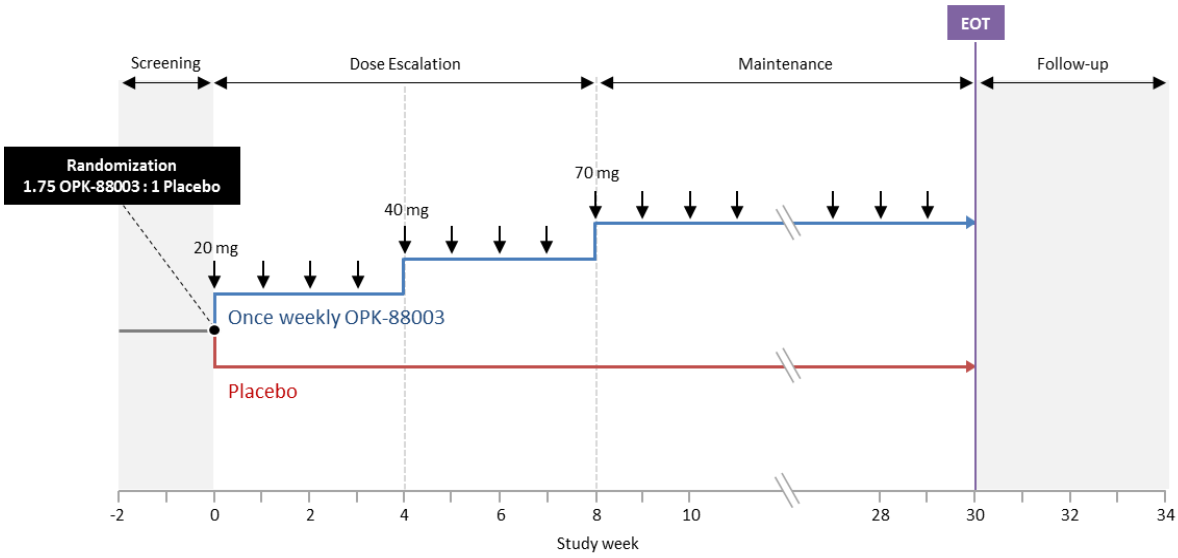
Statistical Methods:
Sample size: A total of 110 subjects will be randomized at a ratio 1.75:1 to OPK-88003 (70 subjects) and placebo (40 subjects). 48 subjects in the active arm and 27 subjects in the placebo arm will provide at least 90% power to detect superior glycemic control over placebo represented by -0.8% in HbA1c levels after 30 weeks of treatment. This assumes a common standard deviation (SD) of 1.0% and a two-sided alpha of 0.05.

Efficacy: The primary efficacy outcome of HbA1c change from baseline to the 30-week endpoint will be performed on the mITT analysis set. The primary efficacy outcome will be analyzed using linear contrasts from an analysis of covariance (ANCOVA) model with treatment arm and BMI strata as factors and the baseline HbA1c value as a covariate. An additional supportive analysis of the primary efficacy outcome will be a mixed-model repeated-measures (MMRM). The factors in the model will be BMI strata, treatment group, baseline value, visit, and the treatment group by visit interactions.. Additional

covariates may be added and will be detailed in the statistical analysis plan (SAP).
The mean percent weight change from baseline at the 30 week endpoint will be analyzed using similar dose response models as the primary analysis. A logistic regression analysis will be performed for the percent of subjects with 5% or greater body weight loss with treatment and HbA1c and BMI strata as fixed effects, and baseline weight as a covariate. Comparisons between treatment groups for the number and percent of subjects achieving HbA1c ≤6.5 will be performed for responses after 30 weeks treatment with LOCF based on a logistic regression model with a factors for treatment group and BMI strata and baseline HbA1c as a covariate.

Study Duration and Dates:
The trial is expected to commence recruitment during Q1 2018 and recruitment is expected to take approximately 5 months.

Study Design for DPO-203



EOT: end of treatment
↓ indicates dosing

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ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AmDA	American Diabetes Association
ANCOVA	analysis of covariance
AP.	acute pancreatitis
AUC	area under the curve
BIW	twice-weekly
BMI	body mass index
CK	creatine kinase
C_{max}	maximum concentration
CNS	central nervous system
CRA	clinical research associate
CSE	clinically significant event(s)
CSR	clinical study report
CV	cardiovascular
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment (visit)
ET	early termination
CCI	[redacted]
FPG	fasting plasma glucose
GcgR	glucagon receptor
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
GLP-1	glucagon like peptide-1
GLP-1R	glucagon-like protein-1 receptor

HbA1c	glycosylated hemoglobin
CCI	[redacted]
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IRT	interactive response technology
LDL-C	low density lipoprotein cholesterol
LOCF	last observation carried forward
LSM	least squares mean
MI	myocardial infarction
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
MRI	magnetic resonance imaging
NAFLD	non-alcoholic fatty liver disease
NOAEL	no observed adverse effect level
OAM	oral antidiabetic medication
OXM	oxyntomodulin
PD	pharmacodynamics(s)
PK	pharmacokinetic(s)
QW	once-weekly
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SMBG	self-monitored blood glucose
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1 INTRODUCTION

1.1 Background

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by insulin resistance and loss of β-cell function. Obesity is a major contributor to the progression of insulin resistance in T2DM. Correlations between adiposity and insulin resistance have been reported in both adults and children. Thus, there is a need for the development of therapies that target both body weight and poor glycemic control.

1.1.1 Incretins

Incretin mimetics class of glucose-lowering drugs offer an alternative approach to the treatment of T2DM with moderate efficacy in lowering glycosylated hemoglobin A1c (HbA1c) and favorable weight loss. Glucagon-like-peptide 1 (GLP-1), an endogenous incretin hormone, regulates postprandial glycemia by stimulating insulin secretion, inhibiting glucagon secretion, promoting satiety and reducing weight gain via both peripheral and central activation of the glucagon-like protein-1 receptor (GLP-1R) (Campbell & Drucker 2013).

While fasting plasma levels of endogenous GLP-1 are normal in subjects with T2DM, they are diminished post-prandially (Baggio & Drucker 2007). GLP-1 is rapidly degraded by the protease dipeptidyl peptidase-IV (DPP-IV) resulting in a half-life of approximately 1-2 minutes in both healthy and subjects with T2DM (Deacon et al 1995). Since the glucoregulatory actions of GLP-1 remain intact in patients with T2DM, current therapeutic strategies have focused on analogs with improved metabolic stability and reduced clearance.

1.1.2 Oxyntomodulin

Oxyntomodulin (OXM) is a 37-amino acid peptide hormone that is released postprandially, along with GLP-1, from the L-cells of the small intestine in proportion to energy intake. OXM reduces body weight in obese patients as a result of enhanced satiety and increased energy expenditure (Wynne et al 2010). The satiety-inducing effects of OXM are believed to be mediated through the activation of the GLP-1R, since its anorectic effects in rodents are blocked by co-administration of the GLP-1R antagonist exendin (9-39) and are not observed in Glp1r-/- mice (Baggio et al 2004, Sowden et al 2007, Wynne et al 2010). Other effects of OXM, including further improvement of β-cell function and increased energy expenditure have been attributed to the glucagon receptor (GcgR) pathway (Kosinski et al 2012). Chronic infusion of OXM had superior weight loss and comparable glucose lowering to OXMQ3E (an OXM analog which has no significant GcgR agonist activity) in diet induced obese (DIO) mice (Kosinski et al 2012). Moreover, OXM improves glucose tolerance and stimulates insulin secretion in mice (Maida et al 2008) further suggesting a role for OXM in glucose homeostasis.

1.1.3 OPK-88003

OPK-88003 is a long-acting polyethylene-glycol (PEG)-conjugated (PEGylated) synthetic peptide analog of mammalian OXM. Similar to native OXM, OPK-88003 binds and activates both the GLP-1R and the GcgR. In addition to the well-documented insulin secretion-promoting and glucose-lowering effects of GLP-1R agonists, OPK-88003 may have additional benefits via its action on the GcgR, including effects on satiety and weight loss. Among currently available therapies for T2DM, GLP-1 agonists are most effective in glycemic control with favorable effects on body weight and without the risk of hypoglycemia. However, the weight loss with GLP-1 agonists is modest due to dose-dependent gastrointestinal (GI) side effects. OPK-88003 is designed to improve upon existing GLP-1 agonists by offering both non-inferior glycemic control and superior weight management.

1.2 Nonclinical Studies

Nonclinical studies support that OPK-88003 may be safely administered to subjects with T2DM. The toxicity profile of OPK-88003 has been characterized in rats and monkeys using sub-chronic and chronic repeat-dose toxicity, and safety pharmacology studies. The nonclinical testing program has followed a standard development pathway for a chronically used biological product.

Safety pharmacology evaluations including central nervous system (CNS), cardiovascular (CV), and respiratory assessments were performed in monkeys at doses up to 5 mg/kg. The no observed adverse effect level (NOAEL) for effects on CNS, CV, and respiratory safety pharmacology in the monkey was 5 mg/kg. Because OPK-88003 is a synthetic peptide, no genetic toxicity studies were conducted.

OPK-88003-related changes in both rat and monkey repeat-dose toxicity studies (4 and 26 weeks in duration) were generally consistent with, or secondary to, typical GLP-1R agonist pharmacology. In the 4-week studies, OPK-88003 was injected SC twice-weekly (BIW) with doses of 1.5 to 15 mg/kg and 0.5 to 5 mg/kg in rats and monkeys, respectively. Important findings were limited to reversible pharmacodynamic (PD) reductions in food consumption, with secondary decreases in body weight at all doses in rats and the high-dose in monkeys. The maximum tolerated dose (MTD) and NOAELs for target organ toxicity were 15 mg/kg and 5 mg/kg, respectively.

In the 26-week studies, SC OPK-88003 doses of 0.3 to 3.0 mg/kg and 0.5 to 5.0 mg/kg BIW were evaluated in rats and monkeys, respectively. The primary effects were dose-dependent decreases in food consumption with secondary decreases in body weight gain. The NOAELs for target organ toxicity in chronic repeat-dose toxicity studies in rats and monkeys were 3 mg/kg and 1.5 mg/kg, respectively.

1.3 Previous Human Experience

OPK-88003 has been investigated for the treatment of patients with T2DM and accompanying unhealthy body weight as a once-weekly (QW) subcutaneous (SC) administration. Cumulatively, 402 subjects have received OPK-88003 to date in the clinical program. Single and multiple ascending doses up to 60 mg QW were tested in a two-part, phase 1 double–blind, randomized, placebo-controlled, clinical pharmacology trial DPO-101. Doses ranging from 10 mg to 50 mg per week were tested in a 24-week double-blind (for the first 12 weeks), randomized, placebo- and active comparator (2 mg exenatide ER)-controlled phase 2 trial XNAA. Supratherapeutic multiple SC doses of 40 mg once daily for 7 days and titrated doses of 15 to 60 mg over 6 days were tested in a double-blind, placebo controlled clinical pharmacology study XNAB.

Clinical data from the phase 1 trial DPO-101 indicated that QW SC administration of OPK-88003 produced an improvement in HbA1c and fasting glucose and resulted in progressive decrease in body weight. Changes from baseline in body weight after 5 weeks of dosing in T2DM and obese non-diabetic patients ranged from -1.55 kg to -2.23 kg, compared with -0.81 kg in the placebo group for dose levels between 25 mg to 60 mg. Glucose tolerance and fasting plasma glucose (FPG) were significantly improved in subjects with T2DM.

In the phase 2 trial, XNAA administration of OPK-88003 at 10, 15, 30 and 50 mg doses QW for 6 months in subjects with T2DM resulted in dose-dependent effects on blood glucose and body weight reduction. Statistically significant reduction in mean HbA1c (up to 1.43%) was observed for all doses at 12 and 24 weeks. OPK-88003 significantly decreased HbA1c levels versus placebo and was non-inferior to 2 mg exenatide ER at the 30 mg and 50 mg doses ($p=0.994$ and 0.628, respectively). Greater reductions in FBG with OPK-88003 resulted in similar 7-point self-monitored blood glucose (SMBG) profile values compared to treatment with exenatide ER and lower values compared to placebo.

OPK-88003 also produced a dose-dependent weight loss of up to 3.3 kg by week 24. In comparison to placebo and exenatide ER, OPK-88003 50 mg resulted in statistically significant percent change in body weight from baseline at 12 ($p<0.001$ and $p=0.011$, respectively) and 24 ($p= 0.007$ and $p=0.05$, respectively) weeks. At least twice as many OPK-88003-50 mg (35.5%) subjects lost ≥5% of their body weight compared to placebo (11.8%) ($p=0.004$) and exenatide ER (18.3%) ($p=0.025$) by week 24.

Safety findings were consistent with what would be expected from a GLP-1 agonist effect. The most frequent OPK-88003 dose-related adverse events (AEs) have been GI symptoms, including nausea, vomiting, diarrhea, and decreased appetite. Most of the events were single episodes, mild in severity, transient and self-limited. These events occurred most commonly after the first dose and the incidence then declined to near control levels by the fourth weekly dose. Rates of nausea, vomiting and diarrhea were dose-dependent with moderate tolerability at the highest dose of 50 mg in study XNAA.

Some injection site reactions (rash/redness) with OPK-88003 treatment were observed although the incidence was lower than for exenatide ER and the severity of the reactions

tended to be mild or moderate with very few severe reactions reported in 3.21% of subjects (9/280). In addition, in almost all cases the reactions decreased in severity over time. Incidence of anti-drug antibodies (ADA) development was <4%.

There was no evidence of a hypoglycemia-promoting effect of OPK-88003. Potential pancreatic AEs occurred in 10 subjects with 11 events requiring adjudication. Of these, only one event in the OPK-88003 treatment group was adjudicated to be an actual pancreatic event.

Mean heart rate (HR) increased with OPK-88003 by approximately 5 beats per minute (bpm) in study XNAA compared to placebo, although the differences were not statistically significant.

Additional safety parameters including SAEs, other treatment emergent adverse events (TEAEs), other laboratory measurements and other vital signs were not different between treatment groups or were modified in a favorable direction by OPK-88003 treatment (notably systolic and diastolic blood pressure).

In study XNAB, an increase in supine and standing pulse rate was observed 48 and 72 hours following single doses, that returned to predose values at 7 days post dose. Mean supine and standing pulse rate increased and then generally remained high up to at least 7 days after the final dose following repeated doses and returned to predose values by follow-up. The increases in pulse rate for individual subjects were not associated with AEs. There was no indication of prolongation of QTc interval. No additional novel safety findings, other than the expected increase in rate of nausea and vomiting were observed at surpatherapeutic doses of OPK-88003.

1.4 Rationale for the Study

Equivalent effects on HbA1c and greater weight loss effects were observed for OPK-88003 compared to exenatide ER in the phase 2 trial XNAA. These findings are consistent with the hypothesis that the additional glucagon activity associated with OPK-88003 provides equivalent glycemic control and superior weight loss compared to GLP-1 modulation alone. Since it has been demonstrated that additional weight loss can be obtained by increasing the dose of GLP-1 agonists (Davies et al 2015), it seems likely that increasing the dose of OPK-88003 will demonstrate additional weight loss benefits.

XNAA investigated the dose-response relationship of OPK-88003 versus placebo and positive control exenatide ER, and established that QW injections over 24 weeks could reduce HbA1c by up to 1.43% and weight by up to 3.3 kg. The severity of the OPK-88003 AE profile observed so far, including the 50 mg QW dose tested in the phase 2 trial, does not outweigh the anticipated favorable benefits on glucose and body weight. Thus, the benefit-risk balance of OPK-88003 supports additional clinical testing of OPK-88003 at doses higher than 50 mg QW.

There was also a dose-dependent increase in GI side effects with higher OPK-88003 doses in prior human studies, however, these effects were transient in nature. In efforts to optimize OPK-88003 for glucose control and body weight reduction, it is likely that dose escalation could be key for reducing GI side effects through gradual up-titration of doses to target dose levels. Other GLP-1 agonists, such as liraglutide QD (once daily) and semaglutide QW, show that when slow dose escalation is implemented, higher doses are achieved and the rates of patients reporting GI disorders can be significantly reduced. In the multiple ascending dose portion of the phase 1 trial in diabetics DPO-101, GI tolerability of OPK-88003 was improved with the use of a titration regimen for 60 mg QW. Thus, it is reasonable to anticipate that a slower dose-escalation regimen will exhibit improved tolerability to nausea and vomiting at dose levels higher than the 50 mg dose administered in the previous phase 2 trial (XNAA). As such, for this trial, a slow dose-titration schedule over 8 weeks will be employed to help mitigate the gastrointestinal AEs.

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1.4.1 Rationale for Dose Selection

Study DPO-203 will include OPK-88003 target dose of 70 mg administered weekly. Based on data from subjects with T2DM in study XNAA, the 70 mg QW dose is anticipated to produce maximal reduction in fasting glucose and HbA1c and yield a greater weight loss than the 50 mg QW dose from the dose-range finding phase 2 trial.

The 70 mg QW dose level will be administered using a fixed dose escalation schedule over 8 weeks. Plasma levels of OPK-88003 reach steady state over 5 weeks with the accumulation ratio for C_{max} and area under the curve (AUC) up to 2.6-fold. Thus, it is reasonable to apply slow dose titration with dose escalation every 4 weeks. For the first 4 weeks of dose escalation subjects will receive 20 mg followed by 4 weeks of 40 mg administered QW. Safety and tolerability from the previous phase 2 trial support evaluation of the dose levels planned for the 8-week dose escalation period.

A population PK model with a first order absorption and first order elimination, along with inter-individual variability for all PK parameters was used to simulate the proposed 70 mg QW dose. This dose is 33% higher (for C_{max} and AUC) when compared to the 50 mg dose that had acceptable safety and tolerability over 24 weeks. Simulated PK exposures derived from XNAA modeling in conjunction with the phase 1 XNAB trial with supratherapeutic exposures and nonclinical safety margins support a multiple dose of 70 mg, administered QW, in the targeted population.

OPK-88003 at the target level of 70 mg QW dose at steady state following dose titration (week 30) is predicted to have mean C_{max} value of 3755 ng/mL and AUC value of 560

µg•h/mL based on population PK modeling of the proposed titrated dosing regimen (20 mg/40 mg/70 mg QW). In the clinical pharmacology trial XNAB multiple SC doses of 40 mg administered daily for 7 days resulted in supratherapeutic exposures. The geometric mean C_{max} of OPK-88003 after 7 days of dosing was 11700 ng/mL with the corresponding AUC of 1789 µg•h/mL. The exposures from study XNAB were three-fold higher than the modelled exposures with currently proposed titrated dosing regimen, for both C_{max} and AUC. Supratherapeutic exposures in XNAB study persisted for approximately three weeks after the last dose due to the long terminal half-life of OPK-88003. The once-a-day dosing regimen resulted in high rates of moderately severe nausea and vomiting that required concomitant medication, however most events resolved within a week after the last dose. The intensity and/or duration of these events is expected to be reduced by a slow dose titration in the current study. In previous OPK-88003 trials, there were no safety concerns reported based on clinical laboratory evaluations and ECGs and no severe or serious AEs (SAEs) at supratherapeutic exposures.

The safety data from the human studies confirm dose-related, monitorable AEs related to GI tolerability. Most of the events were single episodes, mild in severity, transient, and self-limited. These events occurred most commonly after the first dose and the incidence then declined to near control levels by the fourth dose, consistent with a GLP-1R agonist effect.

Furthermore, studies of molecules with similar mechanism demonstrate improved tolerability with slow dose titration and longer duration of dosing and have not demonstrated new, unexpected toxicities with longer duration of dosing.

The toxicology program for OPK-88003 provided continuous plasma exposure in rats and monkeys with a BIW dosing schedule and supports the proposed dosing regimen. The safety margins for the 70 mg dose based on the exposures (AUC) derived from population PK modeling in humans and the NOAELs for organ toxicity as determined in rats (3 mg/kg) and monkeys (1.5 mg/kg) after chronic dosing correspond to exposure multiples of 0.7-fold and 10-fold, respectively.

Taking into consideration clinical efficacy and tolerability, QW doses of 70 mg are expected to be tolerated with slow dose-escalation and produce glycemic control and weight loss benefits. The data from this trial together with the data from the previous phase 2 trial will enable robust benefit-risk characterizations in T2DM and will form the basis to assess the effect of dose escalation on OPK-88003 efficacy, safety and tolerability, and support the selection of dose(s) and dose regimen to be included in phase 3 trials.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is: To evaluate the effect of dose escalation of QW SC OPK-88003 vs placebo injections on HbA1c absolute change from baseline to after 30 weeks treatment in subjects with T2DM inadequately controlled with diet and exercise alone, or treated with a stable dose of metformin.

2.2 Secondary Objectives

The secondary objectives of this study are to determine the effect of OPK-88003 vs placebo on:

1. Mean percent (%) body weight change from baseline to after 30 weeks treatment
2. Percent (%) of subjects with 5% or greater body weight loss after 30 weeks treatment
3. Change of FPG from baseline to after 30 weeks treatment
4. Number and percent of subjects achieving HbA1c ≤6.5

2.3 Other Objectives

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3. Percent (%) of subjects permanently discontinued from the study due to hyperglycemia
4. Incidence and rate of gastrointestinal (GI) events, major cardiovascular (CV) events, hypoglycemia, injection site reactions, hypersensitivity reactions and pancreatic events
5. To evaluate immunogenicity of OPK-88003

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3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

Study DPO-203 is a randomized, double-blind, dose-escalation, placebo-controlled multicenter phase 2 trial to examine the efficacy and safety of SC OPK-88003 administered

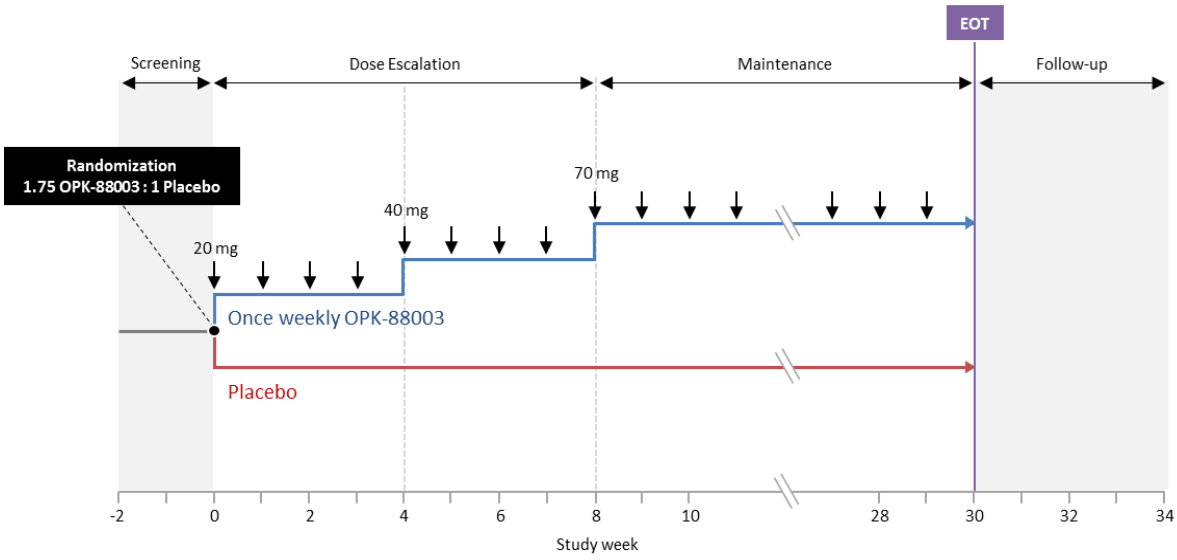
at 70 mg QW compared to placebo in subjects with T2DM who have inadequate glycemic control with diet and exercise alone or on a stable dose of metformin.

This trial will be conducted at up to approximately 30 investigational sites in the US. Approximately 200 subjects are expected to be screened and 110 subjects will be randomized to OPK-88003 and placebo in a 1.75:1 ratio.

After randomization, the subjects will follow a fixed dose escalation that includes a dose escalation over 8 weeks. The target dose of 70 mg QW will be reached after receiving 20 mg for 4 weeks followed by 4 weeks of 40 mg QW. A safety review of the 70 mg QW dose level will be performed by the DSMB, after which the target level may be reduced to 60 mg QW. The study duration for individual subjects will be up to 36 weeks. Blinding will be maintained throughout the study.

The design for study DPO-203 is illustrated in Figure 1.

Figure 1 Study Design for DPO-203



EOT: end of treatment
↓ indicates dosing

Study procedure timing is outlined in the Schedule of Events (Appendix 1). Eligibility of subjects will be based on the results of a screening medical history, physical examination, vital signs and clinical laboratory tests. At visit 2, eligible subjects will be randomized (V2), receive training on study drug preparation and injection technique and conduct of routine SMBG, and receive their first dose of study drug. Subjects will return for 11 study visits, CCI during the 30-week treatment period. A final safety follow-up visit occurs four weeks after the treatment period (V14). Subjects who develop ADA will be asked to return to the clinic approximately four months after the last dose for an additional blood draw.

Throughout the entire study, subjects treated with metformin will remain on the same dose they were receiving at visit 1, unless a temporary increase in dose is needed to treat hyperglycemia (see section 6.11).

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3.2 Rationale for Study Design and Control Group

This phase 2 trial is designed to establish the effect of a dose-escalation regimen on safety, tolerability and efficacy of 70 mg QW OPK-88003 in subjects with T2DM, relative to placebo. The study duration, target population and efficacy endpoints are typical of phase 2 trials and are consistent with FDA guidance[1]. A four-week follow-up after the treatment period will ensure an adequate time to assess reversibility of any clinical or laboratory abnormalities. Subjects who develop ADA will have one additional follow-up assessment approximately four months post last dose.

This clinical study will enroll subjects with inadequate glycemic control based on HbA1c values ranging from 7.0% to 10.5%, inclusive. Similar ranges of screening HbA1c have been used in numerous studies of T2DM treatments.

Subjects treated with diet and exercise alone or in combination with stable metformin monotherapy (≥1000 mg/day), will be enrolled. Subjects on a second oral anti-hyperglycemic medication (OAM) may be also be eligible if the second OAM was discontinued 3 months or more prior to visit 1. Stable metformin treatment for at least 3 months is required to minimize baseline glucose drift prior to study entry.

3.3 Study Duration and Dates

The study duration for individual subjects will be up to 36 weeks and will consist of four phases: screening (up to 2 weeks prior to first dose), dose escalation (8 weeks), target dose/maintenance (22 weeks) and follow-up (4 weeks).

The trial is expected to commence recruitment during Q1 2018. Recruitment for this trial is expected to take approximately 5 months.

4 STUDY POPULATION

Overweight and obese T2DM subjects treated with diet and exercise alone or on a stable dose of metformin.

[1] Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. Draft guidance February 2008

4.1 Inclusion Criteria

Subjects are eligible to be included in the study only if they meet all of the following criteria at the indicated visit:

1. Have T2DM for at least 6 months before entering the trial based on the disease diagnostic criteria (AmDA 2018), controlled with diet and exercise alone or with a stable dose of metformin (≥1000 mg/day) for at least 3 months prior to visit 1.

2. Males or females 18 to 80 years of age inclusive.

3. Females must be not of childbearing potential due to surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation) or menopause. Women with an intact uterus are deemed postmenopausal if they are ≥45 years old, and

   - have not taken hormones or oral contraceptives within the last year and had cessation of menses for at least 1 year

     OR
   - have had at least 6 months of amenorrhea with follicle-stimulating hormone (FSH) levels consistent with a postmenopausal state (FSH ≥40 mIU/mL).

4. Have an HbA1c value at screening of ≥7.0% and ≤10.5%.

5. Have a Body Mass Index (BMI) ≥27 and ≤45 kg/m^2 at screening.

6. In the investigator's opinion, are capable and willing to:

   - administer weekly study medication injection (with assistance if necessary)
   - complete study diaries
   - follow lifestyle counseling advice
   - perform SMBG

7. Are willing to be available for the duration of the trial, comply with the required study procedures and visits, and abide by the clinical research site policy.

8. Have given written informed consent.

4.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following criteria at visit 1, unless otherwise specified:

1. Participation in any other interventional trial within 30 days.

2. Have Type 1 diabetes mellitus.

3. Previous exposure or known allergies to OPK-88003 or its components.

4. Previous treatment with incretin mimetic drugs (GLP-1 agonists), excluding DPP-IV inhibitors.

5. Have used insulin for diabetic control for more than 6 consecutive days within the prior year.

6. Use of thiazolidinedione, or any other drugs, including investigational drugs, for treatment of hyperglycemia (except metformin), within the prior 3 months.

7. Use of systemic (including nasal and inhaled) glucocorticoids within the prior month, or subjects likely to require systemic doses of glucocorticoids during study participation are also excluded. Topical applications are permitted.

8. Evidence of hepatitis B and/or positive hepatitis B surface antigen. Evidence of hepatitis C.

9. Evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies.

10. Have cardiac disease with functional status that is NYHA Class III, or IV or in the last 6 months have had any of the following: myocardial infarction (MI), unstable angina, acute coronary syndrome, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI; diagnostic angiograms are permitted), transient ischemic attack (TIA), cerebrovascular accident (for example, stroke) or decompensated congestive heart failure.

11. Have hypertension (mean systolic blood pressure >160 mm Hg or mean diastolic blood pressure >100 mm Hg), malignant hypertension, renal artery stenosis, and/or evidence of labile blood pressure including symptomatic postural hypotension at visit 1. If on treatment for hypertension, doses of antihypertensive medications must be stable for the prior 30 days.

12. Have obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or an alanine transaminase (ALT) or aspartate aminotransferase (AST) levels >2.5 x upper limit of normal (ULN) or serum total bilirubin >2.0 mg/dL.

13. Evidence of hypothyroidism or hyperthyroidism based on clinical evaluation and/or an abnormal thyroid-stimulating hormone (TSH). Subjects on a stable dose of thyroid replacement therapy for at least the prior two months may be eligible if they meet the other criteria.

14. Evidence of obesity induced by other endocrinologic disorders (eg. Cushing Syndrome).

15. Clinically significant peripheral vascular disease in the opinion of the investigator.

16. Active proliferative diabetic retinopathy.

17. Known significant autonomic neuropathy as evidenced by urinary retention, resting tachycardia, orthostatic hypotension or diabetic diarrhea.

18. Have an active or untreated malignancy or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix or in situ prostate cancer) for less than five years. Have a personal or family history of thyroid medullary C-cell hyperplasia, focal hyperplasia, carcinoma (including sporadic, familial or part of Multiple Endocrine Neoplasia syndrome type 2A or 2B), or a serum calcitonin ≥20 pg/mL.

19. Impaired renal function (eGFR <60 mL/min/1.73 m^2).

20. Triglycerides >600 mg/dL (6.84 mmol/L) at screening. If subject is on lipid lowering therapies doses must be stable for 30 days prior to screening.

21. Any subject having experienced a keto-acidotic episode requiring hospitalization in the prior 6 months.

22. Have an ECG considered by the investigator indicative of active cardiac disease or with abnormalities that may interfere with the interpretation of changes in ECG intervals. A QTcB interval greater than 450 msec in men and greater than 470 msec in women at visit 1 or visit 2 is specifically excluded.

23. Personal or family history of long QT syndrome, family history of sudden death in a first-degree relative (parents, sibling, or children) before age 40 or personal history of unexplained syncope within the last year. Use of prescription or over-the-counter medications known to prolong the QT or QTc interval.

24. History or presence of CV, respiratory, hepatic, renal, GI, endocrine (other than diabetes), hematological, or neurological disorders capable of significantly altering the absorption, or metabolism or elimination of drugs or of constituting a risk when taking the study medication or interfering with the interpretation of data.

25. Diagnosis of gastroparesis or bariatric surgery prior to screening, or planned bariatric surgery for the trial duration period.

26. Have had more than one episode of severe hypoglycemia within 6 months prior to visit 1, as defined by hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery, or has a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms. Any subject that the investigator feels will not be able to communicate an understanding of hypoglycemic symptoms and the appropriate treatment of hypoglycemia should also be excluded.

27. Have had two or more emergency room visits or hospitalizations due to poor glucose control within the prior 6 months.

28. Have taken prescription or over-the-counter medications to promote weight loss within the prior 3 months.

29. Have had a significant change in weight, defined as a gain or loss of more than 5% in the prior 3 months.

30. Are currently taking CNS stimulants (eg, Ritalin-SR®) with the exception of caffeinated beverages.

31. Have had a blood transfusion or severe blood loss within the prior 3 months or have known hemoglobinopathy, hemolytic anemia, sickle cell anemia, or have a hemoglobin value <11 g/dL (males) or <10 g/dL (females), or any other condition known to interfere with HbA1c methodology.

32. Blood donation of 450 mL or more in the prior 3 months or any blood donation within the prior month.

33. Have a history of alcohol or drug dependence or abuse within the last 2 years and/or have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females) [1 unit = 12 oz. or 360 mL of beer; 5 oz. or 150 mL of wine; 1.5 oz. or 45 mL of distilled spirits].

34. Have a history of atopy (severe or multiple allergic manifestations) or clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, anaphylaxis, angioedema, or exfoliative dermatitis).

35. Have a history of acute or chronic pancreatitis or confirmed elevation in serum lipase/amylase (>2 x ULN).

36. Have any other condition or psychiatric disorder that, in the opinion of the investigator, may preclude the subject from following and completing the protocol related procedures.

37. Are unsuitable for inclusion in the study in the opinion of the investigator or sponsor.

38. Are unable to undergo MRI for any reason[redacted]

5 DISCONTINUATIONS

5.1 Discontinuation of Study Drug

5.1.1 Temporary Discontinuation of Study Drug

After randomization, the investigator may decide to temporarily discontinue study drug, for example, due to an AE or a clinically significant laboratory value. Every effort should be made by the investigator to maintain subjects in the study and to restart study drug promptly as soon as it is safe to do so. The dates of study drug discontinuation and re-start will be documented. If a subject misses more than four doses of study drug throughout the course of the study or two consecutive doses during the dose escalation phase, they should be discontinued from the study (see section 5.2).

Subject noncompliance with study drug regimen should not be recorded as temporary discontinuation of study drug (see section 7.11).

5.1.2 Permanent Discontinuation of Study Drug

Permanent discontinuation of the study drug during the dose escalation and maintenance phase should be considered by the investigator, after consultation with the sponsor designated medical monitor, when the subject meets the following conditions:

- Abnormal liver tests:
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 x ULN
  - ALT or AST >5 x ULN for more than 2 weeks
  - ALT or AST >3 x ULN and (total bilirubin level >2 x ULN or INR >1.5)
  - ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5% compared to baseline)
- AEs:
  - Confirmed pancreatitis or pancreatic cancer (see section 8.3.5)
  - Estimated glomerular filtration (eGFR) <30 mL/min/1.73 m^2
  - Any severe injection site reaction or two or more moderate injection site reactions occurring a week or more apart (see section 8.3.1)
  - Any study drug related systemic hypersensitivity reaction (see section 8.3.2)
  - Any nonfatal major CV events (see section 8.3.6)

- Any SAE or clinically significant event (CSE) judged to be related to study drug A CSE is defined as a moderate to severe AE, abnormal clinical sign, or clinical laboratory finding that may pose a risk to the wellbeing of the subject. A CSE will be determined by the investigator, and may include findings that do not fulfil the criteria for SAEs (Appendix 2).

- Any other TEAE, SAE or clinical significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken.

- Serum calcitonin with an absolute value of ≥50 pg/mL on repeat testing

- The subject intentionally or repeatedly takes more than the prescribed dose of study medication.

Subjects who are permanently discontinued from study drug will be discontinued from the study (see section 5.2).

5.2 Discontinuation of Subjects

If the investigator site identifies a subject who did not meet eligibility criteria but was inadvertently randomized, the sponsor-designated medical monitor must be contacted.

If the sponsor or designee identifies a subject who did not meet enrollment criteria and who was inadvertently randomized, the investigator site will be notified. A discussion must occur between the sponsor-designated medical monitor and the investigator to determine whether the subject may continue in the study. Inadvertently randomized subjects may be maintained in the study when the sponsor agrees with the investigator that it is medically appropriate for that subject. The investigator must obtain documented approval from the sponsor to allow the inadvertently enrolled subject to continue in the study.

A subject will be discontinued from the study in the following circumstances:

- The subject requests to be withdrawn from the study.

- The subject is permanently discontinued from study drug (see section 5.1.2).

- The subject misses more than four doses of study drug over the course of the study, or misses two consecutive doses of study drug during the dose escalation phase.

- Enrollment in any other interventional clinical trial.

- The sponsor stops the study or stops the subject's participation in the trial for medical, safety, regulatory or other reasons consistent with applicable laws, regulations and good clinical practice (GCP).

- The investigator decides it is in the best interests of the subject not to continue in the study.
- The subject and/or blinded study staff become unblinded to the subject's treatment assignment.
- Any medication for weight loss is given for more than one week.
- If the subject, for any reason requires treatment for greater than one week with another therapeutic agent that has been approved for treatment of diabetes. A change in dose of metformin is not allowed, unless a temporary increase in dose is needed to treat hyperglycemia (see section 6.11). However, a change to an equivalent dose strength of metformin from immediate-release to extended-release (or vice versa) formulations is allowed.

Subjects discontinued from the study will be requested to complete an early termination (ET) visit as soon as possible (section 9.5). Subjects will be requested to complete a follow-up visit (see section 9.5) four weeks after their final dose.

5.3 Discontinuation of Study Sites

Study site participation may be discontinued if the sponsor or its designee, the investigator, or the institutional review board (IRB) of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

5.4 Discontinuation of the Study

The study will be discontinued if the sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

6 STUDY TREATMENT(S)

6.1 Randomization

Subjects who meet all eligibility criteria will be randomized to treatment at visit 2 (day 1). via the Interactive Response Technology system (IRT). Randomization will be stratified using the following variables: screening HbA1c (<8.5%, ≥8.5%) and baseline BMI (<30, ≥30 kg/m^2). The randomization to the treatment arms will be 1.75:1 for the active and placebo groups, respectively. Following randomization, study drug will be dispensed in a double-blinded manner.

6.2 Description of Treatment(s)

OPK-88003 and matching placebo are provided in single-use 2 mL glass vials with blue flip-off lid, an aluminum seal and a rubber stopper (septum).

6.2.1 *OPK-88003 Injection*

Dosage form: solution for SC injection

Dose strength: 70 mg/vial (extractable volume 1 mL)

Description: clear, colorless liquid

Nonactive components: CCI

Storage conditions:

6.2.2 *Placebo Injection*

Dosage form: solution for SC injection

Dose strength: 0 mg/vial (extractable volume 1 mL)

Description: clear, colorless liquid

Nonactive components: CCI

Storage conditions:

6.3 Packaging and Labeling

Vials of OPK-88003 and placebo will be supplied in cartons, each containing four vials, each for single use. Vials and cartons will be labeled according to regulatory requirements. The labels will include protocol number, sponsor name, investigational statement, storage conditions and instructions for use.

6.4 Storage and Accountability

While at the study site, vials will be stored frozen at -20 ± 5°C in the supplied packaging until assigned to a subject by IRT, and thereafter refrigerated (2-8°C) with access granted to authorized personnel only.

All sites must ensure that study drug has been kept under required conditions prior to dispensing. A temperature log recording the daily study drug storage conditions will be

maintained at each site. If temperature excursions occur during shipping or storage at site, study drug should not be dispensed, and the investigator or designee should contact the sponsor's designee as soon as possible for further instruction.

Once study drug is dispensed the subject will be instructed to transport the vials in the provided cool container and store refrigerated at home. Subjects will be instructed to return all used and unused vials in cool bags to the study site for study drug accountability.

The investigator or their designee(s) will maintain study drug accountability records throughout the course of the study from receipt of study drug until final reconciliation and return to the sponsor. Specifically, the investigator or their designee will confirm that all study drugs and supplies are received intact and in the correct amounts per the shipping forms. A study drug accountability and dispensing log will be maintained on site to record the study drug dispensed to subjects, including dates, quantity received and returned vial numbers. The investigator should ensure that the study drug is used only in accordance with the protocol.

The sponsor's designee will routinely verify the inventory of study drug supplies throughout the course of the study. All used and unused cartons/vials of study drug are to be retained at the site until the sponsor's designee has performed a complete verification.

Any discrepancies identified will be indicated with a specific explanation of each discrepancy. The investigator (or designee) must return all used and unused study drug in accordance with the sponsor's instructions, and a copy of the clinical supplies return documentation will be returned to the sponsor or designee. Drug accountability records, clinical drug supply receipts, and returns must be maintained by the investigator.

6.5 Treatments Administered

This trial will evaluate 20 mg and 40 mg dose escalation and 70 mg target dose of OPK-88003 QW over a 30-week treatment period. Treatment allocation will be assigned by the IRT. The group randomized to OPK-88003 will initially receive 20 mg QW for four weeks, followed by 40 mg QW for four weeks. Once eight weeks of dose escalation are complete, subjects will receive a target dose of 70 mg QW OPK-88003 for 22 weeks. The control group will receive matched placebo SC injections QW for 30 weeks.

Site staff will train the subject on correct storage, preparation and administration of study drug, aiming for subject self-administration. The subject will administer the study drug at the study site visits as per schedule of events under supervision of an unblinded site personnel (eg, research nurse) to ensure injection technique is satisfactory. The subject will administer doses QW at home, with assistance if necessary.

Prior to injection, if the vial is frozen it should be allowed to thaw/equilibrate for a minimum of 1 hour and a maximum of 4 hours at room temperature. If the vial is refrigerated it should be allowed to equilibrate for a minimum of 30 minutes and a maximum of 4 hours at room temperature.

Detailed study drug handling and dosing instructions will be provided to support subject dosing.

All injections will be administered SC into the abdominal wall (or other sites if approved by the investigator). Instructions for rotation of injection sites and assessment of potential injection site reactions will also be provided.

The investigator or their designees are responsible for the following:

- explaining the correct use of the study drug to the subject
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensing and collection, and the return of all used and unused medication to the sponsor or designee at the end of the study

Subjects will be instructed to contact the investigator as soon as possible if they have any questions or issues concerning the injection of study drug or if they have any other study-related concerns so the issue/question can be assessed in a timely manner to ensure subject's safety.

All subjects should be observed for allergic reaction following study drug administration for at least 15 minutes at visits 2, 3, 4 and 5.

6.6 Materials and Supplies

6.6.1 Study Drug Supplies

Study drug cartons containing OPK-88003 or placebo for SC injection will be supplied to study sites. Ancillary supplies including needles and syringes will be provided separately. Study drug vials must always be stored in a secure location with access limited to designated study staff members.

6.6.2 Laboratory Supplies

The sponsor or assigned designee will supply vacutainers, blood collection tubes, labels, boxes with labels for storage of serum and plasma samples and all necessary shipping supplies/containers, as specified in the laboratory manual. The investigator will supply centrifuge equipment. The investigator will ensure that all biohazard wastes are disposed of in accordance with investigator, site standard operating procedures (SOPs) and local regulations.

6.7 Selection and Timing of Dose for Each Subject

There are no restrictions on the time of day each dose is administered, but it is advisable to administer the SC injections on the same day and time of the week. If a subject misses a dose on the scheduled day, then they should administer the dose as soon as possible and then

resume their regular schedule. Study drug should not be administered within four days of the previous injection.

6.8 Blinding

OPK-88003 and placebo injections are identical in appearance in order to maintain a double-blind status. An unblinded site staff member will be available to support subject dosing as needed. Study drug will be managed using IRT. Each user will have a unique username and passcode to access the system. In case of an emergency, when knowledge of the treatment assignment for the subject is essential for the clinical management or welfare of the subject, the investigator may unblind the subject's treatment assignment. Prior to unblinding, the investigator should make every effort to contact the sponsor or designee before proceeding with the unblinding process, if possible. If a subject's treatment assignment is unblinded without sponsor or designee's prior knowledge, the sponsor must be notified immediately.

Each site will be provided with a sealed envelope containing a six-digit code that can be entered into the IRT to unblind a subject's treatment assignment. In order to preserve the double-blind of the study, a minimal number of sponsor personnel will have access to the randomization scheme and treatment assignments before the study is complete.

6.9 Concomitant Therapy

Treatment with medications that are excluded in the entry criteria is not permitted.

The only concomitant anti-hyperglycemic medication permitted during this trial is metformin. Subjects treated with metformin upon entering this trial should remain on the same dose throughout the course of the trial, unless hyperglycemic criteria are met (see section 6.11). If a subject switches from the immediate-release formulation of metformin to the sustained-release formulation, the change will be on a milligram per milligram basis.

Doses of anti-hypertensive and lipid-lowering agents should remain stable during the study unless necessary to protect subject safety.

Doses of other prescription medications (eg, thyroxine, estrogen or progesterone replacement, selective estrogen receptor modulators) for treatment of concurrent medical conditions should remain stable during the study whenever possible.

Anti-emetic drugs that do not increase QTc (eg, cyclizine, meclizine) may be used to treat nausea and vomiting, but they should not be used prophylactically.

Non-steroidal anti-inflammatory medications (including aspirin and acetaminophen), cough suppressants, antihistamines, vitamin/mineral supplements, antibiotics and topical ointments may be used and are not restricted by the stable dosing requirements listed above.

If the need for additional concomitant medication arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with the sponsor or their

designated medical monitor. Any additional medication used during the course of the study must be documented.

6.10 Restrictions

Meals – Subjects shall fast for at least 8 hours overnight prior to each visit where fasting labs are drawn or CCI measurements are taken.

Alcohol – Alcohol will not be permitted at least 8 hours prior to the study visit.

Blood donation – Study subjects should be instructed not to donate blood or blood products during the study and for 8 weeks following study completion.

Contraception – Male subjects or their female partners of child-bearing potential must use reliable contraception during intercourse throughout the treatment period and for three months after the last dose of study drug (as the risk of OPK-88003 to the unborn fetus is unknown). Females must not be of childbearing potential due to surgical sterilization (hysterectomy, bilateral oophorectomy or tubal ligation) or menopause.

Acceptable contraception includes male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate), oral, injected or implanted hormonal methods of contraception, intrauterine device or implant, and barrier methods of contraception (condom or occlusive cap, diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.

6.11 Evaluation and Treatment of Hyperglycemia

Routine fasting (at least 8 hours) SMBGs and central laboratory FPG values will be used to determine the requirement for additional medication. If any fasting SMBG value exceeds the specified limit (Table 1), the subject will be instructed to contact the investigational site and asked to perform fasting SMBG on three consecutive days (see section 7.5).

If fasting SMBG values exceed the specified limit for three consecutive days, an unscheduled visit should be performed to assess FPG by the central laboratory.

Table 1 Threshold Glucose Levels

Study Period	Threshold value
Baseline to week 8	>270 mg/dL (15 mmol/L)
Week 8 to week 12	>240 mg/dL (13.3 mmol/L)
Week 12 to week 30	>200 mg/dL (11.1 mmol/L)

Values must be recorded on three consecutive days

If the SMBG values are confirmed by central laboratory FPG measurement, then an additional therapeutic intervention should be considered at the discretion of the investigator

for subjects who are fully compliant with the assigned therapeutic regimen, in the absence of any acute condition that raises blood glucose. Any subject who requires additional glucose-lowering therapy for more than one week should be discontinued (see section 5.2).

7 STUDY PROCEDURES

7.1 Medical History and Physical Examination

Physical examination will be performed by qualified personnel. A detailed medical history will be obtained at screening (V1).

7.2 Height and Weight, CCI [redacted]

Height is measured once, at screening.

Body weight CCI [redacted] will be measured on fasting (minimum 8 hours) subjects. Duplicate measurements of weight will be performed using digital scales and following emptying of any bowel/bladder contents. Subjects will change into a light hospital gown for weight measurements CCI [redacted]. Scales will be calibrated at least monthly using standard weights, and records of calibration will be kept in the study binder. CCI [redacted] Detailed instructions will be provided in a study manual.

7.3 Electrocardiography (ECG)

ECG and vital sign measurements will precede blood draws and study drug administration when scheduled at the same time.

ECGs will be obtained in a quiet environment after remaining in supine rest for at least 5 minutes. Subjects will remain supine but awake during ECG collection. Triplicate ECGs (when required) will be obtained within a 5-minute window and at approximately 1-2 minute intervals. Collection of more ECGs (more replicates) than expected at a particular timepoint is allowed when needed to ensure high quality records.

ECGs may be obtained at additional times when deemed clinically necessary.

ECGs will be digitally recorded and printed on paper. The printed paper ECG will be used for "real time" ECG assessment by the investigator (or designee) who will be responsible for the overall interpretation, determination of the clinical significance and subject eligibility based on the ECG findings. ECG interpretation categories are: Normal ECG, Abnormal ECG – not clinically significant, Abnormal ECG – clinically significant.

The printed ECGs will be retained in the subject's records at the site. All digital ECG records will also be submitted to the cardiovascular core lab, that will perform the digital ECG analysis and interpretation in this study using standard methodology. If the central

reviewer identifies an abnormality, per the study alert criteria, the investigator will be notified to review the ECG and report any AEs as necessary.

The following variables will be reported: HR, RR, PR, QRS, QT, QTcB, and QTcF intervals.

Any treatment emergent clinically significant ECG finding should be reported as an AE in the eCRF.

7.4 Vital Signs (Blood Pressure and Pulse Rate)

Vital signs will include only supine blood pressure and pulse rate (after a minimum of 5 minutes rest), and will be assessed following 12-lead ECG (if scheduled) and prior to any blood draws or study drug administration. The values for blood pressure and pulse rat at each time point will be the average of at least three measurements.

7.5 Fasting Self-Monitored Blood Glucose (SMBG) Levels

Subjects will be provided and trained on use of a glucometer, necessary glucose testing supplies and study diaries at baseline visit (V2), and will be instructed on how to recognize symptoms of hypo- and hyperglycemia. Subjects will be asked to demonstrate competent use of the glucometer at or before their first dosing visit. Results from SMBG will be recorded in the subject diary (section 7.7.2).

All subjects will be instructed to perform fasting SMBG at least three times a week using a portable glucometer. Subjects will record SMBG readings in their diaries. It will be the investigator's responsibility to remind subjects during study visits to perform their routine fasting SMBGs.

Subjects will be requested to perform additional SMBG measurements at any time that they develop symptoms suggestive of hypoglycemia. If subjects experience hypoglycemic symptoms or glucose value ≤70 mg/dL (≤3.9 mmol/L) they should record the SMBG value and symptoms in their diary and take SMBG measurements every 15 minutes until either the symptoms subside or the blood glucose value reaches >70 mg/dL(>3.9 mmol/L).

Subjects who have an out of range SMBG reading (hyperglycemia, see Table 1) will perform fasting SMBG prior to breakfast on three consecutive days and report the values to the investigator via email or phone if possible on the day each measurement was taken. The investigator will review the results in a timely manner and if possible on the same day as the results were received from the subject.

Subjects who develop/have persistent uncontrolled hyperglycemia or hypoglycemia should contact the clinic. Subjects will be requested to visit the clinic for further testing and appropriate medical management at the investigator's discretion.

7.6 Lifestyle Counseling

At visit 2, subjects will have a lifestyle counseling session (either in a group or individually) with a qualified diabetic educator in accordance with local standards. Subject lifestyle counseling sessions will focus on diet, physical activity and behavioral strategies to achieve a 500-700 kcal/day energy deficit (AmDA 2018 4, AmDA 2018 7). The sessions will occur approximately every four weeks during the dosing period.

The goals of the counseling session are:

- To promote and support healthful eating patterns, emphasizing a variety of nutrient-dense foods in appropriate portion sizes, to improve overall health
- To address individual nutritional needs based on personal and cultural preferences, health literacy and numeracy, access to healthful foods, willingness and ability to make behavioral changes, and barriers to change
- To maintain the pleasure of eating by providing non-judgmental messages about food choices
- To provide an individual with diabetes the practical tools for developing healthy eating patterns rather than focusing on individual macronutrients, micronutrients, or single foods.

Subjects will be encouraged to increase their physical activity. Activities should progress in intensity, frequency and/or duration to at least 150 minutes per week of moderate-intensity exercise. The subject's average daily level of physical activity will be reviewed as part of the lifestyle counseling.

7.7 Diary Completion

Subjects will complete two separate diaries during study participation. The diaries will be dispensed at visit 2 following randomization, and instructions on diary completion will be provided.

7.7.1 Lifestyle Diary

Subjects should complete a 3-day food intake diary prior to visits 4, 5, 9, 10, 11, 12 and 13, when lifestyle counseling will be provided (see section 7.6). Subjects will also document how much physical activity was performed.

The days recorded in the diary should be in the week prior to the counseling visit and ideally include one weekend day. Information in the lifestyle diaries will be reviewed during the counseling as specified in the schedule of events, and not entered into the EDC.

7.7.2 Subject Diary

Subjects should document date and volume of injection of study drug, results of SMBG, and hypoglycemia and ISRs experienced during the study period.

7.8 Clinical Laboratory Tests

7.8.1 Laboratory Parameters

Clinical laboratory tests to be assessed are indicated in Table 2.

Table 2 List of Laboratory Tests

Hematology:

- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

Urinalysis:

- Glucose
- Urine leukocyte esterase
- Occult blood
- pH
- Protein

Serology:

- Hepatitis B surface antigen
- Hepatitis C antibody

Serum calcitonin
Hemoglobin A1c (HbA1c)
Triglycerides
Glucose (fasting)
Serum pregnancy test (females)
Serum FSH (females)

Serum Chemistry:

- Albumin
- Alkaline phosphatase (ALP)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Blood urea nitrogen (BUN)
- Calcium
- Creatinine for eGFR
- Creatine kinase (CK)
- Potassium
- Sodium
- Total bilirubin
- Direct bilirubin
- Total protein
- Uric acid
- Lipase
- Amylase

CDC Lipid Panel (fasting):

- CDC total cholesterol
- CDC triglycerides
- CDC HDL-C
- CDC LDL-C (calculated)

Immunogenicity

- anti-drug antibody (ADA)
- Neutralization assay

CCI [redacted]

7.8.2 Immunogenicity

Blood samples for immunogenicity testing will be collected to determine ADA production. Immunogenicity will be assessed by a validated assay designed to detect ADA in the study drug provided by a specialized laboratory other than the central laboratory. Antibodies may

be further characterized and/or evaluated for their specificity and ability to neutralize the activity of the OPK-88003 at the discretion of the sponsor.

CCI

[redacted]

7.8.4 Sample Collection, Storage, and Shipping

Collection, processing, storage and shipping procedures will be performed in accordance with the instructions provided by the central laboratory. Detailed instructions will be provided in the laboratory manual. Blood samples will be collected and analyzed for clinical laboratory CCI parameters.

Additional blood draws may be needed for unscheduled visits. Missed samples should be drawn whenever possible. The investigator will provide a temperature monitored space with limited access for the study drug and a -20°C or -70°C freezer space for serum and plasma aliquot storage.

Laboratory samples, including antibody and bioanalytical samples, may be stored according to applicable laws, regulatory requirements or laboratory certification standards.

CCI

[redacted]

7.10 Dispensing Study Drug

Study drug will be dispensed to the subject in a 4-vial carton as per schedule of events.

The investigator will be responsible for the maintenance of records of receipt and disposition of study drug including dates, quantities administered and availability, and subject assignment.

7.11 Treatment Compliance

Treatment compliance will be verified by investigative sites. Subjects will be asked to return all their used and unused cartons with vials to the investigative site for accountability as per schedule of events.

Subjects that miss more than four doses of study drug over the course of the study, or miss two consecutive doses of study drug during the dose escalation phase are considered non-compliant. A subject will also be considered non-compliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of study drug. Subjects that are noncompliant will be discontinued from the study (see section 5.2).

7.12 Concomitant Medication Assessments

Medications ongoing at the time of visit 1 as well as any new medication added during the course of the study will be recorded in the source document and eCRF as concomitant medications.

8 SAFETY EVALUATIONS

Investigators are responsible for monitoring the safety of subjects who have entered this trial and for alerting the sponsor or its designee of any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The investigator remains responsible for following through an appropriate health care option, AEs that are serious, considered related to the study treatment or the trial or that caused the subject to discontinue before completing the trial. The subject should be followed until the event is resolved or deemed to be chronic. Frequency of follow-up evaluation is at the discretion of the investigator.

In addition to records of observations made at specific times, unexpected signs and symptoms and concomitant medications will be recorded in the clinical trial records throughout the study.

8.1 DSMB

A sponsor-appointed medical monitor will oversee subject safety in this study. An independent data and safety monitoring board (DSMB) consisting of one statistician and three clinicians with appropriate expertise will monitor the study at regular intervals, and may make recommendations for changes to the conduct of the trial to reflect safety concerns. Specific responsibilities and activities of the DSMB will be defined in the charter to be ratified at the organizational meeting of the DSMB. The DSMB will also perform an assessment of the tolerability of the 70 mg dose level (see section 8.10.2).

8.2 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

All subjects will be monitored, evaluated and queried for AEs at each visit. Subjects may be asked to self-report AEs verbally during visits and they will be encouraged to self-report AEs in their diaries between visits. All AEs, including SAEs occurring after the subject signs the ICF through the subject's final visit will be reported and monitored. AEs that occur following first administration of study drug are TEAEs. Any clinically significant abnormal laboratory results, physical examination findings, ECGs, and vital signs will be reported as AEs. Unless related to protocol procedures as deemed by the investigator, clinically significant findings reported prior to administration of first dose of study drug are exclusionary. All AEs will be reported to the sponsor via eCRF.

All AE/SAEs will be followed through to resolution or until the investigator assesses the AE/SAEs as resolved, chronic or irreversible. The investigator is not obliged to follow-up with subjects for AEs or SAEs that begin after study completion, however if an SAE is reported to the investigator after a subject has completed the study, and it is 'possibly related' to the study drug, then the investigator will report it to the sponsor.

8.2.1 Severity

The intensity of the AE will be rated by the investigator as mild, moderate or severe using the following criteria:

- Mild: Symptoms causing no or minimal interference with usual social and functional activities
- Moderate: Symptoms causing greater than minimal interference with usual social and functional activities
- Severe: Symptoms causing inability to perform usual social and functional activities

It should be noted that the clinical severity and seriousness of an AE are not synonymous, eg, a severe headache is not classified as serious until it meets the required elements as an SAE.

The maximum severity attained for each AE reported will be recorded in the eCRFs.

8.2.2 Relationship

The investigator decides whether he or she interpret the observed AEs as either related to disease, to the study medication, study procedure or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terminologies are defined:

- **Related**: the temporal sequence of the event relative to administration of the study drug is reasonable, it cannot be explained by the disease or other drugs, dechallenge (if performed) is positive and pharmacologically/pathologically plausible, rechallenge (if performed) is positive, or the event shows a pattern consistent with previous knowledge of the study drug or product class

- **Possibly related**: the temporal sequence of the event relative to administration of the study drug is reasonable, and is unlikely to be attributed to disease or other drugs, dechallenge (if performed) is positive

- **Unlikely related:** the temporal sequence of the event relative to administration of the study drug is reasonable, the event could also be explained by disease or other drugs, dechallenge (if performed) is positive or uncertain, rechallenge (if performed) is negative

- **Not related**: the temporal sequence of the event relative to administration of study drug is not reasonable, disease or other drugs provide plausible explanations, dechallenge (if performed) is negative or ambiguous

All "related", and "possibly related" AEs and SAEs will be defined as related to study drug in this study.

8.3 Adverse Events of Special Interest

The AEs of special interest (AESIs) of varying clinical significance will be used to determine the tolerability of OPK-88003 doses selected for this clinical trial. All AESIs that meet the definition of an SAE (section 8.9) must be reported as an SAE.

8.3.1 Injection Site Reactions

Injection site reactions will be collected. Assessment of severity, duration and relatedness to study drug will be recorded.

8.3.2 Hypersensitivity Reactions

All hypersensitivity reactions will be collected. Study drug should be temporarily discontinued in any individual suspected of having a severe or serious allergic/hypersensitivity reaction to study drug. Study drug may be restarted if, in the opinion of the investigator, the event was not related to study drug and when/if it is safe to do so.

8.3.3 Hypoglycemia

Fasting SMBG and central laboratory FPG values will be reviewed for hypoglycemic episodes as defined in the study manual. All episodes (documented symptomatic, asymptomatic or probable symptomatic hypoglycemia) will be recorded as an AE; those falling within AmDA classification Level 3 (see Table 3) will be recorded as an SAE. For each event, assessment of severity, duration and relatedness to study drug will be recorded.

Table 3 Classification of Hypoglycemia

Hypoglycemia Level	Glycemic Criteria	Description
Level 1	≤70 mg/dL (3.9 mmol/L)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Level 2	<54 mg/dL (3.0 mmol/L)	Sufficiently low to indicate serious, clinically important hypoglycemia
Level 3	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

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Subjects should be asked about symptomatic and asymptomatic hypoglycemia at each visit, and trained on treatment of hypoglycemia.

8.3.4 Nausea, Vomiting and Diarrhea

Nausea, vomiting, and diarrhea events will be collected. For each event, assessment of severity, duration and relatedness to study drug will be recorded.

8.3.5 Acute Pancreatitis

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems. The diagnosis of AP requires two of the following three features:

- Abdominal pain, characteristic of acute pancreatitis (generally located in the epigastrium and radiates to the back in approximately half of the cases; the pain is often associated with nausea and vomiting)
- Serum amylase and/or lipase ≥3 x ULN
- Characteristic findings of AP on computed tomography (CT) scan or magnetic resonance imaging (MRI)

If a subject experiences severe or serious abdominal pain or if acute/chronic pancreatitis is suspected, administration of study drug should be temporarily discontinued. If AP is suspected, appropriate laboratory tests (including levels of amylase and lipase) should be obtained. These laboratory tests may be obtained locally but, if possible, a serum lipase and amylase should also be sent to the central laboratory (for capture of data in the clinical trial database) at the time of presentation. If serum amylase and/or lipase values are confirmed ≥3 x ULN, imaging studies, such as abdominal CT scan with or without contrast, MRI, or abdominal ultrasound, to include pancreas and gallbladder, should be performed. If diagnostic testing does not support the diagnosis of acute or chronic pancreatitis then study drug may be resumed as soon as it is safe to do so in the judgment of the investigator. If diagnostic testing supports the diagnosis of acute or chronic pancreatitis or pancreatic cancer,

the subject must permanently discontinue study drug. A review of the subject's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

8.3.6 Cardiovascular Events

Deaths (CV and non-CV), nonfatal myocardial infarctions (MIs), and nonfatal strokes that occur during the treatment phase or follow-up phase will be reviewed by the sponsor-designated medical monitor. Investigative sites will also be asked to report any cases of transient ischemic attack (TIA) or hospitalization for unstable angina to the sponsor-designated medical monitor, to ensure that all true stroke and MI events are captured. CV event definitions will be based on the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials[2] and the ESC/ACCF/AHA/WHF Expert Consensus Document Third Universal Definition of Myocardial Infarction[3].

8.3.7 Electrocardiography (ECG) Findings

Any treatment emergent clinically significant ECG finding should be reported as an AE in the eCRF.

If a clinically significant increase in the QT/corrected QT (QTc) interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the subject will be assessed by the investigator for symptoms (for example, palpitations, near syncope, syncope) and to determine whether the subject can continue in the trial. The investigator or qualified designee is responsible for determining if any change in subject management is needed and must document his/her review of the ECG printed at the time of evaluation from at least one of the replicate ECGs from each time point.

8.4 Liver Function Monitoring

If a study subject experiences elevated ALT or AST >3 x ULN or elevated total bilirubin >2 x ULN, clinical and laboratory monitoring should be initiated by the investigator (Appendix 3). Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure subject safety and comply with regulatory guidance, the investigator will consult with the sponsor-designated medical monitor regarding collection of specific recommended clinical information and follow-up laboratory tests.

8.5 Serum Creatine Kinase Monitoring

If a study subject experiences CK >5 x ULN that suggests muscle damage, the subject should be evaluated for any muscle-associated symptoms as well as any clinical signs of myalgia,

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[2] Hicks KA, Hung J, Mahaffey KW et al. Draft Definition for CDISC. Available at https://www.cdisc.org/system/files/all/standard/Draft%20Definitions%20for%20CDISC%20August%2020%2C%202014.pdf

[3] Thygesen K, Alpert JS, Jaffe AS et al. Third Universal Definition of Myocardial Infarction. Circulation 2012; 126:2020-2035

generalized weakness, or darkened urine. Additional clinical and laboratory monitoring should be initiated by the investigator, in consultation with the sponsor-designated medical monitor. Laboratory monitoring should include repeat CK testing as well as assessment of coagulation factors (prothrombin time, activated partial thromboplastin time, INR), urine myoglobin, cardiac troponin I, and additional testing as clinically indicated.

8.6 Serum Calcitonin Monitoring

Serum calcitonin ≥20 pg/mL at screening is exclusionary (see section 4.2). The subject will be referred to a thyroid specialist for futher evaluation and will be discontinued from screening.

Any treatment-emergent serum calcitonin value ≥20 pg/mL will be reviewed by the DSMB along with relevant supplementary data (eg, demographics and medical history, concomitant medications, supplemental laboratory tests and relevant AE data). The DSMB will provide recommendations to the investigator for individual subjects, including diagnostic procedures, treatment, and continuation of the study drug according to a pre-specified algorithm:

- Calcitonin >ULN and <20 pg/mL

  The investigator shall evaluate factors potentially leading to calcitonin elevation. Calcitonin sampling shall be performed at intervals indicated in the protocol with no further action unless levels rise to ≥20 pg/mL. If the value is the final one in the trial, the subject shall be referred to a thyroid specialist for further evaluation.

- Calcitonin ≥20 pg/mL and ≤50 pg/mL

  Calcitonin sampling shall be performed at intervals indicated in the protocol with no further action unless levels rise to ≥50 pg/mL. No impact on continuation of trial treatment. If the value is the final one in the trial, the subject shall be referred to a thyroid specialist for further evaluation.

- Calcitonin ≥50 pg/mL

  If calcitonin is confirmed to be ≥50 pg/mL, then the DSMB shall recommend the study investigator remove the subject from study treatment. The subject shall be referred to a thyroid specialist for further evaluation.

8.7 Treatment Discontinuations

If a subject's treatment is discontinued as a result of an AE, study site personnel must clearly report (via eCRF) the circumstances and data leading to discontinuation of treatment.

8.8 Pregnancies

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and drug safety evaluation. Pregnancies and female partner pregnancies will be followed until 6 weeks following delivery to determine the outcome.

8.9 Serious Adverse Events (SAEs)

The collection of SAEs begins after the subject has signed the ICF. SAEs occurring after the subject has received study drug are treatment-emergent SAEs (TESAEs).

An SAE is defined by the investigator or sponsor as any AE resulting in any of the following outcomes:

- death
- life-threatening AE
- in-patient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the trial.

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB or are not listed at the specificity or severity that has been observed.

8.9.1 Reporting Serious Adverse Events

8.9.1.1 Initial Report

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to Medpace Clinical Safety **within 24 hours** of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). All known SAEs that the investigator considers related to study drug *occurring after the 30-day follow-up period* must be reported to the sponsor.

To report the SAE, complete the SAE form electronically in the EDC system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form.

If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety (email address listed below) or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information:

Medpace SAE Reporting Phone Line:
Telephone: +1-800-730-5779, dial 3 **or** +1-513-579-9911, dial 3
Facsimile: +1-866-336-5320 **or** +1-513-570-5196

e-mail: medpace-safetynotification@medpace.com

The investigator is responsible for informing his or her IRB of any SAEs at that site.

Subjects who experience one or more SAEs will receive treatment and follow-up evaluations by the investigator, or they will be referred to another appropriate physician for treatment and follow-up. Withdrawal from the study and all therapeutic measures will be at the discretion of the investigator. The investigator must continue to follow the subject until resolution or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject is deceased.

8.9.1.2 Follow-up Reports

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically within the EDC system and submit any supporting documentation (eg, subject discharge summary or autopsy report) to Medpace Clinical Safety using the contacts listed above for initial reporting.

8.10 Safety Monitoring

8.10.1 Safety Monitoring

A study level safety review will be conducted to monitor and assess safety data collected during the study. Specifically, any signs or trends indicating potential underlying safety issues will be identified. The safety review will be scheduled regularly and reviewed by the sponsor-designated medical monitor. More details will be provided in the safety monitoring plan (SMP) including the type of safety data, frequency of review, and unblinding plan if necessary.

The sponsor-designated medical monitor will routinely review:

- trends in safety data laboratory analytes
- serious and non-serious AEs including AESIs (see section 8.2)
- reported pancreatitis and major CV events

8.10.2 Assessment of Tolerability

The safety and tolerability of the 70 mg QW dose level will be assessed by the DSMB following completion of visit 7 (2 weeks of dosing) by at least 10 subjects randomized to OPK-88003. If five or more of those subjects experience severe vomiting or severe nausea defined as an SAE, then the dose of OPK-88003 will be reduced to 60 mg for all subjects including those receiving 70 mg at the time of safety review. Only members of DSMB will gain access to safety data. Members of the DSMB will not have access to efficacy data for this assessment. Study team and site personnel will remain blinded.

9 STUDY ACTIVITIES

9.1 Screening/Visit 1 (Day -14 to Day -1)

At this visit, the following study activities will be performed:

- Informed consent will be reviewed and the ICF signed prior to any study-related activities are performed
- Inclusion/exclusion criteria will be reviewed
- Medical history (including diabetes and medication history), demographics and health habits (alcohol, tobacco use) will be reviewed
- Physical examination will be performed, fasting weight and height will be measured
- Single 12-lead ECG will be obtained after at least 5 minutes of supine rest
- Vital signs will be assessed (supine blood pressure and pulse rate will be assessed following 12-lead ECG and prior to any blood draws)
- Blood samples will be collected:
    - Serum chemistry
    - Serum calcitonin
    - Hematology
    - Triglycerides

- Fasting glucose
- HbA1c
- Serology
- Serum pregnancy test/FSH (females, at the investigator's discretion)

- Urinalysis

9.2 Re-testing and Re-screening

9.2.1 Re-testing

Individuals that do not meet laboratory eligibility criteria are permitted one re-test of any analyte, except for HbA1c, during the screening period and at the discretion of the investigator. In addition, if in the opinion of the investigator, an ineligible laboratory test result (excluding HbA1c) is due to an error or unexpected circumstance, then that analyte can be re-tested once.

9.2.2 Re-screening

Individuals who do not meet the eligibility criteria for participation in this trial (screen failures) may be re-screened once at the discretion of investigator. A new study subject number should be assigned and all screening procedures (including signing a new informed consent form) should be performed. Re-screening should occur at least 30 days after the initial screening visit date.

9.3 Treatment Period - Dose Escalation (Weeks 0-7)

9.3.1 Visit 2 Baseline (Day 1) 20 mg Dose Level

At this visit, the following study activities will be performed:

- Fasting weight, CCI [redacted]
- 12-lead ECG (triplicate)
- Vital signs (supine blood pressure and pulse rate will be assessed following 12-lead ECG and prior to any blood draws or study drug administration)
- Blood samples:
  - Fasting glucose
  - CCI [redacted]

- HbA1c
- CCI [redacted]
- Immunogenicity (pre-dose)

- CCI [redacted]
- AE assessment
- Concomitant medication review
- Distribute glucometers, test strip and diary
- Lifestyle counseling
- Randomization
- Injection technique training
- SMBG training
- The first dose will occur at the investigational site and subject will be monitored post injection for at least 15 minutes for safety.

9.3.2 Visit 3 (Week 1±2 Days) 20 mg Dose Level

At this visit, the following study activities will be performed:

- Concomitant medication review
- AE assessment
- Subject diary review
- CCI [redacted]
- Distribute test strips as needed
- The dose will occur at the investigational site and subject will be monitored post injection for at least 15 minutes for safety
- Study drug dispensed to subject

9.3.3 Visit 4 (Week 4±2 Days) 40 mg Dose Level

At this visit, the following will be performed:

- Fasting weight
- Vital signs (prior to blood draw and IP administration)
- Blood samples:
    - Fasting glucose
    - Serum chemistry
    - Hematology
    - CCI
    - HbA1c
    - CCI
    - Immunogenicity (pre-dose)
- CCI
- Urinalysis
- AE assessment
- Subject diary review
- Concomitant medication review
- Distribute test strips as needed
- Drug accountability
- The dose will occur at the investigational site and subject will be monitored post injection for at least 15 minutes for safety
- Study drug dispensed to subject
- Lifestyle counseling

9.3.3.1 Visit 4A (on any day 1 to 6 days following visit 4)

- CCI
- Concomitant medication review

- AE assessment
- Distribute test strips as needed

9.4 Treatment Period – Target Dose Phase (Week 8 to Week 30)

9.4.1 Visit 5 (Week 8 ±2 Days) Target Dose

At this visit, the following will be performed:

- Fasting weight
- Vital signs (prior to blood draws and IP administration)
- Blood samples:
    - Serum chemistry
    - Hematology
    - Fasting glucose
    - CCI
    - HbA1c
    - CCI
    - Immunogenicity (pre-dose)
- CCI
- Urinalysis
- AE assessment
- Subject diary review
- Concomitant medication review
- Distribute test strips as needed
- Drug accountability
- The dose will occur at the investigational site and subject will be monitored post injection for at least 15 minutes for safety

- Lifestyle counseling

9.4.1.1 Visit 5A (on any day 1 to 3 days following visit 5)

- CCI
- Concomitant medication review
- AE assessment
- Distribute test strips as needed

9.4.1.2 Visit 5B (on any day 4 to 6 days following visit 5)

- CCI
- Concomitant medication review
- AE assessment
- Distribute test strips as needed

9.4.2 Visit 6 (Week 9±2 Days) Target Dose

At this visit, the following study activities will be performed:

- AE assessment
- Subject diary review
- Concomitant medication review
- Distribute test strips as needed
- Drug accountability
- Dose administration

9.4.3 Visit 7 (Week 10±2 Days) Target Dose

At this visit, the following will be performed:

- Vital signs (prior to IP administration)
- AE assessment
- Subject diary review

- Concomitant medication review
- Distribute test strips as needed
- Drug accountability
- Dose administration

9.4.4 Visit 8 (Week 11±2 Days) Target Dose

At this visit, the following study activities will be performed:

- AE assessment
- Subject diary review
- Concomitant medication review
- Distribute test strips as needed
- Drug accountability
- Dose administration

9.4.5 Visit 9 (Week 12±2 Days) Target Dose

At this visit, the following study activities will be performed:

- Fasting weight, CCI [redacted]
- 12-lead ECG (triplicate)
- Vital signs (supine blood pressure and pulse rate will be assessed following 12-lead ECG and prior to any blood draws or IP administration)
- Blood samples:
    - Fasting glucose
    - Serum chemistry
    - Serum calcitonin
    - Hematology
    - CCI [redacted]

- HbA1c
- CCI
- Immunogenicity (pre-dose)

- CCI
- Urinalysis
- AE assessment
- Subject diary review
- Concomitant medication review
- Distribute test strips as needed
- Study drug dispensed to subject
- Drug accountability
- Dose administration
- Lifestyle counseling

9.4.5.1 Visit 9A (any day 1 to 6 days post visit 9)

- CCI
- Concomitant medication review
- AE assessment
- Distribute test strips as needed

9.4.6 Visit 10 (Week 16±2 Days) Target Dose

At this visit, the following study activities will be performed:

- Fasting weight
- Vital signs (prior to blood draw and study drug administration)
- Blood draw:
  - Fasting glucose

- CCI
- Concomitant medication review
- AE assessment
- Subject diary review
- Distribute test strips as needed
- Drug accountability
- Study drug dispensed to subject
- Dose administration
- Lifestyle counseling

9.4.7 Visit 11 (Week 22±4 Days) Target Dose

At this visit, the following study activities will be performed:

- Fasting weight, CCI
- 12-lead ECG (triplicate)
- Vital signs (supine blood pressure and pulse rate will be assessed following 12-lead ECG and prior to any blood draws or study drug administration)
- Blood samples:
    - Fasting glucose
    - Serum chemistry
    - Hematology
    - CCI
    - HbA1c
    - CCI
- CCI
- AE assessment

- Subject diary review
- Concomitant medication review
- Distribute test strips as needed
- Drug accountability
- Study drug dispensed to subject
- Dose administration
- Lifestyle counseling

9.4.8 Visit 12 (Week 26±4 Days) Target Dose

At this visit, the following study activities will be performed:

- Fasting weight
- Vital signs (prior to blood draw and study drug administration)
- Blood draw:
    - Fasting glucose
- CCI [redacted]
- AE assessment
- Subject diary review
- Concomitant medication review
- Distribute test strips as needed
- Drug accountability
- Study drug dispensed to subject
- Dose administration
- Lifestyle counseling
- CCI [redacted]

9.4.9 Visit 13 (Week 30±4 Days) End of Treatment

At this visit, the following study activities will be performed:

- Fasting weight, CCI [redacted]
- 12-lead ECG (triplicate)
- Vital signs (supine blood pressure and pulse rate will be assessed following 12-lead ECG and prior to any blood draws)
- Blood samples:
    - Fasting glucose
    - Serum chemistry
    - Serum calcitonin
    - Hematology
    - CCI [redacted]
    - HbA1c
    - CCI [redacted]
    - Immunogenicity
- CCI [redacted]
- Urinalysis
- AE assessment
- Subject diary review
- Concomitant medication review
- Distribute test strips as needed
- Drug accountability
- Lifestyle counseling
- CCI [redacted]

9.5 Follow-up Visit 14 (Week 34±4 Days)/Early Termination

The following assessments will be performed (as indicated):

- Fasting weight, CCI [redacted]
- 12-lead ECG (single)
- Vital signs (supine blood pressure and pulse rate will be assessed following 12-lead ECG and prior to any blood draws)
- Blood samples:
  - Fasting glucose
  - Serum chemistry
  - Hematology
  - CCI [redacted]
  - HbA1c
  - CCI [redacted]
  - Immunogenicity
- CCI [redacted]
- Urinalysis
- AE assessment
- Subject diary review
- Concomitant medication review
- Drug accountability (ET only)

10 QUALITY CONTROL AND ASSURANCE

A quality assurance audit may be performed by the sponsor and/or its designee at selected sites to verify that the study is conducted in accordance with the protocol, ICH/GCP [International Conference on Harmonisation (ICH) and GCP], and applicable SOPs and regulations, to ensure that the safety and welfare of subjects are addressed, and to confirm that problems reported by the study clinical research associates (CRAs) have been resolved. Verification of study documents and study activities will be conducted to confirm accuracy

of recorded data and its analysis. The sponsor's audit observations and findings will be documented and communicated to appropriate study personnel and management. An inspection may be conducted by regulatory authorities including FDA. The investigator must allow direct access to study documents during any inspection or audit.

Routine monitoring visits will be performed to evaluate study conduct, data integrity, protocol, and GCP compliance. Source documents, eCRFs, laboratory reports and any other additional study documents will be reviewed to ensure that they are accurate and complete.

Each investigator is responsible for the accuracy, completeness, legibility, and timeliness of the data reported. All source documents are to be completed in a neat, legible manner to ensure accurate interpretation of data.

10.1 Data Quality Assurance

To ensure accurate, complete, and reliable data, the sponsor or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- provide study start-up training to instruct the investigators and study coordinators, protocol training, instructions on eCRF completion and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, the sponsor or its representatives will periodically check a sample of subject data recorded against source documents at the study site. Investigators will maintain study records in a secure location upon completion of the study and the file archive location will be provided to the sponsor or its representatives.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable IRBs with direct access to original source documents.

11 STATISTICAL CONSIDERATIONS

11.1 Determination of Sample Size

A total of 110 subjects will be randomized at a ratio 1.75:1 to OPK-88003 (70 subjects) and the corresponding placebo arm (40 subjects) in an effort to obtain 56 subjects completing in the active arm and 32 subjects completing in the placebo arm. A sample size of 48 subjects in the active arm and 27 subjects in the placebo arm will provide at least 90% power of detecting superior glycemic control over placebo represented by -0.8% in HbA1c levels at week 30. This assumes a common SD of 1.0% and a two-sided alpha of 0.05. The assumptions are based on variability in previously obtained HbA1c results from the OPK-88003 phase 2 trial XNAA.

11.2 Planned Statistical Methods

11.2.1 General Considerations

Statistical analysis of this trial will be the responsibility of the sponsor or its designee.

Any change to the data analysis methods described in the protocol will require a protocol amendment only if the study design is modified in a way that it significantly affects the safety of the subjects, the scope of the investigation or scientific quality of the study. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the statistical analysis plan (SAP) or clinical study report (CSR). Only results of exploratory analyses that are potentially relevant to subject safety will be reported in the final CSR. Additional exploratory analyses of the data (eg, secondary endpoint efficacy) may be performed as deemed appropriate and may or may not be reported in the final CSR.

A clinical SAP will be finalized prior to database lock. The SAP will describe statistical methodologies, and the statistical programming specifications and will list planned tables and listings. The SAP will describe study variables and population demographics, anticipated data transformations and manipulations and other details of the analyses not provided in the clinical protocol.

Data from screen failures will not be presented. The number of screen failures will be listed. Data from enrolled subjects will be presented in data listings arranged by treatment group.

All pre-dose and post-dose assessments, including repeat assessments, will be included in the data listings.

Continuous data will be presented with number of observations (n), mean, and median, standard deviation (SD), minimum and maximum. Frequencies and percentages will be used for summarizing discrete (categorical) data. The denominator for all percentages, unless otherwise stated, will be the number of dosed subjects in a given group.

Data that are reported as missing will be presented as unknown (UNK) in the data listings and treated as missing in all data summaries. No imputations for missing data will be made unless otherwise specified for endpoint derivation.

Data handling, tabulation of descriptive statistics and calculation of inferential statistics will be performed using SAS® for clinical data [redacted] CCI [redacted] The versions used will be reported in the final CSR.

11.2.2 Analysis Populations

The intent-to-treat (ITT) population is defined as all randomized subjects. Statistical analyses (including the primary analysis) will be conducted on the modified ITT (mITT) population. The mITT population is defined as all randomized subjects who received at least one dose of study drug and have at least one post-baseline measurement for the primary outcome.

The safety population is defined as all randomized subjects who have received at least one dose of study drug. All safety analyses will be performed on the safety population.

Some efficacy measures will also be analyzed on the per-protocol (PP) dataset. The per-protocol (PP) population is defined as all randomized subjects who were compliant with study drug and completed the protocol and is a subset of the mITT population and include subjects who meet the following additional criteria: The PP population will include all subjects in the mITT population who complete the 30-week, double-blind treatment period without any significant deviations from the protocol procedures. The PP population will be used to assess robustness of the primary analysis results. A final listing of all subjects to be excluded from the PP population will be completed prior to unblinding the study database.

No adjustments for multiplicity will be performed. All tests of treatment effects will be conducted at a two-sided alpha level of 0.05 and/or two- sided 95% confidence interval (CI), unless otherwise stated.

The baseline value used for the analyses will be the last scheduled baseline value obtained for each subject prior to first IP dose administration. Any measurements/events that occurred after the subject started rescue therapy will not be included in the efficacy analyses.

11.2.3 Subject Disposition

Frequencies and percentages of all randomized, discontinued, and completed subjects in the study will be presented for each of the treatment groups. A summary of discontinuations will be presented by treatment group and by visit. The reasons for discontinuations will be summarized by treatment group. Discontinuation rates will be compared among the treatment groups for each reason using a Fisher's exact test.

11.2.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group. Categorical variables will be summarized by frequencies and percentages. For categorical variables, comparisons between treatment groups will be assessed using a Pearson Chi-Square test. For continuous variables, comparisons between the treatment groups will be performed using a one-way Analysis of Variance (ANOVA) with treatment as the fixed effect.

11.2.5 Study Drug Exposure, Compliance, and Concomitant Therapies

Exposure to each therapy during the treatment period of the trial will be calculated for each subject and summarized by treatment group.

Listings and summary of concomitant therapies will be listed and summarized by subject.

Treatment compliance for the mITT population will be listed and summarized. Subjects that miss more than four doses of study drug over the course of the study, or miss two consecutive doses of study drug during the dose escalation phase are considered non-compliant. The frequency and percentage of subjects who are compliant will be summarized and analyzed by treatment group.

11.3 Outcomes Analysis

11.3.1 Primary Outcome Analysis

The primary efficacy outcome of HbA1c absolute change from baseline to the 30-week endpoint will be performed on the mITT analysis set. Endpoint for each subject is defined as the week 30 measurement. If the week 30 measurement is missing, the last valid post-baseline observation (last observation carried forward [LOCF]) algorithm will be applied to impute the missing week 30 value.

This change from baseline to week 30 in HbA1c will be analyzed using linear contrasts from an analysis of covariance (ANCOVA) model with treatment arm and BMI strata as factors and the baseline HbA1c value as a covariate. The least-squares means, standard errors, and the 2-tailed 95% confidence intervals (CIs) for each treatment group and for comparison to placebo will be presented. Additional covariates may be added and will be detailed in the SAP.

The primary efficacy analysis will be repeated on the PP population.

11.3.1.1 Supportive Analysis of Primary Outcome

The change from baseline in HbA1c at each scheduled visit without LOCF will be analyzed using a mixed-model repeated-measures (MMRM). The factors in the model will be BMI strata, treatment group, baseline value, visit, and the treatment group by visit interactions. No imputation will be performed. The least-squares means for change from baseline at each

visit will be estimated and compared between treatment groups. Additional covariates may be added and will be detailed in the SAP.

11.3.2 Secondary Outcome Analyses

The change from baseline of body weight and FPG will be calculated using the similar ANCOVA model used for the primary endpoint analysis. The corresponding baseline will be used in the model instead of the baseline HbA1c levels. The ANCOVA model will also include a term for the HbA1c stratification group.

A logistic regression analysis will be performed for the percent of subjects with 5% or greater body weight loss with treatment and HbA1c and BMI strata as fixed effects, and baseline weight as a covariate.

The number and percentage of subjects achieving HbA1c ≤6.5% will be summarized for each treatment group at each post-baseline visit. Comparisons between treatment groups will be performed for responses at week 30 with LOCF based on a logistic regression model with factors for treatment group and BMI strata and baseline HbA1c as a covariate. Odds ratios, 95% CIs (Wald), and p-values will be presented.

11.3.3 Other Outcome Analyses

CCI [redacted]

The proportion of subjects who discontinued due to hyperglycemia in each group will be analyzed using a logistic regression analysis with fixed effects of treatment and strata.

In addition to change from baseline in weight, CCI [redacted] will be listed and summarized.

CCI [redacted]

11.4 Safety Analysis

The safety population will be used for safety analyses. Safety measures will include vital signs, body weight, hypoglycemia episodes, AEs, laboratory measures (including ADAs), ECGs, injection site reactions, hypersensitivity reactions, major CV, pancreatic, and GI events. Summary statistics will be presented by treatment for the safety measures.

Additional analysis, such as concentration-safety lab plots, may be performed if warranted upon review of the data.

11.4.1 Adverse Events

Safety of all subjects will be monitored during the treatment period and queried at each visit for AEs. AEs will be listed by subject, actual term, preferred term, severity, and relationship to the treatment. AEs will be summarized as TEAEs; defined as events that are newly reported after randomization or reported to worsen in severity from baseline). The incidence of subjects with at least one TEAE and the incidence of TEAEs by preferred term and system organ class will be presented by treatment group. The frequency and percent of TEAEs will be presented. The incidence of subjects with at least one TEAE assessed as related to the investigational drug will be summarized by treatment group, in addition to the incidence of these TEAEs by preferred term. In addition, a summary of TEAEs by severity will be presented descriptively by treatment group.

Reported CV and pancreatic AEs will be listed by subject, and if there are a sufficient number of cases they may be summarized by treatment group.

All SAEs will be listed by subject. If a sufficient number of SAEs are reported, incidence summaries similar to incidence of TEAEs will be included.

Discontinuations due to TEAEs will be listed by subject and summarized by treatment group.

11.4.2 Adverse Events of Special Interest

11.4.2.1 Hypoglycemic Episodes

The incidence of total hypoglycemic episodes will be presented for each visit (incidence between visits) and overall. Listings of severity of hypoglycemic episodes will be presented by visit for each subject.

11.4.2.2 Other Adverse Events of Special Interest (AESIs)

Hypersensitivity reactions, injection site reactions, pancreatitis, major CV and GI events, such as nausea, vomiting, and diarrhea are defined as additional AESIs. Descriptive statistics for these AESIs will be presented by treatment group and visit.

11.4.3 Vital Signs

All vital signs will be listed for the safety population. Descriptive statistics for the actual measurements and changes from baseline for systolic and diastolic blood pressure and pulse rate will be presented by treatment arm and visit. Corresponding figures may be presented.

11.4.4 Laboratory Measures

Summary statistics will be provided for laboratory measures by visit. A listing of laboratory measurements for individual subjects will be presented by visit. An additional listing will be presented for all laboratory measurements that are outside the normal range.

Descriptive statistics for the laboratory analyses will be presented by treatment group and visit, including safety follow-up visits.

Laboratory analyses with categorical responses will be summarized by visit and treatment group using frequency and percentage.

Shift tables will be evaluated at the worst post-baseline observation (as applicable for a lab) will be compared to the baseline observation by examining the proportion of subjects whose test values are within and outside the reference ranges.

11.4.5 Evaluation of Immunogenicity

The frequency of ADA will be determined by the specialized laboratory other than central laboratory using a validated assay. If a neutralization assay is performed, the frequency of neutralizing antibodies will be determined.

11.4.6 Evaluation of Electrocardiography (ECG)

A listing of the individual and averaged ECG measurements by subject will be produced. This listing will include the time elapsed between the onset of ventricular depolarization and the end of ventricular repolarization (QT) corrected values described below.

Descriptive statistics for the absolute measurements, outliers, and changes from baseline for selected ECG parameters will be presented by treatment arm and visit. These include the ECG heart rate, and the following intervals: QT and QT corrected for heart rate using Fridericia's formula (QTcF).

In addition, OPK-88003 concentration-response analysis of QTcF results will be performed as well as a categorical analyses of absolute and change from baseline QTc intervals. Any additional ECG analyses will be detailed in the SAP.

CCI

CCI

12 ADMINISTRATIVE CONSIDERATIONS

12.1 Study Administrative Structure

This trial will be performed at up to approximately 30 clinical sites located in the US.

All study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s) as per ICH E6 GCP. Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (eg, loss of medical licensure, debarment).

At screening, the subject will be offered notification of their primary care physician that he is participating in a clinical study. If the subject accepts, a brief letter outlining the study and identifying the study drug will be sent once the subject is enrolled.

Table 4 lists third-party designees contracted by the sponsor to conduct the study.

Table 4 Third-party Designees

Organization	Responsibility
Medpace 5375 Medpace Way Cincinnati, OH 45227	Clinical data monitoring (CRAs), project management, medical/safety monitoring, data management, statistical analysis, central laboratory, cardiovascular central lab
Sherpa Clinical Package 6166 Nancy Ridge Drive San Diego, CA 92121, USA	Study drug distribution
CCI [redacted]	

12.2 Ethical Conduct of the Study

The study will be conducted in accordance with GCP (ICH GCP) and all applicable laws and regulations including the ethical principles of the Declaration of Helsinki (Edinburgh 2000, with Note of Clarification, Tokyo 2004) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.

In accordance with applicable country-specific regulations, the sponsor will obtain approval from the appropriate regulatory authority(ies) prior to initiating the study in that country.

12.3 Institutional Review Board (IRB) Approval

The investigator will submit all required documentation and obtain IRB approval to implement the study prior to the conduct of any study procedures. At a minimum, the study protocol, protocol amendments, ICF, Investigator's Brochure, and subject-related information, relevant curricula vitae and promotional materials will be submitted.

The sponsor or designee will approve all ICFs before they are used at investigative sites. All ICFs must be compliant with the ICH guideline on GCP.

Documentation of IRB approval of the protocol and the ICF must be provided before the study may begin at the investigative site(s). If it is necessary to amend the protocol during the course of the study, the investigator must ensure that the IRB reviews and approves the amendment. No amendments will be implemented without the agreement of the investigator and the sponsor as well as the IRB, where applicable.

The investigator will comply with requirements for reporting to the IRB.

12.4 Subject Information and Consent

The investigator will obtain a written informed consent form for each subject prior to performing any study-related procedures. The investigator is responsible for ensuring that the subject fully understands the nature of the study, potential risks and benefits of participating, including answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue participation in the study.

The investigator will ensure that the ICF is signed and dated by each subject and that documentation of consent being obtained will be recorded in the subject's medical record/source documents. CCI

As used in this protocol, the term "informed consent" includes all consent and assent given by subjects.

12.5 Confidentiality

12.5.1 Subject Confidentiality

Subject confidentiality will be strictly held in trust by the study investigators, their staff, the sponsor and their authorized representatives. This confidentiality includes clinical information relating to participating subjects and their biological sample testing.

The study protocol, documentation, data, and all other information will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsor.

Authorized representatives of the sponsor, contract research organizations (if applicable), study monitors, employees of government authorities (eg, US FDA or other), and IRB members may inspect all study-related documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The investigator and clinical study site will permit access to such records.

No information that would permit the identification of a specific individual will be provided for entry into the study database or study report. Study documentation submitted to the sponsor will identify study participants by study code and initials. The investigator will keep a separate confidential enrollment log that matches identifying study codes with the subject names and contact information.

12.5.2 Protocol/Study Confidentiality

This protocol contains information that is confidential and proprietary to OPKO. This information is being provided for the purposes of conducting a clinical trial for OPKO. The

investigator may disclose the contents of this protocol to the study personnel under his/her supervision who need to know the contents for this purpose, as well as to the institution's IRB or Ethics Committees, subject to the following condition: the contents of this protocol cannot be used in any other clinical trial and may not be disclosed to any other person or entity without prior written permission of OPKO. The foregoing shall not apply to disclosure required by governmental regulations. Prompt written notice of any such disclosure must be reported to OPKO. Any supplemental information that may be added to this document is also confidential and proprietary to OPKO, and must be kept in confidence in the same manner as the contents of this protocol.

12.6 Electronic Case Report Forms (CRFs) and Study Records

This study will utilize an electronic data capture system for the management of clinical data. Data capture and management will be consistent with applicable ICH/GCP guidelines.

All data collected during the study for subjects will be recorded in an individual, subject-specific electronic case report forms (eCRF) as part of an electronic data capture (EDC) system. Access to the electronic system will be restricted and users will only be able to access the system via authorized individual accounts. The sponsor or designee will provide training to the investigative site on the EDC system and eCRFs. Site staff will complete eCRFS promptly. As electronic data capture will be utilized, instructions, training records, and a log will be maintained to identify the designated site personnel who can enter data and/or sign off on an eCRF.

A subject eCRF must be completed for each subject who signs a consent form and undergoes randomization.

To ensure the quality of the clinical data across all subjects and sites, a clinical data management review will be performed by the sponsor or designee on subject data entered or integrated into the EDC system. During the review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol, and ICH/GCP. Moreover, all data from external sources, eg, central laboratory and PD processing/analysis will be reconciled with subject eCRF data. To resolve any questions arising from the Data Management review process, data queries and/or data clarification notifications will be generated via the EDC system for completion and resolution.

The investigator will sign and date the indicated places on the eCRF via the EDC system's electronic signature. These signatures will indicate that the investigator reviewed the data on the eCRF, the data queries, and the data clarifications and agrees with the content.

12.7 Protocol Deviations

Protocol deviations are any intentional or unintentional changes, divergences, or departures from the study design or procedures of an IRB-approved clinical protocol that have not been approved by the IRB prior to initiation of those changes, divergences or departures.

The investigator is responsible for ensuring protocol and study compliance by all study staff members. Deviations from protocol will be documented in subjects' study records.

The sponsor requires that all protocol deviations be reported to the IRB as per site's institutional regulations. In addition, the investigator is responsible for adhering to his/her IRB's protocol deviation reporting requirements.

12.8 Retention of Data

The investigator/institution will maintain all CRFs and all source documents that support the subject data collected, and all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least two years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until two years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified. 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 study, 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 circumstances shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

12.9 Publication and Disclosure Policy

Data derived from the study are the exclusive property of the sponsor. Publication rights are outlined in the clinical study agreement.

13 REFERENCE LIST

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Appendix 1. Schedule of Events

PHASE		TREATMENT PERIOD															FUP[a]	ET
		DOSE-ESCALATION				TARGET DOSE										EOT		
Study Visit	V1	V2	V3	V4	V4A C	V5	V5A C	V5B C	V6	V7	V8	V9	V9A C	V10	V11	V12	V13	V14	
Study Week	-2 to 0	0	1	4	4	8	8	8	9	10	11	12	12	16	22	26	30	34	
Visit Window (days)	-14 to -1	1	8±2	29±2	1 - 6 post V4	57±2	1 - 3 post V5	4 - 6 post V5[b]	64±2	71±2	78±2	85±2	1 - 6 post V9	113±2	155±4	183±4	211±4	239±4	
Informed consent	X																		
Inclusion/ exclusion criteria	X																		
Demographics	X																		
Health habits (alcohol, tobacco)	X																		
Medical history	X																		
Physical examination	X																		
Fasting weight[c], height[c]	X	X		X		X						X		X	X	X	X	X	X
Vital signs[e]																			
CCI																			
Serum chemistry[f] hematology	X			X		X						X			X		X	X	X
Serum calcitonin[g]	X											X					X		X
Urinalysis[h]	X			X		X						X					X	X	X
Serum pregnancy/FSH[i]	X																		
Serology (Hep B, Hep C)	X																		
Fasting glucose	X	X		X		X						X		X	X	X	X	X	X
CCI																			
HbA1c	X	X		X		X						X			X		X	X	X

PHASE		TREATMENT PERIOD																FUP[a]	ET
		DOSE-ESCALATION				TARGET DOSE											EOT		
Study Visit	V1	V2	V3	V4	V4A C	V5	V5A C	V5B C	V6	V7	V8	V9	V9A C	V10	V11	V12	V13	V14	
Study Week	-2 to 0	0	1	4	4	8	8	8	9	10	11	12	12	16	22	26	30	34	
Visit Window (days)	-14 to -1	1	8±2	29±2	1 - 6 post	57±2	1 - 3 post	4 - 6 post[b]	64±2	71±2	78±2	85±2	1 - 6 post	113±2	155±4	183±4	211±4	239±4	
CCI																			
Immunogenicity (pre-dose)		X		X		X						X					X	X	X
12-lead ECG[l]	X1	X2										X2			X2		X2	X1	X1
Concomitant med. review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Distribute glucometers and diaries		X																	
Distribute test strips as needed		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Lifestyle counseling[m]		X		X		X						X		X	X	X	X		
Subject training[n]		X																	
SMBG[o]			X	X		X			X	X	X	X		X	X	X	X		
Randomization		X																	
At-visit dosing[p]		X	X	X		X			X	X	X	X		X	X	X			
Dispense study drug to subject			X	X								X		X	X	X			
Drug accountability				X		X			X	X	X	X		X	X	X	X		X
CCI																			
AE assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review diary[r]			X	X		X			X	X	X	X		X	X	X	X	X	X
CCI																			

a. Subjects who complete an ET visit should complete a follow-up visit 4 weeks after their final dose
b. Visit 5B must occur before visit 6.
c. Body weight CCI will be measured on fasting subjects (minimum 8 hours). Duplicate measurements of weight will be performed using digital scales after an overnight fast and following emptying of any bowel/bladder contents. Subject will change into a light hospital gown for weight measurements CCI

d. Height is measured only at screening (V1).
e. Vital signs (triplicate supine blood pressure and pulse rate, after minimum 5 minutes rest) will be assessed following 12-lead ECG and prior to any blood draws or study drug administration.
f. Serum chemistry will include: albumin, ALP, ALT, AST, BUN, calcium, creatinine, creatine kinase, potassium, sodium, total and direct bilirubin, total protein, uric acid, lipase and amylase. Hematology will include: Hct, Hgb, MCHC, MCV, platelet count, RBC and WBC with differential.
g. Subjects who do not have a screening calcitonin should be tested at their next visit
h. Urinalysis will include glucose, leukocyte esterase, occult blood, pH and protein.
i. Serum pregnancy/FSH will be tested at the investigator's discretion.

CCI [redacted]

l. ECGs will be obtained in a quiet environment after at least 5 minutes in supine rest. Subjects will remain supine but awake during ECG collection. Consecutive replicate ECGs will be obtained at approximately 1-2 minute intervals within a 5 minute window. X1 single ECG; X2 triplicate ECG.
m. Lifestyle counseling will include lifestyle diary review. Subjects will complete a 3-day lifestyle diary prior to visits.
n. Subjects will receive training on study drug injection technique, routine SMBG and glucose testing supplies.
o. Subjects will perform SMBG prior to breakfast at least three times a week using a portable glucometer. Subjects will perform additional SMBG as per section 7.5 and may be asked to attend an unscheduled visit if needed.
p. There are no restrictions on the time of day each dose is given but it is advisable to administer SC injections on the same day and time of the week for the full 30 week treatment period. All subjects should be observed for allergic reactions following study drug administration for at least 15 minutes at

CCI [redacted]

r. Subject study diary review will include SMBG, AEs and dosing records.

CCI [redacted]

Appendix 2. Clinically Significant Events

Table 5 summarizes the type and severity of symptoms, clinical signs, and clinical laboratory findings that may qualify as a CSE and lead to discontinuation (see section 5.1.2). They are intended as a guideline to the investigator, not as a set of absolute criteria. The underlying principle is to define a level of moderate-to-severe abnormality in safety findings that could cause harm to health, and would preclude further dosing of a subject who experiences this effect. Safety parameters not included in this table may be interpreted in a similar fashion according to investigator judgement.

Table 5 Clinically Significant Events

Parameter	AE level
Symptoms	
Severe Hypoglycemia	One episode of severe hypoglycemia defined as low blood glucose with mental status impairment severe enough to require third-party assistance.
Severe Nausea and Vomiting	Requires IV hydration or emergency department visit or hospitalization, or prevents daily activity.
Dizziness/Hypotension	Orthostatic CNS symptoms (dizziness, confusion) that are not vasovagal responses to provocative stimuli (for example, phlebotomy, nausea, bowel or bladder function), and are associated with orthostatic SBP decrease >20 mm Hg or DBP decrease >10 mm Hg or heart rate >105 bpm, confirmed to persist for >3 hours
Headache/Pain	Any focal or generalized head pain that disrupts normal activities and is not responsive to medical therapies
Pruritus	Generalised itching over >24 hours unresponsive to oral antihistamine
Signs	
Systolic blood pressure	>30 mg Hg increase from baseline values and an absolute level >190 mm Hg[a]
Diastolic blood pressure	>20 mm Hg increase from baseline values and an absolute level >115 mm Hg[a]
Heart rate	Resting (sitting or recumbent) HR >120 bpm
QTc	>500 msec or >60 msec increase from baseline value[a]
QRS morphology	Significant prolongation of QRS interval or new onset of bundle branch block
Clinical Laboratory[a]	
Hemoglobin	Absolute value <10 g/dL and >2 g/dL reduction from baseline
Neutropenia	Absolute neutrophils <1,500/μL and >1,000 μL decrease from baseline
Lymphopenia	Absolute lymphocyte count <800/μL and >500/μL decrease from baseline
Platelet count	<75,000/μL and >50,000/uL decrease from baseline
Creatinine	>2 mg/dL and >0.5 mg/dL increase from baseline value
BUN	>25 mg/L and >10 mg/dL increase from baseline values
Potassium	<2.5 or >5.5 meq/L and >0.5 meq/L change from baseline value

Parameter	AE level
Sodium	<130 or >150 meq/L and >10meq/L change from baseline value

a Must be confirmed by repeat measurement within 48 hours

Appendix 3. Hepatic Monitoring Tests for Treatment-emergent Abnormality

The following hepatic monitoring tests should be considered for subjects with treatment-emergent hepatic abnormalities to ensure safety and comply with regulatory guidance. If the investigator needs to consider alternative hepatic monitoring tests, and/or strategy, he/she is advised to consult with the sponsor-designated medical monitor prior to testing.

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with subjects in consultation with the sponsor-designated medical monitor.

Hepatic Hematology[a]:
Hemoglobin
Hematocrit
Red blood cells (RBC)
White blood cells (WBC)
Neutrophils, segmented
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets

Hepatic Chemistry[a]:
Total bilirubin
Direct bilirubin
Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Gamma-glutamyl transferase (GGT)

Haptoglobin[a]

Hepatic Coagulation[a]
Prothrombin Time
Prothrombin Time, INR (international normalized ratio)

Hepatic Serologies[b]
Hepatitis A antibody, total
Hepatitis A antibody, IgM
Hepatitis B surface antigen
Hepatitis B Core antibody
Hepatitis C antibody
Hepatitis E antibody, IgG
Hepatitis E antibody, IgM

Anti-nuclear Antibody[a]

Anti-smooth muscle Antibody[a]

[a] can be assayed by either sponsor-designated laboratory or local laboratory
[b] reflex/confirmation dependent on regulatory requirements and/or testing availability

Appendix 4. Investigator's Signature

Study Title:	A Phase 2, Double-blind Dose Escalation Regimen of Once-weekly OPK-88003 in Subjects with Type 2 Diabetes
Study Number:	DPO-203
Final Date:	09 October 2018

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, with any future amendments, and with any other written study conduct procedures provided and reviewed and approved by OPKO Ireland Global Holdings Ltd. or its designee(s).
- Not to implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and the written approval from IRB, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational drug, as described in this protocol, and any other information provided by the sponsor including, but not limited to, the following: the current Investigator's Brochure or equivalent document provided by OPKO Ireland Global Holdings Ltd. or its designee(s).
- That I am aware of, and will comply with, GCP and all applicable regulatory requirements, including the regulations governing the use of controlled substances.
- To ensure that all persons assisting me with the study are adequately informed about the investigational drug and of their study-related duties and functions as described in the protocol.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply details about the investigator's ownership interest in the sponsor or the study drug, and more generally about his/her financial ties with the sponsor. OPKO Ireland Global Holdings Ltd. will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply OPKO Ireland Global Holdings Ltd. with any information regarding ownership interest and financial ties (including those of my spouse and dependent children), including with OPKO Health, Inc., and any of its affiliates.
- Agree to update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that OPKO Ireland Global Holdings Ltd. may disclose this information about such ownership interests and financial ties to regulatory authorities.

Signed:_____ Date:_____

Printed Name: _____

Signature Page for Protocol DPO-203 v4.0

Approval	PPD Medical 09-Oct-2018 19:53:38 GMT+0000

Signature Page for RIM-CLIN-000470 v4.0