STATISTICAL ANALYSIS PLAN

A PHASE 2, DOUBLE-BLIND, DOSE ESCALATION REGIMEN OF ONCE-WEEKLY OPK-88003 IN SUBJECTS WITH TYPE 2 DIABETES

Protocol Number:	DPO-203
Phase:	2
Investigational Product:	OPK-88003
IND Number:	113480
Indication:	Type 2 Diabetes Mellitus
Sponsor:	OPKO Ireland Global Holdings Ltd. (a subsidiary of OPKO Health, Inc.)
Sponsor Contact:	Dr. PPD PPD Medical Development Transition Therapeutics Corp. ULC 101 College St, Suite 220 Toronto, ON M5G 1L7 Email: PPD Phone: PPD
Protocol:	V1 / January 24, 2018 V2 / May 16, 2018 V3 / October 9, 2018
SAP:	V2.0 / February 4, 2019

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

Protocol Number:	DPO-203
Current Protocol:	V3 / October 9, 2018
SAP:	V2.0 / February 4, 2019

This Statistical Analysis Plan has been reviewed and approved by:

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4 Feb 2019
DD-MMM-YYYY

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1 SUMMARY OF CHANGES

SAP Version History		
Version	**Date**	**Description of Changes**
1.0	Jan. 15, 2019	Original signed version.
2.0	Feb. 4, 2019	CCI [redacted]

2 INTRODUCTION

This Statistical Analysis Plan (SAP) provides a description of the statistical methods and procedures to be implemented for the analyses of efficacy and safety data from OPKO Ireland Global Holdings Ltd. Protocol DPO-203. Any deviations from this analysis plan will be substantiated by sound statistical rationale and will be documented in the final clinical study report. Analysis of immunogenicity CCI [redacted] analysis will be addressed in separate reports.

3 STUDY OBJECTIVES

3.1 Primary Objective

To evaluate the effect of dose escalation of once-weekly (QW) subcutaneous (SC) OPK-88003 versus 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.

3.2 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 fasting plasma glucose (FPG) from baseline to after 30 weeks treatment, and
4. Number and percent (%) of subjects achieving HbA1c $\leq$ 6.5%.

3.3 Other Objectives

Other objectives of this study are as follows:

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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 (a separate ADA report will be provided);

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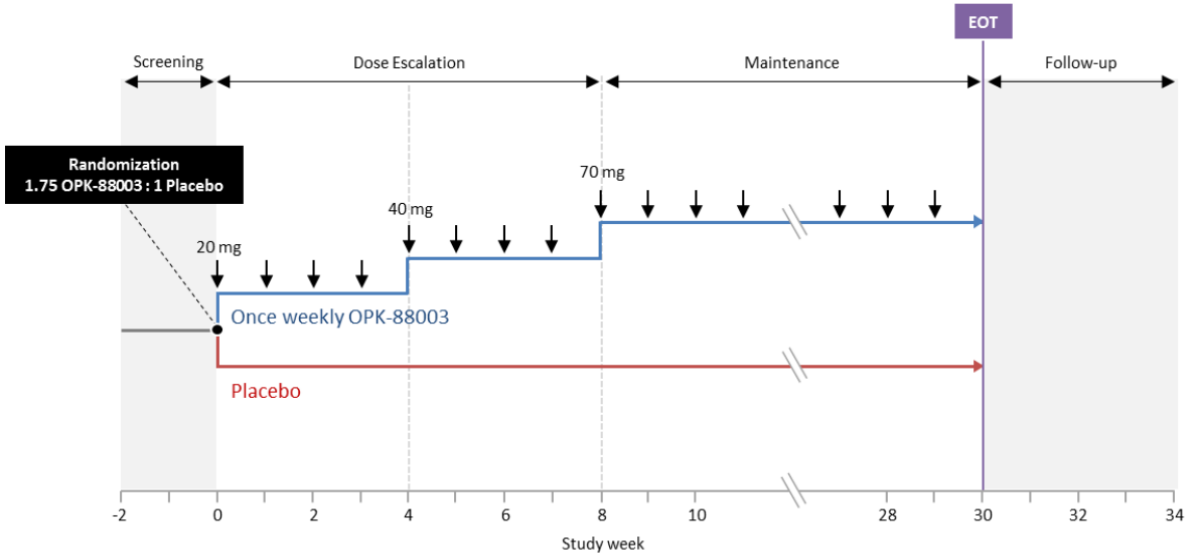
4 STUDY OVERVIEW

4.1 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 Design for DPO-203



EOT: end of treatment
↓ indicates dosing

The schedule of events for the study is provided in Protocol Appendix 1.

4.2 Randomization and Treatments

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

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.

5 ANALYSIS ENDPOINTS

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is absolute change in HbA1c from baseline to Week 30. If the Week 30 measurement is missing, the last valid post-baseline observation (last post-baseline observation carried forward [LOCF]) algorithm will be applied to impute the missing Week 30 value only for subjects that have discontinued early due to hyperglycemia (Week 30/$LOCF_H$). Otherwise, no imputation will be made for the missing Week 30 values.

5.2 Secondary Efficacy Endpoints

- Percent (%) change in body weight from baseline to Week 30,
- Number and percent of subjects with 5% or greater body weight loss at Week 30 (i.e. percent change ≤ -5%),
- Absolute change in FPG from baseline to Week 30/$LOCF_H$, and
- Number and percent of subjects achieving HbA1c ≤ 6.5% at Week 30/$LOCF_H$.

5.3 Additional Secondary Endpoints

- Absolute change in body weight from baseline to Week 30;
- Absolute change and percent (%) change in body weight from baseline to Weeks 4, 8, 12, 16, 22, 26, 30, and 34 without LOCF;
- Number and percent of subjects achieving ≥ 5% weight loss at Weeks 4, 8, 12, 16, 22, 26, 30, and 34 without LOCF;
- Absolute change in FPG from baseline to Weeks 4, 8, 12, 16, 22, 26, 30/$LOCF_H$, and 34;
- Absolute change in HbA1c from baseline to Weeks 4, 8, 12, 22, 30/$LOCF_H$, and 34;
- Number and percent of subjects achieving HbA1c ≤ 6.5% at Weeks 4, 8, 12, 22, 30/$LOCF_H$, and 34;
- Number and percent of subjects achieving HbA1c < 7.0% at Week 30/$LOCF_H$; and
- Number and percent of subjects achieving HbA1c < 7.0% at Weeks 4, 8, 12, 22, 30, and 34 without LOCF.

5.4 Other Endpoints

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- Number and percent of subjects permanently discontinued from the study due to hyperglycemia;

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5.5 Safety Endpoints

- Number and percent of subjects (including number of events) experiencing treatment-emergent AEs (TEAEs) and serious AEs (SAEs);
- Number and percent of subjects experiencing AEs of special interest (AESIs) as defined by protocol (GI events such as nausea, vomiting, and diarrhea; major CV events; hypoglycemia; injection site reactions; hypersensitivity reactions; and pancreatic events);
- Vital signs (blood pressure and pulse rate);
- Safety laboratory measures (chemistry, hematology, and urinalysis); and
- 12-lead electrocardiograms (ECG).

6 STATISTICAL METHODOLOGY

6.1 Sample Size Determination

Subjects will be randomized at an approximate ratio of 1.75:1 (OPK-88003:placebo). A sample size of 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. The assumptions are based on variability in previously obtained HbA1c results from the OPK-88003 phase 2 trial XNAA.

Approximately 110 subjects were enrolled in an effort to obtain 88 completed subjects (56 subjects completing in the active arm and 32 subjects completing in the placebo arm).

6.2 Baseline, Endpoint, and Other Statistical Considerations

The clinical statistical efficacy and safety analyses will be performed by Medpace.

First dose of study drug refers to the first dose of blinded study drug (Week 0 Day 1).

Baseline will be the measurement at Week 0 Day 1. If missing, the last valid measurement prior to the first administration of study drug will be used as baseline.

Any measurements/events that occur after the subject started rescue therapy will not be included in the efficacy analyses.

Unless specified otherwise, treatment groups will be OPK-88003 and placebo for summaries and analyses. Additional explorations may be done by OPK-88003 dose.

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be used to summarize the continuous efficacy and safety data by treatment group. The count and frequency will be used to tabulate categorical measurements.

Data will be used as it is reported. LOCF may be used when specified. The value must be collected within the last dose date +10, inclusive, in order to be used as LOCF. Where specified, $LOCF_H$ (for subjects that have discontinued early due to hyperglycemia) or $LOCF_{All}$ (for all subjects) may be used.

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.

Analysis Visit Windows

For all efficacy and safety assessments, analysis visits will be assigned according to the actual study day, calculated as the assessment date – first dose date for assessments prior to the first dose date and assessment date – first dose date +1 for assessments on or after the first dose date. The analysis visit windows will be defined as the halfway point between the target visit days:

Analysis Visit	Target Visit Day	Analysis Visit Window (Days)
Visit 1 (Screening)	N/A	N/A
Baseline	1	≤ 1
Visit 3 (Week 1)	8	2 – 18
Visit 4 (Week 4)	29	19 – 43
Visit 5 (Week 8)	57	44 – 60

Analysis Visit	Target Visit Day	Analysis Visit Window (Days)
Visit 6 (Week 9)	64	61 – 67
Visit 7 (Week 10)	71	68 – 74
Visit 8 (Week 11)	78	75 – 81
Visit 9 (Week 12)	85	82 – 99
Visit 10 (Week 16)	113	100 – 134
Visit 11 (Week 22)	155	135 – 169
Visit 12 (Week 26)	183	170 – 197
Visit 13 (Week 30)	211	198 to ≤ last dose date + 10
Visit 14 (Week 34/Follow-up)	239	N/A

If there is more than one assessment within a visit window, then the analysis visit will be assigned by the following priorities:

1. Use the visit with the matching visit label
2. Use the visit closest to the target visit day. In the case of ties, use the later assessment.

6.3 Analysis Populations

6.3.1 ITT Population

The Intent-to-Treat (ITT) Population is defined as all randomized subjects.

6.3.2 mITT Population

The Modified Intent-to-Treat (mITT) Population is defined as all randomized subjects who received at least one dose of study drug and have baseline and at least one valid post-baseline measurement for the primary outcome. Statistical analyses (including the primary analysis) will be conducted on the mITT Population. In the event of allocation errors, subjects will be analyzed for efficacy according to the treatment to which they were randomized.

6.3.3 Safety Population

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. In the

event of treatment allocation errors, subjects will be analyzed for safety according to the treatment group they received.

6.3.4 Per-Protocol Population

The Per-Protocol (PP) Population is defined as all randomized subjects who were compliant with study drug, completed at least 26 weeks of treatment or discontinued early due to hyperglycemia, and are a subset of the mITT Population. The PP Population will be used to assess robustness of the primary analysis results.

The following criteria may be evaluated for major deviations prior to unblinding the study database. A final listing of all subjects to be excluded from the PP Population will be completed prior to unblinding the study database.

- No eligibility criterion violations;
- Did not withdrawal prior to Week 26 if the reason is other than hyperglycemia;
- Subjects who did not miss more than 4 doses of study drug throughout the course of the study;
- Subjects who did not miss 2 consecutive doses of study drug during the dose escalation phase;
- Not taking any prohibited medications (treatment with medications that are excluded in the entry criteria is not permitted); and
- No other substantial protocol deviations.

6.4 Subject Disposition

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

6.5 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively by treatment group and total for the ITT Population. If they differ from the ITT Population, summaries will also be provided for the mITT Population, PP Population, and Safety Population.

Demographic and baseline characteristics include, but are not limited to, age at informed consent, gender, race, ethnicity, body weight, BMI, BMI stratification group (<30 or ≥30 kg/m^2), baseline HbA1c, HbA1c stratification group (<8.5% or ≥8.5%), and baseline FPG. The baseline is defined in Section 6.2, Baseline, Endpoint, and Other Statistical Considerations.

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.

6.6 Medical History

Medical/surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1. All medical history will be listed.

6.7 Prior and Concomitant Medications

Medication start and stop dates that are recorded on the Prior & Concomitant Medications case report form will be used to determine whether the medications are prior or concomitant to the study drug. Medications ongoing at the time of first dose of study drug (Visit 2 Week 0) as well as any new medication added during the course of the study will be considered concomitant medications. Prior medications are defined as those used prior to and stopped before the first dose of study drug. All prior and concomitant medication verbatim terms will be coded using the World Health Organization Drug Dictionary September 2017 Global B3 version. The numbers and percentages of subjects taking concomitant medications in each treatment group and in total will be summarized by anatomic therapeutic chemical term and preferred term for the Safety Population. All prior and concomitant medications will be listed.

6.8 Study Medication Exposure and Compliance

Subjects' exposure to study drug will be summarized with descriptive statistics for the Safety Population. Weeks of exposure is defined as:

$$(\text{date of last dose of study drug} - \text{date of first dose} + 1) \div 7$$

The total number of injections administered will be calculated for each subject. A contingency table will be provided to display the number and percentage of subjects in each treatment group with the following number of injections: 1-4, 5-8, 9-12, 13-16, 17-20, 21-24, 25-30.

Subjects that miss more than four doses of study drug over the course of study participation, or miss two consecutive doses of study drug during the dose escalation phase, are considered noncompliant. The frequency and percentage of subjects who are compliant and noncompliant will be summarized by treatment group.

6.9 Efficacy Analysis

6.9.1 Primary Efficacy Endpoint

The primary efficacy analysis is to evaluate the effect of dose escalation of OPK-88003 versus placebo injections on HbA1c absolute change from baseline to Week 30. If the Week 30 measurement is missing, the LOCF algorithm will be applied to impute the missing Week 30 value only for subjects that have early termed due to hyperglycemia (Week 30/$LOCF_H$). Otherwise, no imputation will be made. The primary analysis will be based on the mITT Population. The same analysis will be repeated on the PP Population.

The change from baseline in HbA1c at each scheduled visit will be analyzed using a mixed-model repeated-measures (MMRM). The factors in the model will be BMI strata, treatment group, baseline HbA1c value, visit, and the treatment group by visit interactions. An unstructured covariance matrix will be used (TYPE=UN). No imputation will be performed except for subjects that early term due to hyperglycemia. The least-squares means for change from baseline at each visit will be estimated and compared between treatment groups, with Week 30 being primary, and no adjustments for multiplicity. The sample SAS code can be found below:

```
*********************************************************************
Note:
  USUBJID = unique subject identifier
  TREATMENT = 0 (placebo), 1 (OPK-88003)
  BMI: <30 or >=30 kg/m2
  VISIT = visit
  BASE = baseline value
  CHG = change from baseline to the specified visit
*********************************************************************;
proc mixed;
  class USUBJID BMI TREATMENT VISIT;
  model CHG = BMI TREATMENT BASE VISIT TREATMENT*VISIT;
  Repeated VISIT / TYPE=UN sub=USUBJID;
  lsmeans VISIT*TREATMENT / cl slice=VISIT;
run;
```

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Supportive Analysis

If the Week 30 HbA1c measurement is missing, the LOCF algorithm will be applied to impute the missing Week 30 value for all subjects (Week 30/$LOCF_{All}$). The change from baseline to Week 30/$LOCF_{All}$ in HbA1c will be analyzed using linear contrasts from an analysis of covariance (ANCOVA) model with treatment group and BMI strata (<30, ≥30 kg/m^2) 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 of OPK-88003 to placebo will be presented. The 2-sided p-values testing for significance within treatment group change from baseline and comparison between treatment groups will be presented.

The sample SAS code can be found below:

```
*********************************************************************
Note:
  TREATMENT = 0 (placebo), 1 (OPK-88003)
  BASE: baseline HbA1c
  BMI: <30 or >=30 kg/m2
  CHG: change from baseline to Week 30/LOCF in HbA1c
*********************************************************************;
proc glm;
  class TREATMENT BMI;
  model CHG = TREATMENT BASE BMI / ss1 ss3;
  means TREATMENT;
  lsmeans TREATMENT / cov stderr pdiff cl;
  estimate " OPK-88003 : Placebo" TREATMENT -1 1;
run;
```

Before this analysis is performed, the data will be inspected for normality and homogeneity of variance, and a non-parametric rank test will be applied if necessary.

The appropriateness of the statistical model will be evaluated by testing the treatment group by baseline HbA1c interaction at a significance level of 0.10. CCI [redacted]

6.9.2 Secondary Endpoints

6.9.2.1 HbA1c/Responder Analysis

The number and percentage of subjects achieving HbA1c ≤6.5% will be summarized for each treatment group at each scheduled visit without LOCF, Week 30/$LOCF_H$, and Week 30/$LOCF_{All}$. Comparisons between treatment groups will be performed for responses at each visit, with Week 30/ $LOCF_H$ being primary, based on a logistic regression model with treatment group and BMI strata as factors and baseline HbA1c as a covariate. Odds ratios,

95% CIs (Wald), and p-values will be presented. The same summary and analysis will be performed for HbA1c <7.0%.

6.9.2.2 Body Weight

The change from baseline and percent change from baseline in body weight at each scheduled visit will be analyzed using an MMRM for the mITT Population and repeated on the PP Population. The factors in the model will be HbA1c strata, BMI strata, treatment group, baseline value, visit, and the treatment group by visit interactions. An unstructured covariance matrix will be used (TYPE=UN). No imputation will be performed. The least-squares means for change from baseline at each visit will be estimated and compared between treatment groups.

As a supportive analysis, the change from baseline and percent change from baseline to Week 30/$LOCF_{All}$ in body weight will be analyzed for the mITT Population using linear contrasts from an analysis of covariance (ANCOVA) model with treatment group, HbA1c strata (<8.5%, ≥8.5%), and BMI strata (<30, ≥30 kg/m^2) as factors and the baseline body weight 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 of OPK-88003 to placebo will be presented. The 2-sided p-values testing for significance within treatment group change from baseline and comparison between treatment groups will be presented.

The number and percentage of subjects achieving >5% weight loss will be summarized for each treatment group at each scheduled visit without LOCF and Week 30/$LOCF_{All}$. Comparisons between treatment groups will be performed for responses at Week 30 based on a logistic regression model with treatment group, HbA1c strata, and BMI strata as factors and baseline body weight as a covariate. Odds ratios, 95% CIs (Wald), and p-values will be presented.

6.9.2.3 Fasting Plasma Glucose

The same MMRM and ANCOVA model as for body weight above will be performed for the change from baseline in FPG. If Week 30 measurement is missing, the last valid post-baseline observation (LOCF) algorithm will be applied to impute the missing Week 30 value only for subjects that have early termed due to hyperglycemia (Week 30/$LOCF_H$).

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6.11 Safety Analysis

All safety analyses will be conducted on the Safety Population. The evaluation of safety will be based primarily on discontinuation due to hyperglycemia, TEAEs, vital signs, safety laboratory measures, and 12-lead ECG. Other safety data will be summarized as appropriate.

6.11.1 Adverse Events

An 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 AEs, including SAEs, occurring after the subject signs the informed consent form (ICF) through the subject's final visit will be reported and monitored. All AEs will be coded using MedDRA version 20.1.

TEAEs are defined as events that are newly reported after first dose of study drug or reported to worsen in severity or relationship to study drug after first dose of study drug.

An overview of AEs will be provided by treatment group and in total for the following information:

- All TEAEs,
- Maximum severity of TEAEs,
- Study drug-related TEAEs (defined as related or possibly related),
- Maximum severity of drug-related TEAEs,
- All serious adverse events (SAEs),
- All treatment-emergent SAEs,

- Drug-related SAEs,
- Death due to AEs,
- Withdrawals due to AEs, and
- Withdrawals due to study drug-related AEs.

The numbers and percentages of subjects with TEAEs, including number of events, will be tabulated for each treatment group and in total by MedDRA system organ class and preferred term. Similar summaries will be provided by maximum severity. Drug-related TEAEs will be summarized in the same manner.

Listings of SAEs and AEs leading to study medication discontinuation will be provided.

Hyperglycemia

The number and percent of subjects permanently discontinued from the study due to hyperglycemia will be tabulated by treatment group for the Safety Population. The discontinuation rates will be compared among the treatment groups using a Fisher's exact test. The odds ratio will be provided.

AEs of Special Interest

The number and percent of subjects (including number of events) experiencing AESIs (GI events, major CV events, hypoglycemia, injection site reactions, hypersensitivity reactions and pancreatic events) will be tabulated for each treatment group and in total by category and preferred term. A listing will be provided of all AEs of special interest. For hypoglycemia, listings will be provided of all additional information such as glucose values, symptoms, countermeasures, etc. For injection site reactions, listings will be provided of all additional information such as symptoms, severity of each symptom, etc.

If data allows, the monthly hypoglycemia rate will be calculated as the event rate per subject year divided by 12 months:

$$(365.25 \times \text{total number of hypoglycemia TEAEs} / \text{study duration}) \div 12$$

Where study duration is the date of completion/early termination – date of first dose +1. Summary statistics for the monthly hypoglycemia rate will be provided by treatment group.

6.11.2 Vital Signs

Systolic blood pressure, diastolic blood pressure, and pulse rate will be summarized at baseline and each scheduled post-baseline visit. The change from baseline will also be presented. The triplicate measurements will be averaged prior to summarization.

6.11.3 Clinical Laboratory Evaluations

Summary statistics will be provided for safety laboratory tests at baseline and all scheduled post-baseline visits for chemistry, hematology, and urinalysis assessments by treatment group and in total. The change from baseline to post-baseline visits will also be presented.

The number and frequency of subjects with laboratory abnormalities (worst value post first dose for each subject) will be summarized by treatment group and in total. Shift tables from baseline to worst value post first dose will be presented for ALT and AST (>1xULN to ≤2xULN, >2xULN to ≤3xULN, >3xULN) and CK (>1xULN to ≤5xULN, >5xULN to ≤10xULN, >10xULN).

6.11.4 12-Lead ECG

Summary statistics will be provided for triplicate 12-Lead ECG assessments (vent rate, PR interval, QRS duration, QT interval, RR interval, QTcB, QTcF) at baseline and all scheduled post-baseline triplicate visits. The change from baseline to post-baseline visits will also be provided. The triplicate readings will be averaged prior to summarization. The single ECG assessments (screening and follow-up) will be summarized separately from the triplicate ECG assessments. The overall interpretation will be summarized by scheduled visit with counts and percentages by treatment group and in total. All ECG assessments will be listed.

6.11.5 Other Safety Parameters

All other safety parameters such as physical examination will be listed.

7 GENERAL INFORMATION

The mock-ups for SAS-generated tables/figures/listings will be prepared in a separate document and finalized before database lock for the study.

7.1 Statistical Software

The creation of analysis datasets and all statistical analyses will be done using SAS® version 9.4. The Medpace standard operating procedures will be followed for the validation of all SAS programs and outputs.

8 CHANGES FROM THE PROTOCOL PLANNED ANALYSES

8.1 Sample Size Determination

Per Protocol V2 and V3, 88 subjects are needed to obtain at least 90% power to detect superior glycemic control over placebo. However, the dropout rate (assumed 20%) was considered twice in the derivation. Only at least 73 subjects are needed to obtain 90% power.

8.2 Primary and Secondary Analyses

In the Protocol, an ANCOVA model is specified for the primary efficacy analysis and MMRM is the supportive analysis of the primary outcome. However, there has been a higher than expected number of subjects that have discontinued early, particularly early in the study. Taking into consideration the early dropouts and the current approaches used to analyze data from diabetes trials, the primary efficacy analysis will use MMRM and ANCOVA will be a sensitivity analysis. Analyses of the applicable secondary CCI endpoints will also use MMRM. This change is made prior to database lock and treatment unblinding.

Since MMRM will be used as the primary and secondary endpoint analyses, LOCF will not be applied to the Week 30 endpoints. However, it is deemed appropriate to use LOCF for subjects that discontinued due to hyperglycemia.