STATISTICAL ANALYSIS PLAN

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE-RANGING STUDY OF OPK-88004 ONCE-A-DAY DOSING FOR 16 WEEKS IN MEN WITH SIGNS AND SYMPTOMS OF BENIGN PROSTATIC HYPERPLASIA

Protocol Number:	SAR-202
Phase:	2
Investigational Product:	OPK-88004
IND Number:	CCI
Indication:	Benign Prostatic Hyperplasia (BPH)
Sponsor:	Transition Therapeutics Ireland Ltd. (a subsidiary of OPKO Health, Inc.)
Sponsor Contact:	Dr. PPD PPD Medical Development OPKO Health, Inc. 4400 Biscayne Blvd Miami, FL 33137 Email: PPD Phone: 305.575.4172
Protocol:	V1 / 27-SEP-2017 V2 / 30-OCT-2017 V3 / 06-FEB-2018 V4 / 22-MAR-2018 V5 / 25-JUN-2018 V6 / 19-OCT-2018 (not implemented) V7 / 09-NOV-2018
SAP:	V1.0 / 21-FEB-2019 V2.0 / 06-MAR-2019

Protocol: A Randomized, Double-blind, Placebo-controlled Dose-ranging Study of OPK-88004 Once-a-day Dosing for 16 Weeks in Men with Signs and Symptoms of Benign Prostatic Hyperplasia

Protocol Number:	SAR-202
Current Protocol:	V7 / 09-NOV-2018
Current SAP:	V2.0 / 06-MAR-2019

This Statistical Analysis Plan has been reviewed and approved by:

PPD
PPD MS
Project Statistician
Medpace

07-MAR-2019
DD-MMM-YYYY

PPD
PPD MD
Medical Monitor
Medpace

07-MAR-2019
DD-MMM-YYYY

PPD
PPD MD
PPD Medical Development
OPKO Health, Inc.

06-MAR-2019
DD-MMM-YYYY

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1 SUMMARY OF CHANGES

SAP Version History		
Version	**Date**	**Description of Changes**
1.0	21-FEB-2019	Original signed version.
2.0	06-MAR-2019	Prior to database lock, remove analyses which are no longer considered to be needed: • DXA percent change from baseline 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 Transition Therapeutics Ireland Ltd. Protocol SAR-202. Any deviations from this analysis plan will be substantiated by sound statistical rationale and will be documented in the final clinical study report. CCI [redacted]

3 Study Objectives

3.1 Primary Objectives

1. To evaluate the effect of 15 mg and 25 mg OPK-88004 daily for 16 weeks on serum prostate-specific antigen (PSA) compared with placebo
2. To evaluate the safety of 15 mg and 25 mg OPK-88004 daily for 16 weeks compared with placebo

3.2 Secondary Objectives

1. To assess the effects of OPK-88004 on body composition by dual energy X-ray absorptiometry (DXA), specifically lean body mass and fat mass
2. CCI [redacted]

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[redacted]

4 STUDY OVERVIEW

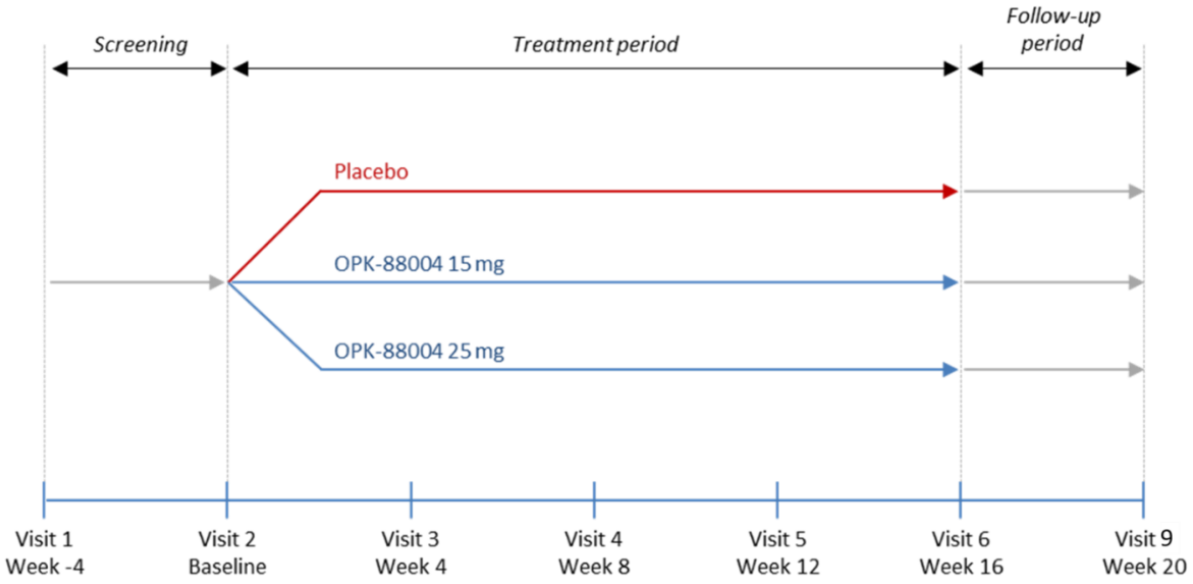
4.1 Study Design

Study SAR-202 is a phase 2 multicenter, placebo-controlled, double-blind trial to evaluate the effect of OPK-88004 doses (OPK-88004 15 mg, or OPK-88004 25 mg) on serum PSA compared to placebo in men with BPH. Subjects will be instructed to take one dose (1 capsule) of study drug with water at approximately the same time each morning. Approximately 115 men with BPH will be enrolled in the study, randomized 1:1:1 across three arms (placebo, OPK-88004 15 mg, or OPK-88004 25 mg). The trial will be conducted at up to approximately 35 sites within the US.

The study duration for individual subjects will be up to 24 weeks and will include three phases:

- a screening period (up to 4 weeks, including 1-week washout if required),
- a treatment period (16 weeks), and
- a follow-up period (4 weeks).

Study Design for SAR-202



* Visit 7 (4 days post final dose) and 8 (7 days post final dose) are for PK blood draw only

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

4.2 Randomization and Blinding

Subjects who have completed the screening visit and meet all of the inclusion and none of exclusion criteria are randomized into the study on day 1. Randomized treatment assignment and randomization numbers are assigned via interactive web response system (IWRS) / interactive voice response system (IVRS). Randomization is stratified by prostate volume <60 cm^3 or ≥60 cm^3 and lower urinary tract symptoms (LUTS) severity (total IPSS [Question 1 – Question 7] of <16 or ≥16). Following randomization, study drug will be dispensed in a double-blind manner. The sponsor and all clinical site personnel (investigator, pharmacist, etc.) are blinded to the treatment group for each subject. Subjects also are blinded to the treatment they receive.

5 ANALYSIS ENDPOINTS

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is percent change in PSA from baseline to Week 16. Since the primary analysis model will use mixed model repeated measures (MMRM), no imputation will be made for the missing Week 16 values.

If certain events occur that complicate the description and interpretation of the treatment effect on PSA (e.g. prostatitis, riding a bike prior to a study visit, or sexual activity), then the PSA results affected by those intercurrent events will be excluded from all efficacy

summaries and analyses. The PSA results to be excluded due to intercurrent events will be defined prior to study unblinding.

5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are the observed change from baseline to Week 16/last observation carried forward (LOCF) in lean body mass and fat mass by DXA.

If certain events occur that complicate the description and interpretation of the treatment effect on DXA parameters (e.g. going on a weight-loss diet or excessive exercise program), then the DXA results affected by those intercurrent events will be excluded from all efficacy summaries and analyses. The DXA results to be excluded due to intercurrent events will be defined prior to study unblinding.

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5.4 Safety Endpoints

Safety assessments include all adverse events (AEs), laboratory measurements (lipids, chemistry, hematology, coagulation, fasting HbA1c, glucose, insulin, hormone panel, CRP, and urinalysis), vital signs, physical examinations, ECGs, and semen analysis.

6 STATISTICAL METHODOLOGY

6.1 Sample Size Determination

Approximately 115 subjects will be enrolled in the study, randomized 1:1:1 across three arms (placebo, OPK-88004 15 mg, or OPK-88004 25 mg). The primary efficacy objective is to evaluate the ability of OPK-88004 doses to reduce PSA compared to placebo from baseline to week 16. CCI

[redacted]

From historical data, the treatment difference of percent reduction of PSA from baseline to week 16 endpoint between any OPK-88004 dose and placebo is over 30% with common standard deviation <40%. With a sample size of 28 completed subjects per treatment group, the power for the test significance of PSA reduction for any OPK-8804 dose compared to placebo is over 80%. A dropout rate of 10% from randomization to study completion is anticipated.

The treatment effect, standard deviation, and dropout rate used in the sample size calculation are based on historical data.

6.2 Baseline, Endpoint, and Other Statistical Considerations

The clinical statistical efficacy and safety analyses will be performed by Medpace. Analysis of population PK will be addressed in a separate report.

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

Baseline will be the pre-dose value obtained at the scheduled baseline visit CCI [redacted] Day 1 for PSA). If missing, the last valid measurement prior to the first administration of study drug will be used as baseline.

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 days, inclusive, in order to be used as LOCF.

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 PSA, 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 2 (Day 1), Baseline	1	≤ 1 (pre-dose)
Visit 4 (Week 8)	56	2 – 84
Visit 6 (Week 16)	112	85 to ≤ last dose date + 10

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.

For all other efficacy and safety assessments, analysis visits will be assigned according to the visit recorded on the electronic case report form (eCRF). For efficacy, assessments must be within 10 days of the last dose date in order to be included for analysis.

6.3 Analysis Populations

6.3.1 Randomized Population

The Randomized Population includes all subjects who sign the informed consent form and are assigned a randomization number. Baseline and demographic characteristics will be summarized for this population.

6.3.2 Safety Population

The Safety Population includes subjects in the Randomized Population who receive at least 1 dose of randomized study drug. All safety analyses will be conducted based on the Safety Population. In the event of treatment allocation errors, subjects will be analyzed for safety according to the treatment group they received.

6.3.3 mITT Population

The modified Intent-to-Treat (mITT) Population includes all subjects in the Safety Population who have a baseline efficacy endpoint and at least 1 valid (i.e. within last dose date +10 days and without intercurrent events) post-dose efficacy endpoint. The mITT Population is the primary analysis population, and all efficacy analyses will be performed using the mITT Population. In the event of allocation errors, subjects will be analyzed for efficacy according to the treatment to which they were randomized.

Since each efficacy assessment has a different schedule of events, the number of subjects included in other efficacy assessments may be different than the overall mITT Population. The analysis of each efficacy endpoint will be performed on all subjects that have a baseline efficacy result and at least 1 valid post-dose result for the specified efficacy parameter.

Exclusion of results due to intercurrent events will be determined prior to study unblinding. Subjects may be included in the mITT Population but have certain results excluded due to intercurrent events. For example if the subject has baseline and Week 8 PSA but Week 16 PSA is excluded due to an intercurrent event, the subject will still be included in the mITT Population.

6.3.4 Per-Protocol Population

The Per-Protocol (PP) Population will include all subjects in the mITT Population who complete the 16-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.

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 16;
- Subjects with overall study drug compliance 80 – 120%;
- Not taking any prohibited medications; and
- No other substantial protocol deviations, including but not limited to significant changes in pre-study diet and activity levels.

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. Frequencies and percentages of subjects in each analysis population will also be provided. The reasons for discontinuations will be summarized by treatment group. Summaries for the total OPK-88004 treatment group (i.e. 15 mg and 25 mg combined) will be provided as well.

6.5 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively by treatment group and total for the Randomized Population. If they differ from the Randomized Population, summaries will also be provided for the mITT Population, PP Population, and Safety Population. Summaries for the total OPK-88004 treatment group (i.e. 15 mg and 25 mg combined) will be provided as well for the mITT Population and the PP Population.

Demographic and baseline characteristics include, but are not limited to, age at informed consent, gender, race, ethnicity, body weight, BMI, baseline PSA, baseline DXA assessments, prostate volume stratification group (<60 cm^3 or ≥ 60 cm^3), LUTS severity stratification group (total IPSS of <16 or ≥ 16). 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 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 randomized study drug will be summarized with descriptive statistics for the Safety Population. Days of exposure is defined as:

date of last dose of study drug – date of first dose + 1

If the date of last dose of study drug is unavailable, then days of exposure will be defined as the early termination (ET) visit date – date of first dose for subjects that discontinue prior to Week 16, and the Week 16 visit date – date of first dose for subjects who complete Week 16.

A contingency table will be provided to display the number and percentage of subjects in each treatment group with exposure in the following categories: 1-28 days (>0-4 weeks), 29-56 days (>4-8 weeks), 57-84 days (>8-12 weeks), 85-112 days (>12-16 weeks), and >112 days (>16 weeks).

Summary statistics will be presented for percent overall compliance to study medication by treatment group and total. The count and percentage of subjects will also tabulated by groups with overall compliance < 80%, 80% - 120% (inclusive), and > 120%. The percent overall compliance to study medication will be calculated as:

100 × number of capsules / days of exposure

The number of capsules is the total number of capsules dispensed minus the total number of capsules returned as reported on the eCRF. If a bottle is not returned, it will be assumed that all capsules from that bottle were used.

6.9 Efficacy Analysis

6.9.1 Primary Efficacy Endpoint

The primary efficacy analysis is to evaluate the effect of 15 mg and 25 mg OPK-88004 daily for 16 weeks versus placebo on PSA percent change from baseline to Week 16. Analysis of the percent change from baseline of PSA to Week 16 will be performed using a MMRM based on the mITT Population, implemented using SAS® Proc Mixed. The factors in the model will be treatment, prostate volume stratification group, and IPSS stratification group, visit, and the treatment group by visit interactions and baseline PSA as a covariate. Treatment difference between OPK-88004 doses and placebo at Week 16 will be estimated from the MMRM model, as well as confidence intervals and p-values. This analysis will be based on the mITT Population and repeated on the PP Population. Sample SAS code is provided below.

```
**********************************************************************
Note:
  USUBJID = unique subject identifier
  TREATMENT = 0 (placebo), 1 (OPK-88004 15 mg), 2 (OPK-88004 25 mg)
  PV: prostate volume stratification <60 or >=60 cm3
  LUTS: total IPSS <16 or >=16
  VISIT = visit (Week 8 and Week 16)
  BASE = baseline PSA
  PCHG = percent change from baseline to the specified visit
**********************************************************************;
proc mixed;
  class USUBJID PV LUTS TREATMENT BASE VISIT;
  model PCHG = PV LUTS TREATMENT BASE VISIT TREATMENT*VISIT;
  Repeated VISIT / TYPE=UN sub=USUBJID;
  lsmeans VISIT*TREATMENT / cl slice=VISIT;
run;
```

The appropriateness of the statistical model will be evaluated by testing the treatment group by baseline PSA interaction at a significance level of 0.10. If the interaction term is significant, the nature of the interaction will be investigated CCI [redacted]

The same analysis will be performed for total OPK-88004 (i.e. 15 mg and 25 mg combined) versus Placebo.

Supportive Analysis

Results for Week 8 from the primary MMRM model above will also be reported.

The number and percentage of subjects that have an increase or zero change in PSA (i.e. non-responder) or a decrease in PSA (i.e. responder) at Weeks 8 and 16 relative to baseline will be tabulated. Cochran-Mantel-Haenszel tests will be performed adjusting for the prostate volume and IPSS stratification groups. The general association p-value will be provided. Then for each OPK-88004 treatment group compared to placebo, the odds ratio, 95% confidence interval, and Breslow-Day test for homogeneity of the odds ratio p-value will be provided. The analysis will be performed on the mITT Population and repeated for the PP Population. The analysis will be performed based on observed data, i.e. only including subjects with a result at the specified visit. The same analysis will be performed for total OPK-88004 (i.e. 15 mg and 25 mg combined) versus Placebo.

6.9.2 Secondary Endpoints

The observed change from baseline to Week 16/LOCF in lean body mass and fat mass will be analyzed using ANCOVA modeled with treatment, prostate volume stratification group and IPSS stratification group as fixed effects and baseline result as a covariate. If the Week 16 measurement is missing, the LOCF algorithm will be applied to impute the missing Week 16 value for all subjects (Week 16/LOCF). The least-squares means, standard errors, and the 2-tailed 95% confidence intervals (CIs) for each treatment group and for comparison of each OPK-88004 dose 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. This analysis will be based on the mITT Population and repeated on the PP Population. The same analysis will be performed for total OPK-88004 (i.e. 15 mg and 25 mg combined) versus Placebo.

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[redacted]

6.11 Safety Analysis

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

6.11.1 Adverse Events

All AEs, including serious AEs (SAEs) occurring after the subject signs the ICF through the subject's final visit will be reported and monitored. Any clinically significant abnormal laboratory results, physical examination findings, ECGs, and vital signs will be reported as an AE. 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 definitely, probably, 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.

AEs of Special Interest

The number and percent of subjects (including number of events) experiencing AEs of special interest (AESIs) (see Protocol Section 8.2) and treatment-emergent AESIs will be tabulated for each treatment group and in total by system organ class and preferred term. A listing will be provided of all AESIs, which will be identified prior to database lock. Analysis will be performed using Fisher's exact tests across all treatment groups.

6.11.2 Clinical Laboratory Evaluations

Summary statistics will be provided for safety laboratory tests at baseline and all scheduled post-baseline visits for chemistry (including glucose and insulin), hematology, lipids, coagulation, 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); where ULN = upper limit of normal.

6.11.3 Physical Examination Including Body Weight

Counts and percentages of the physical examination overall interpretation (normal, abnormal clinically significant, abnormal, not clinically significant) will be tabulated at baseline and each scheduled post-baseline visit by treatment group and in total.

Body weight will be summarized at baseline and each scheduled post-baseline visit by treatment group and in total. The change from baseline will also be presented.

6.11.4 Vital Signs

Systolic blood pressure, diastolic blood pressure, pulse rate, temperature and respiratory rate will be summarized at baseline and each scheduled post-baseline visit by treatment and in total. The change from baseline will also be presented.

6.11.5 12-Lead ECG

Counts and percentages of the 12-lead ECG overall interpretation as reported on the eCRF (normal, abnormal clinically significant, abnormal, not clinically significant) will be tabulated at baseline and each scheduled post-baseline visit by treatment group and in total.

12-Lead ECG parameters (heart rate, PR, RR, QRS, QT, T Wave Amplitude, QTcB, and QTcF) will be summarized at baseline and each scheduled post-baseline visit by treatment group and in total. The change from baseline will also be presented.

6.11.6 Semen Analysis

Results from semen analysis will be summarized at baseline and Week 16/ET by treatment group and in total. The observed change and percent change from baseline will also be presented. All results, including the 3-month post-treatment follow-up visit if applicable, will be listed.

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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

Per Protocol, a sensivity analysis of the percent change from baseline to Week 16 in PSA will be performed using an ANCOVA model. This sensitivity analysis has been removed since the study will terminate early; only the primary analysis model (MMRM) will be used.

The Protocol specifies that the observed change and percent change from baseline will be summarized and analyzed for lean body mass and fat mass by DXA CCI [redacted]. However, only the observed change from baseline will be summarized and analyzed. The percent change from baseline is no longer considered to be needed.

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[redacted]

Per Protocol, AEs that occur following first administration of study drug are TEAEs. However, for analysis, TEAEs will be defined as new or worsening AEs (see Section 6.11.1)