16.1.9 Documentation of Statistical Methods

OTL-2016-OTL38-006 Statistical Analysis Plan V1, Dated 16 May 2017

STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Randomized, Single Dose, Open-Label Study to Investigate the Safety and Efficacy of OTL38 Injection (OTL38) for Intra-operative Imaging of Folate Receptor Positive Ovarian Cancer.
Sponsor:	On Target Laboratories, LLC
Protocol No.:	OTL-2016-OTL38-006
Protocol Version/Date	Version 1, 16 May 2017
Phase of Development:	3
Analysis Plan Version/Date:	Version 1, 16 May 2017

Table of Contents

List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ADE	Adverse Device Effect
BMI	Body Mass Index
CI	Confidence Interval
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FN	False Negative
FP	False Positive
FR+	Folate Receptor Positive
FPR	False Positive Rate
GLMM	Generalized Linear Mixed Model
IC	Informed Consent
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
ML	Maximum Likelihood
NB2	Negative Binomial 2
PPAS	Per Protocol Analysis Set
PPV	Positive Predictive Value
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
TN	True Negative
TP	True Positive
TPR	True Positive Rate

1 INTRODUCTION

This statistical analysis plan (SAP) provides detailed information and guidance regarding the planned analyses to be conducted to address the trial objectives outlined in protocol OTL-2016-OTL38-006, Version 1 dated May 16, 2017, "A Phase 3, Randomized, Single Dose, Open-Label Study to Investigate the Safety and Efficacy of OTL38 Injection (OTL38) for Intra-operative Imaging of Folate Receptor Positive Ovarian Cancer". Should an amendment to the finalized SAP become necessary prior to conducting the analysis, the Sponsor or its representatives will document any amendments including the date of the change and the rationale. Additional analyses beyond those planned in the SAP will be identified and described in the clinical study report (CSR). Draft tables, listings and figures will be provided in a separate document.

The statistical analysis, data integrity processes, and computer software validation will follow the SOPs provided by the Contract Research Organization conducting the operational aspects of the trial and should follow the statistical principles as outlined in ICH E9[1].

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to confirm the efficacy of OTL38 in combination with fluorescent light to detect additional Folate Receptor-positive (FR+) ovarian cancer lesions not detected by palpation and visualization under normal light in patients with FR+ ovarian cancer scheduled to undergo primary surgical cytoreduction, interval debulking, or recurrent ovarian cancer surgery.

2.2 Secondary Objectives

The secondary objectives are:

- To estimate the proportion of folate positive ovarian cancer patients in whom all lesions detected by fluorescent light only are histologically negative, the patient level False Positive Rate (FPRp)
- To estimate the Sensitivity and False Positive Rate for OTL38 in combination with fluorescent light with respect to the detection of FR+ ovarian cancer lesions confirmed by [redacted] pathology.
- To assess the safety of using OTL38 and [redacted] Imaging System for intraoperative imaging with OTL38.

2.3 Exploratory Objects

The exploratory objectives are:

- [redacted]

[1] Guidance for Industry: E9 Statistical Principles for Clinical Trials. September 1998.

- [redacted]
- [redacted]
- [redacted]

3 OVERALL STUDY DESIGN

This is a phase 3, randomized, multi-center, single dose, open label, pivotal study in patients diagnosed with, or with high clinical suspicion of, ovarian cancer scheduled to undergo primary surgical cytoreduction, interval debulking, or recurrent ovarian cancer surgery.

All patients participating in the study are expected to receive OTL38 and undergo normal light evaluation; however, to guard against the possible "under-calling" of lesions during the normal light assessment, patients will be randomized to a no fluorescent imaging group. [redacted]

Efficacy will be assessed for patients undergoing both normal light and fluorescent light imaging. All patients exposed to OTL38, regardless of randomized group assignment, will be followed for safety. Further details are provided in the protocol.

4 STUDY POPULATION

The study population will consist of adult female patients diagnosed with, or with a high clinical suspicion of, ovarian cancer who are scheduled to undergo primary surgical cytoreduction, interval debulking, or recurrent ovarian cancer surgery. For a full list of eligibility criteria, refer to Section 5.2 of the protocol.

5 TREATMENT ASSIGNMENT

The study design results in an open-label single-arm for the assessment of efficacy and safety. There is (are) no comparator group(s), and it is anticipated that all participating patients will receive OTL38. However, some patients receiving OTL38 will be randomized to undergo lesion assessment under normal light only and will not undergo fluorescent imaging. The goal of the randomization is not the assignment of patients to a comparator group, but to guard against the

possible "under-calling" of lesions during the normal light assessment by creating the possibility that any patient, following evaluation by normal light, may not continue to assessment by fluorescent imaging. To achieve this safeguard, a blinded randomization of patients to undergo fluorescent imaging, or not, will occur after normal light assessment, but prior to fluorescent imaging or surgery. The randomization will be generated from a single centralized randomization.

[redacted]

Patients receiving OTL38 and randomized to not to undergo fluorescent imaging will be evaluated for safety only.

6 SAMPLE SIZE DETERMINATION

[redacted]

7 GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following is a list of general analysis and reporting conventions to be applied for this study.

- Baseline will be defined as the last recorded non-missing observation prior to exposure to study drug.
- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (xx.x)". Percentages will be based on the relevant total category count excluding missing data if not otherwise mentioned. To ensure completeness, where relevant, summaries for categorical and discrete variables will include all categories, even if no patients had a response in a particular category.
- Continuous variables will be summarized using mean, SD, minimum, maximum, median, and number of patients. The mean and median will be reported to one more level of precision than the original observations, and the SD will be reported to 2 more levels of precision than the original observations. The minimum and maximum will be the same precision as the original data.
- For tests of hypotheses, the associated p-value and confidence interval (CI) will be reported, where applicable. All p-values will be rounded to 3 decimal places; p-values that round to "0.000" will be presented as "<0.001".
- Dates will be displayed as ddmmmyyyy (e.g., 24Jan2005).
- Age (in years) will be calculated using the date of birth and the date of informed consent as (date of informed consent – date of birth) / 365.25.

8 ANALYSIS POPULATIONS

The following definitions will be used to derive the analysis sets for the study.

8.1 Full Analysis Set (FAS)

The FAS for the primary analysis of the primary endpoint will include patients exposed to OTL38 and randomized to undergo fluorescent imaging (OTL38+Imaging) who:

- Were evaluated under both normal light and fluorescent light imaging, and
- Had central pathology and histology confirmation for at least one FR+ Ovarian Cancer lesion detected under normal light or fluorescent light imaging

For the evaluation of the primary efficacy endpoint, only the evaluable lesions contributed by FAS subjects will be considered (see Section 8.4). The FAS will also be referred to as the modified Intent-to-Treat (mITT) analysis set.

8.2 Per Protocol Analysis Set (PPAS)

The per protocol analysis set will include all patients meeting the FAS criteria in addition to the following criteria:

- Meeting all the inclusion and none of the exclusion criteria
- Having no major protocol deviations
- [redacted]
- [redacted]

8.3 Safety Analysis Set (SAS)

The safety analysis set will include all patients exposed to OTL38.

8.4 Evaluable Lesions

Evaluable lesions are defined as follows: lesions that do not appear on an organ or tissue that was intended for removal regardless of the absence or presence of tumor based on the Pre-Fluorescence Surgical Plan.

The primary efficacy endpoint will be determined based on evaluable lesions for FAS subjects.

Unless otherwise specified, exploratory efficacy endpoints [redacted] sensitivities, FPRs, and PPVs for FR+ with ovarian cancer and other disease+/test+ configurations will be estimated using lesions without regard to evaluable lesion status.

Efficacy endpoints calculated without input from lesion data will be estimated without regard to evaluable lesion status.

8.5 Pharmacokinetic Analysis Set

All patients receiving a full dose of OTL038 and with one or more measurable drug-plasma concentrations will be included in the PK Analysis Set.

9 SUBJECT DISPOSITION AND PROTOCOL DEVIATIONS

9.1 Subject Disposition

Patient disposition will be summarized and include the following:

- The number of patients signing informed consent
- The number and percent of patients exposed to study drug
- The number and percent of patients randomized to each group
- The number and percent of patients who completed the study overall and by randomized group assignment

- The number and percent of patients who did not complete the study and the reason for early withdrawal overall and by randomized group assignment

Patients will be considered enrolled if they sign the informed consent (IC) and are exposed to study drug. Patients who signed the IC and receive study drug will serve as the denominator for the calculation of percentages. An exception will be the percentages calculated for early withdrawal reasons which will be based on the number of patients not completing the study. A data listing for all enrolled patients with regard to disposition will also be provided.

Patients who sign the IC but are not exposed to study drug will not be represented in any further analyses or line listings.

9.2 Protocol Deviations

All protocol deviations will be recorded on the protocol deviation case report from (eCRF) and will be reported in line listings. Major protocol deviations will be identified prior to database freeze for the final analysis of endpoints other than [redacted] (see Section 15; Interim Analyses and Data Monitoring). Major protocol deviations will be analyzed by aggregate summary and line listings. For aggregate summaries, data will be presented overall and by randomized group assignment and for each analysis population. If the number of major protocol deviations is small, aggregate summaries will not be presented.

10 SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Descriptive statistics for patient demographics and baseline disease status will be provided. Demographics will be grouped by patients exposed to OTL38, patients randomized to no fluorescent light imaging, and patients randomized to undergo fluorescent light imaging, and overall randomized groups. If all patients exposed to OTL38 are subsequently randomized, the separate category for patients exposed to OTL38 may be omitted. Demographic variables will include, but are not limited to: age, sex, and race/ethnicity.

Baseline characteristics will include, but are not limited to: medical history, ovarian cancer history, ovarian cancer type, ovarian cancer stage, height, weight, and body mass index (BMI). Summaries will be tabulated for the mITT (FAS) group and the Safety Analysis Set. Individual demographic and baseline characteristics data will also be presented in line listings.

11 MEASUREMENTS OF TREATMENT COMPLIANCE

Study drug is administered as a single infusion. The number of patients signing the IC but not receiving study drug will be presented in the disposition summary. For patients exposed to study drug, the dose received will be listed in the study drug administration line listing.

12 EFFICACY EVALUATIONS

12.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients with at least one evaluable FR+ ovarian cancer lesion confirmed by [redacted] pathology [redacted] that was detected using the combination of OTL38 and fluorescent light but not under normal light or palpation. [redacted]

12.2 Secondary Efficacy Endpoints

- False Positive Rate at the patient level (FPRp) will be a major secondary efficacy endpoint and is defined as the proportion of folate positive ovarian cancer patients in whom all lesions, without regard to evaluable lesion status, detected by fluorescent light only are histologically negative.
- Sensitivity or True Positive Rate (TPR) for OTL38 in combination with fluorescent light: [redacted]
- False Positive Rate (FPR) for OTL38 in combination with fluorescent light: For the purpose of this protocol, [redacted]

[redacted]

12.3 Exploratory Endpoints

[redacted]

12.4 Safety Endpoints

- Incidence rates of treatment-emergent AEs (TEAEs), SAEs, and Adverse Device Effects (ADEs), and changes in clinical laboratory values, vital signs, physical examination, concomitant medications and ECG through Visit 4.

12.5 Pharmacokinetic Endpoints

- Primary plasma pharmacokinetic (PK) parameters for OTL38, including systemic clearance (CL), volume of distribution of the central and peripheral compartments (V_c, V_p), and distributional clearance(s) (CL_d), on a population and individual patient level.
- Effects of patient specific covariates (e.g. baseline demographics and laboratory value indicators of renal and hepatic function) upon PK parameters, reported as coefficients demonstrating significance at the alpha level of 0.05.

13 STATISTICAL ANALYSIS METHODS FOR EFFICACY

The primary analysis of the primary efficacy endpoint will be conducted using the evaluable lesions for FAS subjects. Analyses of secondary and exploratory efficacy endpoints will use the FAS with additional, or modified, criteria as appropriate and as described in Section 8.4 and below. Baseline values are defined as the last non-missing value for a particular efficacy endpoint recorded prior to exposure to study drug. Unless otherwise noted, all p-values will be two-tailed and all confidence intervals two-sided.

13.1 Analytic Methods for the Primary Efficacy Endpoint

The primary analysis of the primary efficacy endpoint will be a one-sample test for a proportion via an exact binomial test conducted at the two-tailed alpha level of 0.05. [redacted]

13.1.1 Description of Subgroups to be Analyzed

Using the FAS, descriptive summary statistics for the primary efficacy endpoint will also be provided for the following subgroups:

- Age: < 70 Yrs. Vs. ≥ 70 Yrs.
- Race/Ethnicity
- Study Center
- Imaging System, if applicable
- [redacted]
- Stage of Cancer: 1 through 4
- Miliary vs. Non-Miliary Disease

For each subgroup, the point estimate and the exact 95% CI for the primary efficacy endpoint will be provided. These subgroup analyses will be conducted only if the subgroup sample sizes are large enough to provide meaningful summary statistics.

13.1.2 Sensitivity Analyses for the Primary Efficacy Endpoint

Sensitivity analyses for the primary efficacy endpoint will be conducted separately for the Per-Protocol analysis set. The analytic methods will follow those outlined for the primary analysis and include only evaluable lesions.

13.2 Analytic Methods for Secondary Efficacy Endpoints

The patient level False Positive Rate (FPR_p) will be analyzed descriptively, providing the point estimate and the two-sided 95% Wilson (score) confidence interval. The analysis will be conducted using the FAS. [redacted]

13.3 Analytic Methods for Exploratory Endpoints

13.3.1 Sensitivities, False Positive Rates, and Positive Predictive Values

Sensitivities, FPRs, PPVs, and the inoperability rate for FR+ with ovarian cancer and other disease+/test+ configurations will be estimated following similar analytic approaches to that outlined above for the secondary efficacy endpoints. The FAS will be used for these analyses, but will be modified for the lesion type requirement as appropriate, without regard to the evaluable status of the lesions.

13.3.2 Proportion of Subjects With at Least One Additional Lesion Detected by OTL38 and Fluorescent Light Not Detected by Normal Light – Various Lesion Types

For other endpoints reflecting the proportion of patients with at least one additional lesion detected by OTL38 in combination with fluorescent light not detected by normal light, but for other cell types and FR outcomes, the point estimates and exact 95% CIs for the observed proportions will be provided. The statistical methods will be similar to those outlined above for the primary efficacy endpoint, except no formal hypothesis testing will be conducted and only the point estimates and CIs will be provided. The FAS will be used for these analyses, but will be modified for the lesion type requirement as appropriate. Unless otherwise specified, only evaluable lesions will be analyzed.

13.3.3 Number of Additional Lesions Detected by OTL38 and Fluorescent Light Not Detected by Normal Light – Various Lesion Types

Other endpoints estimating the mean number of additional evaluable fluorescent light positive lesions (of a specific type) not detected by normal light, will be estimated via a [redacted] model along with 95% CIs. [redacted] The point estimate for the average number of additional lesions will be provided along with the 95% CIs.

The analyses described above include patients with zero additional lesions detected by fluorescent light not detected by normal light. Analyses will also be conducted excluding patients with zero additional lesions detected by fluorescent light. F[redacted]

13.3.4 Surgical Plan Changes

The proportion of patients in whom the Pre-Fluorescence Surgical Plan was changed based on fluorescent imaging, both prior to initiation of the surgical procedure and upon reimaging of the surgical field after the surgical procedure immediately prior to surgical closure, will be estimated along with 95% CIs.

13.3.5 Pharmacokinetics

The pharmacokinetics (PK) of OTL38 will be estimated by fitting compartmental pharmacokinetic models to the serial plasma concentration-time (Ct) data using established methods including maximum likelihood parameter estimation and nonlinear mixed-effects (NLME) modeling approaches, with the patient serving as the random effect. Various structural PK and error models will be fit to data using a qualified, standard software package. Primary PK parameters will be estimated at the population level and for individual patients as post-hoc empirical Bayesian estimates (EBEs). The actual primary parameters may vary depending on the supported model, but are likely to include systemic clearance (CL), volumes of distribution of the central and peripheral compartment(s) (V_c, V_p), distributional clearance (CL_d), or derivatives thereof. Inter-patient variability in select PK parameters will be assessed as part of the model, as will the residual error. Secondary parameters may include, but are not limited to: model predicted maximum concentration (C_{max}), time of C_{max} (T_{max}), area under the concentration-time curve (AUC) to the last time point (AUC_{last}) and to infinity (AUC_{inf}), and the terminal elimination half-life ($T_{1/2}$). The model predicted Ct profiles and observed Ct data will be presented as figures for the population and individual level. Individual primary EBE and secondary parameters will be presented as listings at the patient level.

Potential covariates explaining inter-subject PK variability, and their influence upon PK parameters, will be initially screened using a two-stage approach with standard parametric statistical tests on the individual patient EBEs, focusing on CL. Covariates of interest will include baseline demographic values (e.g. height, weight, age, BSA, BMI, race), and laboratory values predictive of renal or hepatic function (e.g. BUN, creatinine, calculated creatinine clearance or GFR, AST, ALT, alkaline phosphatase, albumin, and total bilirubin). If warranted, a single stage approach with direct incorporation of covariates into the NLME PK model may be undertaken using a forward addition - backward deletion method at an alpha level of 0.05.

The final model PK parameter estimates, and any bootstrapped results, will be reported as a table, including the estimates, their standard errors, or confidence intervals. The covariate coefficient estimates, their standard errors, and the associated P values for those significant at the alpha level of 0.05 will be tabulated. Relationships between covariates and PK parameters will be graphically presented as figures. Additional details will be found in the pharmacokinetics analysis plan (PKAP).

13.3.6 [redacted]

Descriptive summary statistics for [redacted] pre-surgery (baseline), post-surgery, and the change from pre-surgery will be calculated along with the percent change. In addition, the number

and percent of patients whose post-surgery [redacted] have increased, decreased, or remained the same as pre-surgery [redacted] will also be provided. This analysis will use all patients with non-missing [redacted]

13.4 Handling of Missing Data and Subject Withdrawals

For the primary efficacy endpoint, all patients included in the FAS with at least one evaluable lesion will be included in the primary analysis.

For secondary and exploratory efficacy endpoints, patient inclusion for the analysis of a specific endpoint will depend on the lesion type or patient subgroup under specific consideration.

In general, missing safety data will not be imputed with the possible exception of missing or partial dates for adverse events and concomitant medication.

14 SAFETY EVALUATIONS

14.1 Overview of Safety Analysis Methods

Safety will be evaluated using the safety analysis set and will include treatment emergent adverse events (TEAEs), adverse device effects (ADEs), serious adverse events (SAEs), vital signs, physical examinations, clinical laboratory measurements, electrocardiograms, and concomitant medications. For all safety assessments, the baseline value will be the last non-missing value recorded for a particular safety parameter before exposure to study drug. In general, the analysis of safety will be descriptive. No data will be imputed except for partial dates if required to determine if an adverse event is treatment emergent or a medication concomitant with exposure to study drug.

14.1.1 Imputation of Partial Adverse Event Dates

If only a partial date is available and is required for a calculation, the following imputation algorithm will be applied for missing or partial dates related to Adverse Events and concomitant medications:

- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]

[redacted]

14.2 Extent of Exposure

Study drug will be administered as a single infusion. A summary of the number of patients exposed to study drug and any patients not receiving their full dose will be described. Start and stop times with respect to exposure to florescent light imaging will also be tabulated. More detailed study drug administration as well as camera start and stop times will be provided in line listings.

14.3 Adverse Events

Adverse events occurring prior to exposure to OTL38 administration will be provided in line listings. Treatment emergent adverse events (TEAEs) will be summarized via the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term using patient incidence rates. Data will be tabulated by severity, physician assessment of relationship to study drug, serious TEAEs, and TEAEs leading to death or early study withdrawal. Further description of TEAEs may be defined by temporal onset to study drug infusion. Additional summaries of TEAEs identified as potential ADEs will also be provided.

Treatment-emergent AEs will be summarized for all patients in the safety analysis set. Summary tables will reflect the number and percent of patients experiencing at least 1 TEAE in each system organ class and preferred term. The overall number and percent of patients experiencing any treatment-emergent AE will also be provided. All percentages will use the number of patients in the safety analysis set as the denominator. An exception will be the presentation of ADEs which will use all patients undergoing fluorescent light imaging as the denominator. If a patient has more than one AE within a system organ class, the patient will be counted only once in that system organ class. If a patient has more than 1 AE that codes to the same preferred term, the patient will be counted only once for that preferred term. The tabular summary will be sorted by descending order of overall incidence.

Treatment-emergent AEs will also be summarized by the maximum relationship to study drug as determined by the Principal Investigator as well as the maximum severity of the event. Relationship to drug will be scored as Definite, Probable, Possible, or Not Related. Related AEs will be classified as those scored as Definite, Probable, and Possible. Severity will be rated as Mild, Moderate, or Severe. If a patient experiences more than 1 AE within system organ class or preferred term, that patient will be counted only once for that event under the maximum severity or most related category within the relevant category. In the event that the relationship to study drug or the severity of the event is missing, for tabulation purposes the maximum relationship or severity will be assumed.

Incidence of TEAEs will also by summarized by age group, race, and gender if there is sufficient numbers of patients within these subgroups. Otherwise only line listings will be provided.

All AEs will be presented in data listings for safety patients. If required, the line listings will distinguish between adverse events occurring prior to exposure to study drug and TEAEs. If a partial date was imputed, the line listings will include both the observed and imputed date. Imputations for missing relationships and severities of AEs will not be included in the line listings.

14.4 Deaths, Serious Adverse Events and Adverse Events of Special Interest

Treatment-emergent serious AEs (SAEs), TEAEs leading to early study withdrawal, and TEAEs resulting in death will be summarized for all patients in the safety analysis set. Summary tables will reflect the number and percentage of patients experiencing at least 1 TEAE in each system organ class and preferred term within each AE subset (serious, leading to early study withdrawal, or death). In addition, the number of patients experiencing any TEAE in the respective subset will be reported. The tabular summary will be sorted by descending order of overall incidence.

Adverse events leading to early study withdrawal, AEs resulting in death, and SAEs will also be presented in data listings. Treatment-emergent AEs of special interest are those classified as infusion reactions which will be separately tabulated, or listed separately if numbers are not sufficient for meaningful summary statistics.

14.5 Clinical Laboratory Evaluations

The analysis of laboratory parameters will include descriptive statistics for the change from baseline to each post-baseline study visit as well as shifts from baseline to each post-baseline study visit for categorical lab parameters. In addition, shift tables (i.e., low-normal-high at baseline versus low-normal-high at last visit will be provided. Urinalysis and pregnancy results will not be summarized but will be provided in a data listing. For all relevant laboratory data, values above or below normal limits will be flagged along with the direction of abnormality in line listings.

14.6 Vital Signs, Physical Exams and ECGs

The analysis of vital signs will include descriptive statistics for the change from baseline to each post-baseline study visit. Vital signs will also be included in line listings and flagged for abnormal values. Results for physical exams and ECGs will be provided in line listings only.

14.7 Pathology and Immunohistochemistry

Pathology and immunohistochemistry results will be included in line listings only.

14.8 Imaging System

Times on and off for the imaging system will be included in the line listings for each patient. Aggregate mean "on" times may also be tabulated.

14.9 Prior and Concomitant Medications

The prior and concomitant medications will be coded to identify the drug class and preferred drug name. Concomitant medications will include all medications that started, or were continuing, during or after administration of the study drug. Prior medications will include all recorded medications that started and stopped prior to administration of the study drug.

The number and percent of patients using concomitant medications will be tabulated by drug class and preferred drug name for all patients in the safety analysis set. If a patient has more than one medication within a drug class, the patient will be counted only once in that drug class. If a patient has more than one medication that codes to the same preferred drug name, the patient will be counted only once for that preferred drug name. All percentages will use the number of patients in the safety analysis set as the denominator. The tabular summary will be sorted by descending order of overall incidence for concomitant medications only. Prior medications will be presented in line listings only. Concomitant medications will also be provided in line listings.

15 INTERIM ANALYSES AND DATA MONITORING

There are no planned interim analyses. Safety data will be continuously monitored by a Medical Monitor.

16 CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL OR STATISTICAL ANALYSIS PLAN

Any changes to the planned analyses outlined in the protocol and/or SAP not already documented via amendment prior to undertaking any analyses will be described in the CSR.

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