PrE0505 Statistical Analysis Plan (SAP)

Open Label, Phase II Study of Anti - Programmed Death – Ligand 1 Antibody, Durvalumab (MEDI4736), in Combination with Chemotherapy for the First-Line Treatment of Unresectable Mesothelioma

NCT #:	NCT02899195
Version Number:	1.0
Version Date:	May 23, 2018

Statistical Analysis Plan	
Study code	PrE0505
Version	Final V1.0
Date	23 May 2018

Open Label, Phase II Study of Anti - Programmed Death – Ligand 1 Antibody, Durvalumab (MEDI4736), in Combination with Chemotherapy for the First-Line Treatment of Unresectable Mesothelioma

DOCUMENT:	Statistical Analysis Plan
PROTOCOL	
Number:	PrE0505
Title:	Open Label, Phase II Study of Anti - Programmed Death – Ligand 1 Antibody, Durvalumab (MEDI4736), in Combination with Chemotherapy for the First-Line Treatment of Unresectable Mesothelioma
Version Date	March 19, 2018, Version 5.0
SAP STATUS	Final 1.0
SAP VERSION DATE	23 May 2018
SPONSOR:	PrECOG
PREPARED BY:	[redacted] Statistician Quality Data Services, Inc.

SIGNATURES/APPROVAL PAGE

AUTHORS

[redacted] 7/17/2018
Date

Statistician
Quality Data Services, Inc.

[redacted] Date

Sr. Statistician
Quality Data Services, Inc.

APPROVERS

[redacted] 5/24/18.
Date

Statistician
PrECOG

Carolyn Andrews RN 24 May 2018
Project Manager Date
PrECOG

SIGNATURES/APPROVAL PAGE

AUTHORS

[redacted]
Statistician
Quality Data Services, Inc.

Date

[redacted]
Sr. Statistician
Quality Data Services, Inc.

5/23/18
Date

APPROVERS

[redacted]
Statistician
PrECOG

5/24/18
Date

Carolyn Anderson RN
Project Manager
PrECOG

24 May 2018
Date

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE(s)	Adverse event(s)
ATC	Anatomical Therapeutic Chemical
BP	Blood pressure
CR	Complete response
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CT	computed tomography
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full analysis set
ICF	Informed consent form
ICH	International Conference on Harmonization
irAE	Immune-related adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
PFS	Progression free survival
PR	Partial response
PD	Progressive disease
PFS	Progression-free survival
QDS	Quality Data Services, Inc.
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation or special term	Explanation
SD	Stable Disease
STD	Standard deviation
TEAE	Treatment Emergent Adverse Event
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

2. INTRODUCTION

2.1. Objective of the Statistical Analysis Plan

This statistical analysis plan (SAP) describes the planned analysis of the safety and efficacy data from the study. A detailed description of the planned tables, figures and listings (TFLs) to be presented in the analysis is provided in the accompanying TFL template document.

The intent of this document is to provide guidance for the analysis of data related to safety and efficacy to describe any applicable statistical procedures. In general, the analyses come directly from the protocol, unless they have been modified by agreement between the Sponsor and Quality Data Services, Inc. (QDS). A limited amount of information concerning this study (e.g., objectives, study design) is summarized to help the reader interpret the accompanying TFL templates. That information is not a synopsis of the study and does not require review or approval because it is simply extracted from the protocol. Attached signatures indicate approval of the statistical analysis sections of the SAP, as well as accompanying TFL templates. These sections must be agreed upon prior to database lock. When the SAP and TFL templates are agreed upon and finalized, they will serve as the template for a portion of this study's report.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the report. Any substantial deviations from this SAP will be agreed upon between the sponsor and QDS. Deviations from this SAP, both substantial and non-substantial, will be documented in the report. Any updates to their respective analyses, study designs, and TFL presentations after this SAP is finalized and approved will be documented in a running Note to the SAP document.

Various outputs may be required during the conduct of this trial which will necessitate the production of some but not all of the Figures, Summary Tables and Key Data Tabulations detailed in this document. The SAP will not be updated to reflect these potential changes.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this phase II study is to demonstrate improved overall survival (OS) compared to a historic control with the addition of concurrent and maintenance durvalumab to standard chemotherapy for unresectable pleural mesothelioma.

3.2. Secondary Objectives

The secondary objectives of this study are:

1) To evaluate the safety and tolerability of durvalumab and durvalumab in combination with chemotherapy in subjects with malignant pleural mesothelioma.

2) Percentage of patients progression-free at 24 weeks from the time of registration. Disease status at 24 weeks will be compared to disease status at the time of registration, and response coded based on modified RECIST 1.1 criteria.

3) Progression-free survival (PFS) will be measured from the time of study registration until radiologic progression, clinical progression or death.

4) Best Objective Response Rate (ORR) evaluation will continue up to 1 year on therapy and response will be coded based on modified RECIST Version 1.1 criteria for mesothelioma.

3.3. Exploratory Objectives

The exploratory objectives of this study are to study laboratory measurements that may correlate to response:

1) Assessment of tumor baseline PD-L1 expression may be performed.

2) Assessment of the genomic and neoantigen landscape of baseline tumors may be performed.

3) Assessment of dynamics of circulating cell free tumor DNA (ctDNA) may be performed.

4) Serial assessment of soluble biomarkers may be performed.

4. STUDY DESIGN

4.1. Overview

This is a single arm, unblinded, open-label phase 2 study of durvalumab administered concurrently with pemetrexed/cisplatin chemotherapy as first-line treatment for unresectable pleural mesothelioma. The first 6 patients enrolled will be monitored for safety of the combination. The combination will be declared intolerable if ≥ 2 of the 6 patients experience a dose limiting toxicity event occurring during the first 2 cycles of concurrent therapy phase, and the study will be stopped. Otherwise, the study will proceed with enrollment for a maximum of 55 patients (including the initial 6 patients) to receive up to 6 three-week cycles of concurrent durvalumab with chemotherapy. Patients with responding or stable disease after six cycles of concurrent treatment will continue on durvalumab as a single agent administered once every 3 weeks. Maximum duration of durvalumab treatment is 12 months (inclusive of any treatment delays or missed treatments) starting from Cycle 1 of concurrent treatment.

All subjects will be evaluated regularly and their clinical status classified according to RECIST guidelines Version 1.1 with modifications for pleural mesothelioma. Beginning with Cycle 1, radiographic response will be assessed with imaging every 6 weeks until completion of concurrent phase of treatment. Subjects will continue to receive treatment until disease progression or other discontinuation criteria are met.

Following documentation of non-fatal confirmed disease progression, all subjects will be followed for survival every 3 months until death or the close of the study.

4.2. Patient Registration

Patients must not start protocol treatment prior to registration.

Patients must meet all of the eligibility requirements prior to registration. Treatment should begin ≤ 10 working days from study entry (date of registration).
Upon determination that a subject meets eligibility criteria, the subject will be registered in the study by site personnel via an electronic data capture (eDC) system. Confirmation of registration will be displayed in the eDC system.
Mandatory tumor tissue samples are required to be available for enrollment. Mandatory peripheral blood samples will also be collected at protocol specified time points.

4.3. Dose Limiting Toxicity

DLT will be evaluated for the first 2 cycles (2 doses, 42 days) of concurrent therapy with durvalumab, pemetrexed and cisplatin. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The following will be DLTs:
• Any Grade 4 immune-related adverse event (irAE)
• Any ≥ Grade 3 colitis
• Any Grade 3 or 4 non-infectious pneumonitis irrespective of duration
• Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
• Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
• Liver transaminase elevation >8x ULN or total bilirubin >5x ULN

DLTs occurring beyond the first 2 cycles window will be taken into account when determining whether to proceed to enroll the full planned cohort of 55.

4.4. Duration of Therapy

Patients will receive protocol therapy unless:

- Disease progression per modified RECIST Version.1.1 guidelines or clinical progression.
- Toxicities considered unacceptable by either the patient or the investigator, despite optimal supportive care and dose modifications.
- Development of an inter-current illness that prevents further administration of study treatment.
- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued.
- Patient withdraws consent or is unable to comply with study procedures.

4.5. Duration of Follow-Up

Patients will be followed for adverse events for 90 days after their last dose of durvalumab or until initiation of alternative anticancer therapy.
If a patient is removed from treatment for reason(s) other than progression, follow with regular tumor assessments per standard of care until progression or start of new treatment.
Following documentation of non-fatal confirmed disease progression, all subjects will be followed for survival every 3 months until death or the close of the study.

4.6. Criteria for Removal from Study

A genuine effort will be made to determine the reason(s) why a patient fails to return for the necessary visits or is discontinued from the trial, should this occur. It will be documented whether or not each patient completed the clinical study. If for any patient study treatment or observations were discontinued, the reason will be recorded.
Any patient who receives at least one dose of study drug, durvalumab, will be included in the safety analysis. Patients who discontinue study treatment early should be followed for response assessments, if possible.

5. MEASUREMENT OF EFFECT

5.1. Solid Tumor Response Criteria (RECIST 1.1)

5.1.1. Malignant Disease Evaluation

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline Version 1.1 with modifications for pleural mesothelioma.

To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least one measurable lesion.

All measurements should be recorded in metric notation by use of a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified lesion at baseline and during follow-up. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.

The term evaluable in reference to measurability will not be used because it does not provide additional meaning or accuracy.

At baseline, tumor lesions will be characterized as either measurable or non-measurable.

5.1.1.1. Measurable

Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of:
• ≥ 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
• ≥ 10 mm caliper measurement by clinical exam (when superficial)
• ≥ 20 mm by chest x-ray (if clearly defined and surrounded by aerated lung)

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

5.1.1.2. Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis (perpendicular to longest diameter) when assessed by CT scan.

5.1.1.3. Non-Measurable

All other lesions (or sites of disease), including small lesions not meeting the criteria in 5.1.1.1 and 5.1.1.2, are considered non-measurable lesions. This includes lymph nodes measured at ≥ 10 to <15 mm in the short axis. Lymph nodes measured at <10 mm in the short axis are considered normal.

Lesions considered to be non-measurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Tumor lesions that are situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

5.1.2. Definitions of Response

5.1.2.1. Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs are identified as target lesions. Target lesions should be selected on the basis of their size (those with the longest diameters), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

The sum of the target lesions (longest diameter for non-nodal lesions, short axis for nodal lesions) will be calculated and reported as the baseline sum. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters/axes will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Complete Response (CR)

The disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be “0” if there are target nodes). To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed ≥ 4 weeks after the criteria for response are first met.

Partial Response (PR)

At least a 30% decrease in the sum of the diameters/axes of target lesions, taking as reference the baseline sum diameters/axes. To be assigned a status of partial response, changes in tumor measurements must be confirmed by repeat assessments performed ≥ 4 weeks after the criteria for response is met.

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters/axes of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm over the nadir. The appearance of one or more new lesions is also considered progression.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters/axes while on study. A change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease.

5.1.2.2. Non-Target Lesions

All other lesions or sites of disease including any measurable lesions over and above the 5 target lesions and lymph nodes measured at ≥ 10 to <15 mm in the short axis should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of unequivocal progression of each should be noted throughout follow-up.

Complete Response (CR)

The disappearance of all non-target lesions and normalization of tumor marker levels, if applicable. All lymph nodes must be non-pathological in size (<10 mm short axis). To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed ≥ 4 weeks after the criteria for response are first met.

Non-CR/Non-PD

The persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker levels above the normal limits. To be assigned a status of Non-CR/Non-PD, measurements must have met the Non-CR/Non-PD criteria at least once after study entry at a minimum interval of ≥ 4 weeks.

Progressive Disease (PD)

The appearance of one or more new lesion(s) and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion

status. It must be representative of overall disease status change, not a single lesion increase.

5.1.3. Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

5.1.4. Symptomatic Deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

5.2. Evaluation of Patient's Best Overall Response

The best overall response is the best response recorded from the start of the treatment until confirmed disease progression or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Overall Response for all Possible Combinations of Tumor Response				
Target Lesions	Non-Target Lesions	New Lesion	Overall Response	Remarks
CR	CR	No	CR	Confirmation at ≥ 4 weeks
CR	Non-CR/Non-PD	No	PR	Confirmation at ≥ 4 weeks
CR	Not Evaluated	No	PR	Confirmation at ≥ 4 weeks
PR	Non-PD/Not Evaluated	No	PR	Confirmation at ≥ 4 weeks
SD	Non-PD/Not Evaluated	No	SD	Documented at least once ≥ 4 weeks from study entry
Not All Evaluated	Non-PD	No	Not Evaluable	
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed ≥ 4 weeks after the criteria for response are first met.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of ≥ 4 weeks.

5.3. Frequancy of Evaluation

Response assessments will be performed every 6 weeks (2 doses of treatment) for the first 18 weeks. After 18 weeks of treatment, response assessments will be performed every 9 weeks (3 doses of treatment).

Following documentation of non-fatal confirmed disease progression, all subjects will be followed for survival (either routine clinic visit or telephone contact) every 3 months until death or the closure of the study.

6. STATISTICAL CONSIDERATIONS

This study will initially enroll 6 patients to monitor for safety and tolerability of the combination of durvalumab with pemetrexed/cisplatin (or carboplatin). The study will proceed to the expansion phase to enroll a total of 55 patients (including the first 6 patients) if <2 patients among the first 6 patients enrolled experience a DLT during the first 2 cycles of concurrent therapy.

The statistical analysis described in this section applies only if the study proceeds to the expansion phase.

6.1. Sample Size Considerations

The primary comparison is for overall survival and will include all eligible patients who started protocol treatment, of whom 50 will be accrued. After inflating for an ineligibility rate of 10%, the total planned accrual is 55 patients. Based on the randomized phase III trial conducted by Vogelzang in this setting, it is assumed that the null hypothesis is that the median overall survival (OS) time is 12 months with pemetrexed/cisplatin alone. Using a one-sided 0.10 level test, a sample size of 50 will achieve 90% power to detect a 37% reduction in the OS hazard rate of 0.058 to 0.037 (with an accrual period of 24 months for the 50 patients in the primary analysis, and an additional 18 months for treatment and follow-up); assuming exponential survival, this corresponds to a 58% improvement in the median OS of 12 months to 19 months. The number of OS events needed to achieve this power is 32 events.

6.2. General Methodology

Continuous data will be summarized with the following descriptive statistics: number of observations (n), mean, standard deviation (STD), median, minimum (min), and maximum (max). Categorical data will be summarized with frequencies and percentages.

Kaplan-Meier method will be used to analyze time-to-event variables. Cox proportional hazards models will be used to estimate the hazard ratios between subgroups.

Baseline is defined as the last non-missing measurement prior to the first dose of study treatment.

The last record will be used for analysis if there are multiple records for a visit/time point.

Statistical analysis and programming of tables, listings and figures will be conducted by QDS, using SAS® Release 9.4 or a later version (SAS Institute Inc., Cary, North Carolina, USA).

6.3. Handling of Dropouts or Missing Data

All attempts will be made to prevent any missing values. Missing or invalid data will be treated as missing, not imputed.

No data imputation will be done for missing data except for adverse events (AEs) with missing onset date. If the AE onset date is completely missing, then the date of first study therapy will be used for classification of AEs that were experienced following administration of study therapy.

6.4. Interim Analyses and Data Monitoring

There is no formal interim safety analysis planned for this study. A toxicity assessment is planned when safety data are collected for the first 15 patients when they complete the first two cycles of concurrent therapy without suspension to accrual. The safety monitoring will be done based on the electronic case report form (eCRF) database. Accrual will be suspended for further review of non-hematologic toxicity if at least 5 Grade 4/5 non-hematologic events among the first 15 patients are observed.

6.5. Endpoints

6.5.1. Primary Endpoint

The primary endpoint is overall survival (OS), defined as the time from registration to death from any cause. Patients that have not had an event reported at time of analysis will be censored at their date of last follow-up.

6.5.2. Secondary Endpoints

- Progression-free survival (PFS), defined as the time from registration to documented disease progression or death from any cause, whichever occurs first. Patients who have not experienced an event of interest by the time of analysis will be censored at the date they are last known to be alive and progression-free.
- Progression-free survival (PFS) at 24 weeks from the time of registration.
- Best objective response rate (ORR)
- Dose limiting toxicity events and adverse events of the treatment regimen

6.6. Analysis Populations

6.6.1. Full Analysis Set (FAS)

The Full Analysis Set is defined as all eligible patients who started study therapy. Primary and secondary endpoints analyses will be conducted for the FAS population.

6.6.2. Safety population

Safety population is defined as all patients who received at least one dose of study therapy. Safety analysis will be conducted for the safety population.

6.7. Subgroup Analysis

Subset analyses are planned for known prognostic factors such as performance status, age, gender, etc. Subset analyses of all variables, including correlatives, are considered to be exploratory in nature.

6.8. Analysis Methods

6.8.1. Analysis of Primary Endpoint

The primary test for Overall survival (OS) is based on Wald test for the log failure rate parameter and test at a one-side type I error rate of 10% by using Cox proportional hazards model.

Logrank test and Cox proportional hazards modeling will be used to assess the effect of gender, baseline ECOG PS, and age on overall survival for full analysis set. OS survival curve will be plotted.

Point estimates and 95% confidence interval will be presented for median survival time and hazard ratio.

6.8.2. Analysis of Secondary Endpoints

Analysis of progression free survival (PFS) will be performed in a similar way as for OS, without the comparison with historical control patients.

Percentage of progression free patients at 24 weeks from registration, best objective response rate (ORR) will be summarized for the FAS population. Point estimate of proportion and its 95% exact binomial confidence interval for each response category will be presented.

Adverse events severity will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE V4.03). Analysis of AEs will be on treatment-emergent AEs (TEAEs), those occur or worsening after administration of the first study dose, for the safety population. In the case where the start date of the AE is unknown, it will be assumed to be treatment-emergent.

Treatment-emergent AEs (TEAEs) will be summarized by system-organ-class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®). The frequency of subjects who experience TEAEs will be summarized along with 95% exact binomial confidence interval for the proportion. Subjects having the same AE more than once will be counted once at maximum intensity for each preferred term and once within each system organ class. The summary AE tables will display the number of subjects with treatment-emergent AEs by maximum intensity (CTCAE grading).

Additional treatment-emergent AEs by strongest relationship to Durvalumab will be presented by system organ class and preferred term.

6.8.3. Analysis of Other Study Parameters

6.8.3.1. Subject Accountability and Subject Disposition

The number of subjects enrolled, completing the study, with protocol deviation, and study discontinuation will be tabulated. Protocol deviations will be categorized by deviation classification, and study discontinuation will be categorized by reason for discontinuation. Number of subjects in full analysis set will also be summarized.

6.8.3.2. Demographics and Baseline Characteristics

Demographic data (e.g age, sex, race, etc.) and disease characteristics will be summarized descriptively for FAS population.

6.8.3.3. Concomitant Medications

The use of concomitant medications will be recorded and coded to a World Health Organization Drug Dictionary (WHO- DD) term.

The use of concomitant medications will be summarized. The number and percentage of subjects taking each medication will be presented by ATC Classification.

6.8.3.4. Lesion Assessments

Lesion assessments (target lesions, non-target lesions) are used for tumor overall response at each assessment (Protocol Table 9-1). The target response, non-target response and overall response are collected in CRF page after every 2 doses treatment at first 18 weeks. After 18 weeks the response assessments are collected after every 3 doses treatment.

6.8.3.5. Response Assessment

Disease response assessment (target, non-target, overall, and best overall response) will be described using descriptive statistics by visit.

6.8.3.6. Treatment Cycles and Follow-up Duration

Number of cycles of treatment patients received will be summarized descriptively. Follow-up durations from time of registration to time of last patient contact will be calculated as last contact date – registration date +1, and be summarized descriptively.

6.8.3.7. Clinical Laboratory Data

Clinical laboratory data includes hematology, chemistry, coagulation and urinalysis. Numeric laboratory tests at baseline will be summarized using descriptive statistics

Clinically significant worsening from baseline or new clinically significant laboratory test abnormalities that were considered AEs by the investigator will be presented in the AE analyses.

7. SUMMARY OF CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

No changes are planned.

8. REPORTING CONVENTIONS

The mean and median will be displayed to one decimal place greater than the original value and the standard deviation will be displayed to two decimal places greater than the original value. All statistical programming and analyses will be performed using SAS® Release 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

The following standards will be used in the data presentation:

- Section 10 tables should be in landscape format. Output should adhere to US / International Conference on Harmonization (ICH) margins and should not require changes for European page size. For item 10 tables, a blank row will separate the header from the content of the table listing. For tables that have "n (%)", the placement should be centered below "N=xx" in the column header. Frequency tables will be center justified. Descriptive statistics will be decimal aligned.

- Percentages presented in in-text tables should be rounded to one decimal using the SAS rounding function. If "%" is part of the column heading, do not repeat the "%" sign in the body of the table. Unless specified otherwise, "%" should reflect the total population of the treatment groups. Any deviation from that should be part of the footnote. For 0 counts, leave the corresponding percentage blank.

- The format for minimum and maximum should be "Min, Max". STD should be the default for representing scale, unless standard error has been specified. Standard deviation should be abbreviated as "STD", and presented next to the mean value, without any +/- sign. The STD should have one additional decimal place beyond that of the mean (e.g. mean has one decimal place, STD should have two).

- "N" will represent the entire treatment group for the population group being analyzed, while "n" will represent a subset of the treatment group. For tables with population designated as a row heading, "N" should be used (i.e. tables where all participant data is not available for every variable within a treatment group). As a guideline, if the number is used in a denominator it should be presented as "N". If the number is used in the numerator, it should be presented as an "n".

- The heading should consist of four lines. Line 1: Sponsor identifier. Line 2: Protocol identifier. Line 3: blank line. Line 4: Table/Appendix number Table Title – Population. The title for in-text tables should begin with the Table/Appendix number.

- The date format for all dates is DDMMMYYYY.

A solid line should appear both above and below the column headings of a table. A solid line should appear at the end of the table or at the bottom of each page if the table extends to more than one page. Footnotes should start after the bottom solid line.

9. REFERENCES

References are provided in the protocol.

10. TABLES, FIGURES, AND LISTINGS

See separate template document.

DOCUMENT HISTORY

Version Date	Modified By	Summary of Changes
Draft 03April2018	[redacted]	Removed comparison column in primary efficacy tqable
Draft 18April2018	[redacted]	Removed following tables and listing: Listing 16.2.2.1 Failed Inclusion Criteria Listing 16.2.2.2 Protocol Deviations Table 14.2.1.1 Summary of Lesion Assessments– Full Analysis Set Table 14.3.2.3 Summary of Coagulation Results at Baseline - Full Analysis set Table 14.3.2.4 Summary of Numerical Urinalysis Results at Baseline - Full Analysis set
Final 23May2018	[redacted]	Reviewed and approved by [redacted], PhD and PrECOG