STATISTICAL ANALYSIS PLAN

Study Protocol Number:	MORAb-003-011
Study Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Efficacy and Safety of Farletuzumab (MORAb-003) in Combination with Carboplatin plus Paclitaxel or Carboplatin plus Pegylated Liposomal Doxorubicin (PLD) in Subjects with Low CA125 Platinum-Sensitive Ovarian Cancer
Date:	31-OCT-2019
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Revision History

Date	Version number	High-level Summary of Changes (Section/Change)
31-OCT-2019	V1.0	Original statistical analysis plan

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LIST OF FIGURES

2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
ADA	(Human) Anti-Drug Antibody
AE	Adverse Event
AEI	Adverse Event of Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC4	Anatomical Therapeutic Chemical (Classification)
BSA	Body Surface Area
CA125	Cancer Antigen 125
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CRF	Case Report Form
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DHAE	Drug Hypersensitivity Adverse Event
DMC	Data Monitoring Committee
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
HR	Hazards Ratio
kg	Kilogram
KM	Kaplan-Meier
IgG	Immunoglobulin Isotype G
ILD	Interstitial Lung Disease
IRT	Interactive Response Technology (web or voice randomization system)
LLN	Lower Limit of Normal
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
Min	Minimum
MRI	Magnetic Resonance Imaging
ORR	Objective Response Rate

OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PH	Proportional Hazards
PK	Pharmacokinetic
PLD	Pegylated Liposomal Doxorubicin
PR	Partial Response
PT	(MedDRA) Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SMQ	Standardized Medical Dictionary for Regulatory Affairs Query
SOC	(MedDRA) System Organ Class
TEAE	Treatment-Emergent Adverse Event
TRAE	Treatment-Related Adverse Event
TTR	Time to Response
ULN	Upper Limit of Normal
WHO DD	World Health Organization Drug Dictionary

3 INTRODUCTION

The purpose of the statistical analysis plan (SAP) is to document and describe the statistical analyses planned for the protocol MORAb-003-011 titled "A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Efficacy and Safety of Farletuzumab (MORAb-003) in Combination with Carboplatin plus Paclitaxel or Carboplatin plus Pegylated Liposomal Doxorubicin (PLD) in Subjects with Low Cancer Antigen 125 (CA125) Platinum-Sensitive Ovarian Cancer." This SAP corresponds to version 4.0, amendment 3.0, of the study protocol dated 06 November 2018.

Any deviations between this SAP and the statistical methods and analyses applied to data collected during the study will be described in the final clinical study report.

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of the study is to demonstrate that farletuzumab has superior efficacy compared with placebo in improving Progression-Free Survival (PFS), as determined by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1, when added to the standard chemotherapy regimens of carboplatin plus paclitaxel or carboplatin plus PLD, in subjects with platinum-sensitive ovarian cancer in first relapse who have a CA125 ≤ 3x Upper Limit of Normal (ULN) (105 U/mL) at study entry.

3.1.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the effect of farletuzumab on Overall Survival (OS) in this population (key secondary endpoint)
- To assess the effect of farletuzumab in prolonging second platinum-free interval longer than first platinum-free interval
- To assess the effect of farletuzumab on best Objective Response Rate (ORR), Time to Response (TTR), and Duration of Response (DOR) by RECIST 1.1 criteria
- To assess the safety and tolerability of farletuzumab
- To assess the Pharmacokinetics (PK) and exposure-response relationships between farletuzumab and PFS and OS

3.1.3 Exploratory Objectives

The exploratory objectives of the study are:

- To explore blood/serum CA125 levels and evaluate changes during study
- To explore biomarkers that may correlate with the efficacy-related endpoints and farletuzumab mechanism of action

- To explore expression of CA125 and folate receptor alpha in blood, urine, and tissue to correlate to disease characteristics, exposure, efficacy-related endpoints, farletuzumab mechanism of action, and other biomarkers

3.2 Overall Study Design and Plan

This is a global, multicenter, double-blind, randomized placebo-controlled study in subjects with platinum-sensitive ovarian cancer in first relapse that have low serum CA125 levels (≤ 3xULN, or 105 U/mL).

The study is being conducted in approximately 210 subjects enrolled into 1 of 2 chemotherapy treatment arms at the investigator's discretion: either carboplatin (AUC 5) plus paclitaxel (175 mg/m^2 IV every 3 weeks) or carboplatin (AUC 5) plus PLD (30 mg/m^2 IV every 4 weeks). Subjects will then be randomized in a 2:1 ratio to receive farletuzumab or placebo. All subjects will receive a loading dose for the first 2 weeks of 10 mg/kg farletuzumab (or matching placebo), followed by 5 mg/kg weekly. Subjects will be stratified at randomization by individual chemotherapy treatment regimen and platinum-free interval following first-line therapy (6-12 months versus >12-36 months).

All subjects will have serum CA125 ≤ 3xULN (105 U/mL) confirmed for study entry at Screening using a central laboratory designated by the sponsor to assure the use of a standardized assay (Architect CA 125 II assay). An archival tumor tissue sample taken at the time of initial diagnosis of ovarian cancer will be provided at Screening for analysis. In addition, blood and urine samples will be collected at time points throughout the study for other supporting exploratory analyses.

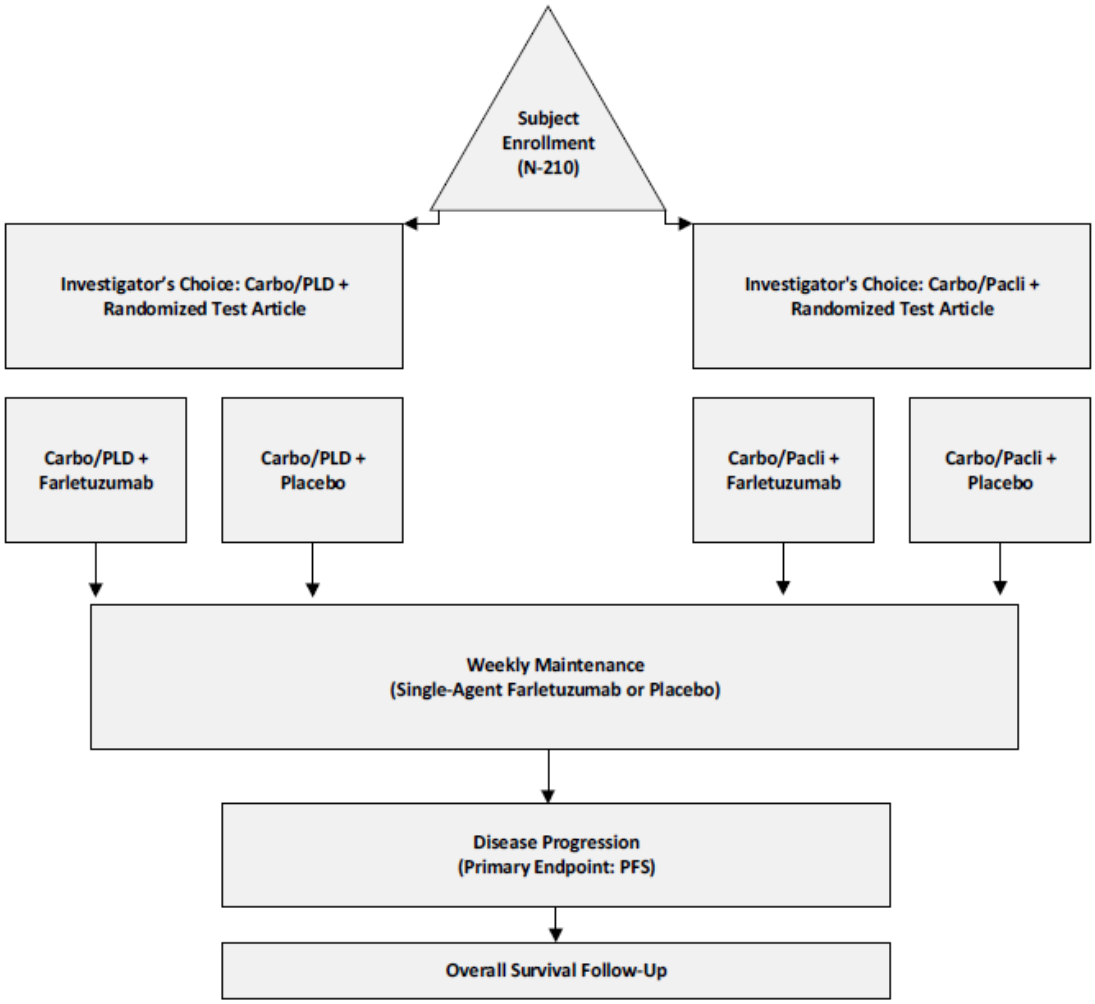
An independent, unblinded Data Monitoring Committee (DMC) will be utilized to monitor the safety profile of the study and to enhance safety oversight. The first DMC review of safety data will occur when the 15th subject completes Cycle 1 of the Combination Treatment Phase to assure that the tolerability of the modified farletuzumab dosing and chemotherapy combinations are acceptable.

The study will consist of 4 phases: Screening, Combination Treatment, Maintenance, and Follow-up. At the end of the Combination Treatment Phase, subjects who have not experienced disease progression will enter the Maintenance Phase until disease progression.

For this study, either farletuzumab or placebo is considered Test Article. Subjects who discontinue Test Article for reasons other than disease progression will be followed radiographically until documentation of disease progression or start of any new anticancer therapy. All subjects who discontinue Test Article for any reason, except for withdrawal of consent from the study, will be followed for survival. Subjects may choose to discontinue Test Article therapy and continue to be followed for disease progression and survival.

The study design is presented in Figure 1.

FIGURE 1. STUDY DESIGN



3.3 Schedule of Assessments

The schedule of events for the carboplatin plus PLD chemotherapy and the carboplatin plus paclitaxel chemotherapy are published in the study protocol (Table 6 and 7) and are copied in Appendices 12.1 and 12.2, respectively.

4 DETERMINATION OF SAMPLE SIZE

Sample size considerations are based on the primary PFS endpoint to compare the effect of farletuzumab versus placebo on PFS irrespective of the chemotherapy (the 2 strata combined).

The study is designed to detect with approximately 85% power a PFS HR of 0.667 (33.3% risk reduction) in the farletuzumab arm compared with the placebo arm with a 1-sided type I error rate of 0.10, which translates into a 50% increase in median PFS from 11 months in the placebo arm: 10 months for carboplatin plus paclitaxel (Data on file), and 11.3 months for carboplatin plus PLD (Pujade-Lauraine, et al., 2010) to approximately 16 months in the farletuzumab arm. A variable accrual period of approximately 38 months and a 20% loss to imaging follow-up rate has been assumed. Using a treatment allocation of 2:1 (farletuzumab: placebo), 210 subjects will be enrolled in the study and a target of at least 143 PFS events in the combined chemotherapy strata will be required for the primary analysis.

Assuming a median PFS time of approximately 11 months in the control arm, the primary PFS analysis target events milestone is projected to be reached approximately 12 months after the last subject is randomized in the study.

Survival follow-up considerations were based on the same target HR and significance level, but 80% power. A 5% per year loss to survival follow-up rate was assumed. Based on a median survival time of approximately 32 months in the control arm, the final OS analysis target events milestone (a total 124 death events) is projected to be reached approximately 35 months after the last subject is randomized in the study.

In order to preserve the overall type 1 error rate at 1-sided 10%, the following sequential testing scheme will be employed for the PFS primary analysis and OS analyses:

1. PFS comparison in combined chemotherapy strata
2. OS comparison in combined chemotherapy strata

5 STATISTICAL METHODS

In general, summary statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated for continuous data, and the number and percentage of subjects in each category will be displayed for categorical data. Kaplan-Meier (KM) curves will be produced for time-to-event endpoints. Durations of time (e.g., times-to-event endpoints) will be reported in proportional “months” according to the formula

$$\text{months} = \frac{12}{365.25} \times \text{days}$$

Baseline value of a characteristic is defined as the last measured value prior to the first dose of any study medication (or prior to randomization for subjects not treated). Study Day 1 is defined as the date of the first dose of Test Article.

Statistical p-values will be rounded for display at the fourth digit following the decimal point. P-values below 0.0001 will be displayed as "<0.0001."

All data collected via electronic CRFs will be included in subject data listings. At a minimum, data listings will include the subject's ID number, assigned chemotherapy regimen, and randomized treatment arm.

5.1 Study Endpoints

5.1.1 Primary Endpoint

The primary efficacy endpoint for this study is the PFS based on the investigators' radiographic assessments utilizing RECIST 1.1 criteria. PFS is defined as the time (in months) from the date of randomization to the date of the first observation of progression (RECIST 1.1), or date of death, whatever the cause. If progression or death is not observed for a subject, the PFS will be censored at the date of last tumor assessment without evidence of progression prior to the date of initiation of further anticancer treatment of the cut-off date.

5.1.2 Secondary Endpoints

The secondary efficacy endpoints for the study are as follows:

Overall Survival (OS): Defined as the time from the date of randomization to the date of death, due to all causes. If death is not observed for a subject, the OS time will be censored at the last date known to be alive or the cut-off date, whichever is earliest.

Length of First versus Second Platinum-Free Interval: Length of first platinum-free interval (from end of previous platinum based chemotherapy to the first relapse) is a randomization stratification factor (6-12 months, >12-36 months), and its value will be based on IRT data. Length of second platinum-free interval is defined as the period of time (in months) from the date of completion of platinum based chemotherapy (last dosing date) during the study to the date of progression or death, with its ending point, with censoring if applicable, same as PFS.

Tumor Response (ORR, TTR, and DOR per RECIST 1.1): ORR is defined as either a CR or a PR using RECIST 1.1 criteria. Tumor assessments performed up to the initiation of further anticancer treatment will be considered. TTR is defined as the time (in months) from the date of randomization to the date of first observation of response (PR or CR). DOR is defined as the time (in months) from the date of first observation of response (PR or CR) to the date of the first observation of progression based on the investigator's radiographic assessment (RECIST 1.1), or date of death, whatever the cause.

5.1.3 Exploratory Endpoints

The exploratory endpoints for the study are: (a) changes in CA125 from baseline, and (b) to identify a potential predictive biomarker or elucidation of correlation between key biomarkers and potential farletuzumab PK or clinical benefit.

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

There will be 4 analysis sets, and 2 safety subsets for this study. The analysis sets are as follows:

Intent-to-Treat (ITT) Population (also called the Full Analysis Set) is defined as all randomized subjects, analyzed by the treatment assigned according to the IRT system. This is the primary analysis population for all efficacy endpoints.

Safety Analysis Set is defined as all randomized subjects who received at least 1 dose of Test Article and who had at least 1 safety assessment following the first dose of Test Article. Treatment assignments will be designated according to the actual study treatment received. This is the primary analysis population for safety evaluation. Two additional safety analysis subpopulations will also be defined:

Combination Therapy Analysis Set: based on exposure to farletuzumab or placebo in combination with carboplatin and taxane (combination therapy);

Single Agent Maintenance Therapy Analysis Set: based on exposure to single-agent maintenance therapy.

Tumor Response (TR) Evaluable Analysis Set is defined as all randomized subjects who received at least 1 dose of Test Article and who had a baseline and at least 1 on-treatment tumor assessment performed. This population will be used as a secondary analysis population for tumor response, according to treatment as randomized.

Pharmacokinetic (PK) Analysis Set is defined as all subjects who have at least one measureable farletuzumb serum concentration data value.

Data summaries will, in most cases, be presented by treatment group (farletuzumab or placebo) unless otherwise specified.

5.2.2 Subject Disposition

The numbers of subjects who have been screened (if available), randomized and dosed will be summarized by treatment group. The number of subjects who discontinued study treatment or study follow-up will be summarized by treatment group, along with the reasons for discontinuation. In addition, the number of subjects in each analysis population and the reason for exclusion will be summarized by treatment group and a listing of each subject's status within a given analysis population (i.e., included versus excluded) will be provided.

5.2.3 Protocol Deviations

Major protocol deviations will be presented in a data listing.

5.2.4 Demographic and Other Baseline Characteristics

Demographic information (e.g., age, sex, race, height, weight, Body Surface Area [BSA], and ECOG) and stratification factors (i.e., individual chemotherapy treatment regimen and platinum-free interval following first-line therapy) will be summarized, for the ITT population, by treatment group and overall with summary statistics for continuous/categorical variables.

5.2.4.1 Disease Characteristics

Ovarian cancer histology, ovarian cancer primary site, stage of disease at initial diagnosis, prior ovarian cancer medications, length of first platinum-free interval, and baseline CA125 will be summarized, for the ITT population, by treatment group and overall with summary statistics for continuous/categorical variables. CA125 will be summarized by categories: ≤1 ULN, >1 to ≤2 ULN, >2 to ≤3 ULN, and >3 ULN. Ovarian cancer history and prior ovarian cancer surgeries will be presented in data listings.

5.2.4.2 Exposure to Study Medication

The study drug administration profile will be summarized for each treatment group with respect to the number of infusions/cycles taken, dose intensity, dose modifications, dose omissions, and reasons for deviations from the planned regimen.

Study Drug tolerability will be summarized within treatment groups by the numbers of treatment discontinuations, treatment delays, and dose reductions.

Extent of exposure parameters will be summarized by treatment group for the Safety Analysis Set in the combination therapy and single-agent maintenance therapy sub-populations using descriptive statistics. Summaries for the carboplatin plus paclitaxel or carboplatin plus PLD regimen in each treatment group will include duration of exposure, number of cycles received, number of dose reductions, and number of dose delays. A summary of AEs leading to dose delay and/or reduction will also be provided. Additionally, cumulative dose (mg/kg), actual dose intensity (mg/kg/week), and relative dose intensity (actual dose intensity divided by the planned dose intensity) will be summarized by treatment group. Summaries for the farletuzumab treatment will include duration of exposure, number of infusions received, and dose delays.

5.2.5 Prior and Concomitant Therapy

The counts and percentages of subjects who took prior medications will be summarized on the Safety Analysis Set by treatment group and overall. Prior medication is defined as medications that stopped before the first dose of Test Article. Summaries will include the ATC4 classification and WHO DD preferred term (see section 5.3.2).

A similar summary will be produced for concomitant medications by treatment group. Concomitant medication is defined as medication that was taken any day from the first dose of Test Article until 30 days after the last dose, regardless of whether the medication was initiated prior to the first dose of Test Article.

For the purpose of this study, if a partial date is reported, then missing date imputations will be utilized (see section 7.1.2). Prior and concomitant medication use will be presented in subject data listings.

5.2.6 Medical History

General medical history will be summarized by frequency tables by treatment group and overall on the ITT population. General medical history will be presented in subject data listings.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Coding Dictionaries

Reported medical history and adverse event terms will be mapped to standard terminology in the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1or higher. Pre-study and concomitant medications will be mapped to standard drug names in the World Health Organization Drug Dictionary (WHO DD) September 2014 release or later. Reported terms paired with preferred terms will be shown in data listings, but summaries of medical history, adverse events, and medications received will be based exclusively on preferred terminology.

5.4 Efficacy Analysis

The data cutoff date of the primary PFS analysis will be determined prior to database lock and treatment unblinding. The data cutoff date of the primary PFS analysis will be determined as the latest of the following two occurrences:

1. The date of occurrence of the 143rd PFS event among all study subjects
2. Six months (183 days) following the date the last subject was randomized

The cut-off date for the PFS will be used for all secondary efficacy variables, as well as survival data supporting the interim survival analysis.

5.4.1 Primary Efficacy Analysis

5.4.1.1 Progression-Free Survival

PFS is defined as the number of months from the date of randomization to the date of the first observation of RECIST 1.1 disease progression or date of death regardless of cause. If RECIST 1.1 disease progression or death is not observed for a subject, PFS time will be censored on the last on study tumor assessment (radiographic imaging) date prior to data cutoff. The PFS censoring rules will follow the FDA guidelines.

The stratified log rank test will be used to compare PFS between farletuzumab and placebo at the 1-sided 10% level of significance. Both one-sided and two-sided p-values of the stratified log rank test will be calculated. The stratification factors are: (1) chemotherapy (carboplatin plus

paclitaxel versus carboplatin plus PLD), and (2) length of platinum-free interval following first line therapy (6-12 months versus >12-36 months). PFS will be summarized using Kaplan-Meier curves and will be further characterized in terms of median PFS and PFS probabilities at 6, 12, 18, and 24 months. Hazard ratio (HR) and its 2-sided 80% CI will be estimated using a Cox proportional hazard (PH) model stratified by the same two factors, with treatment as a covariate.

A sensitivity analysis will be performed using the unstratified log rank test. An additional stratified Cox PH model will be used to evaluate the treatment effect controlling for the following potential prognostic baseline factors: age (<65 years, ≥65 years), race (white, non-white), ECOG (0, 1/2), stage of disease at initial diagnosis [4 categories: I/II (combining IA, IB, IC, IIA, IIB, IIC), IIIA/B (combining IIIA, IIIB), IIIC, IV], baseline albumin level (lower 10% of distribution, other), baseline total protein level (lower 10% of distribution, other), baseline liver and/or brain lesions (yes, no), and baseline CA125 (≤1 ULN, >1 to ≤2 ULN, >2 to ≤3 ULN, >3 ULN).

5.4.2 Secondary Efficacy Analyses

5.4.2.1 Overall Survival

OS is defined as the number of months from the date of randomization to the date of death regardless of cause. If death is not observed for a subject, the OS time will be censored at the last date known to be alive or the cutoff date, whichever is earliest.

An interim and final analysis of OS are planned to be performed. The alpha allocation between the interim and final OS analyses will be determined based on the Lan-DeMets spending function with O'Brien-Fleming boundary.

5.4.2.1.1 Overall Survival at PFS lock – Interim OS

Overall survival will be assessed in the interim at the time of the PFS lock. A stratified log rank test will be utilized to compare OS between farletuzumab and placebo. One-sided p-value of the stratified log rank test will be calculated. The stratification factors are: (1) chemotherapy (carboplatin plus paclitaxel versus carboplatin plus PLD), and (2) length of platinum-free interval following first line therapy (6-12 months versus >12-36 months). OS will be summarized using Kaplan-Meier curves and will be further characterized in terms of median OS and OS probabilities at 6, 12, 18, and 24 months. The HR and its 80% CI will be estimated based on Cox's proportional hazards model stratified by the same two factors.

In addition to the OS analysis, anti-cancer therapy after on-study disease progression will also be summarized. Time to the first non-study anti-cancer therapy will be summarized by Kaplan-Meier curves by treatment.

5.4.2.1.2 Overall Survival – Final OS

An additional cut-off date for final OS analysis will be determined based on the time when there are at least a total number of 124 OS events. The final OS analysis is estimated to occur approximately 3 years after the last subject is randomized.

OS will be analyzed using methods similar to the interim OS analysis. Additionally, the time to first non-study anti-cancer therapy will be summarized by Kaplan-Meier curves by treatment and the anti-cancer therapy after on-study disease progression will also be summarized.

5.4.2.2 Length of First versus Second Platinum-Free Interval

Length of first platinum-free interval (from end of previous platinum based chemotherapy to the first relapse) is a randomization stratification factor (6-12 months, >12-36 months), and its value will be based on IRT data. Length of second platinum-free interval is defined as the period of time (in months) from the date of completion of platinum based chemotherapy (last dosing date) during the study to the date of progression or death, with its ending point, with censoring if applicale, same as PFS.

The number and proportion of subjects (with 95% CI) in each length category of second platinum-free interval will be presented within each treatment group and by length of first platinum-free interval (6-12 months versus >12-36 months).

5.4.2.3 Objective Response Rate

The Objective Response Rate (ORR) is defined as percentage of subjects achieving either a complete response (CR) or partial response (PR) according to RECIST 1.1 criteria. Tumor assessments performed up to the initiation of further anticancer treatment will be considered. Subjects who have no radiographic evaluations subsequent to the first dose of Test Article will be included in the count of subjects who fail to achieve a Complete Response (CR) or Partial Response (PR). In addition, the best of response (complete response, partial response, stable disease, progressive disease, not evaluable, or not applicable) will be summarized by treatment group.

A stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare ORR. Stratification factors are: (1) chemotherapy (carboplatin plus paclitaxel versus carboplatin plus PLD), and (2) length of platinum-free interval following first line therapy (6-12 months versus >12-36 months). Treatment estimates and differences in proportions will be presented with corresponding two-sided 95% CIs.

5.4.2.4 Disease Control Rate

The Disease Control Rate (DCR) is defined as percentage of subjects achieving a CR, PR or stable disease (SD) according to RECIST 1.1 criteria. Tumor assessments performed up to the initiation of further anticancer treatment will be considered. Subjects who have no radiographic evaluations subsequent to the first dose of Test Article will be included in the count of subjects who fail to achieve a CR, PR or SD.

A stratified CMH test will be used to compare DCR utilizing a method similar to comparisons of ORR (see section 5.4.2.3).

5.4.2.5 Time to Response

The Time to Response (TTR) will be defined among CR and PR responders only. TTR is defined as the number of months from the date of randomization to the date of first observation of CR or PR according to RECIST 1.1 criteria.

TTR will be summarized using descriptive statistics and KM curves.

5.4.2.6 Duration of Response

The DOR is defined as the number of months from the date of first observation of CR or PR to the first observation of disease progression according to RECIST 1.1 criteria or the date of death regardless of cause. DOR will be defined only for subjects who achieve a CR or PR according to RECIST 1.1 criteria. If RECIST 1.1 disease progression or death is not observed for a subject, DOR time will be censored on the last on-study tumor assessment (radiographic imaging) date prior to data cutoff.

DOR will be summarized using descriptive statistics and KM curves for both the PFS data cutoff and final data.

5.4.2.7 Exposure-Response

Exposure response analysis will be presented in a separate document.

5.4.3 Exploratory Efficacy Analysis

Serum CA125 change pattern during the study will be explored to assess if there is treatment effect on CA125 in this predefined population with baseline serum CA125 3xULN (105 U/mL). Longitudinal serum CA125 levels will be collected during the study. Change pattern in CA125 will be explored. Average of time point CA125 will be summarized by treatment group, and will also be plotted.

Exploratory analyses for efficacy endpoints including PFS, OS, ORR, and DOR will also be conducted in each of the two chemotherapy strata (carboplatin plus paclitaxel and carboplatin plus PLD). Similar analyses described for the two chemotherapy strata combined will be conducted in each of the two chemotherapy strata, in which the stratified analyses will be stratified only by length of platinum-free-interval following first line therapy (6-12 months versus >12-36 months).

CMH analyses will be conducted specifically for:

- ORR in each of the two chemotherapy strata, in which the stratified analyses will be stratified only by length of platinum-free interval following first line therapy (6-12 versus >12-36 months).
- DCR in each of the two chemotherapy strata.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Phamacokinetic Analyses

PK concentrations will be measured by the Sponsor Bioanalytical group. Listing and summary tables will be provided by Syneos Health.

Descriptive statistics (n, median, minimum [min], maximum [max], etc.) will be used to summarize farletuzumab serum level data at each planned relative time point in the farletuzumab serum level evaluable population. Below limit of quantitation (BLQ) values will be set to zero prior to calculations of descriptive statistics. If the mean (or median) results in a BLQ value, it will be reported as such. The Safety Analysis Set will be used for analysis on individual serum concentrations.

Farletuzumab serum level data will be analyzed using a population PK approach to estimate population PK parameters. Exposure-response relationships between farletuzumab exposure and key efficacy variables, including PFS and OS, will be analyzed via a population PK/Pharmacodynamic analyses. Details of the planned population PK and PK/Pharmacodynamic analyses will be outlined in a separate analysis plan.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Correlation analysis will be conducted to evaluate the relationship between serum and tissue CA125 levels, as well as the relationship between serum and tissue folate receptor alpha levels. Exploratory analyses of molecular markers (DNA, RNA, miRNA, tumor gene/protein expression and/or serum/plasma proteins) will be performed to determine if a correlation can be established between the presence or change in level of a marker and the response to therapy. They may be performed and reported separately. Details of these analyses may be described in a separate analysis plan.

5.6 Safety Analysis

Safety data, presented by treatment group, will be summarized on the Safety Analysis Set. Data will be summarized by n, mean, standard deviation, median, minimum, and maximum for continuous variables; and, n [%] for categorical variables.

Safety variables include extent of exposure to study drugs, measures of drug tolerability (treatment discontinuations, treatment delays, and dose reductions), Treatment-Emergent Adverse Events (TEAEs), Treatment-Related Adverse Events (TRAEs), clinical laboratory parameters, 12-lead ECG results, Eastern Cooperative Oncology Group (ECOG) performance status assessments, and Anti-Drug Antibody (ADA).

Study Day 1 for all safety analyses will be defined as the date of the first dose of Test Article. All subjects included in the Safety Analysis Set will be evaluated by treatment group. In addition, analyses will be provided for the Combination Treatment and single-agent Maintenance

Treatment safety sub-populations. Exposure and dosing modification summaries will be repeated for each chemotherapy (carboplatin, paclitaxel, PLD).

5.6.1 Adverse Events

Adverse events for this study will be reported in many forms; i.e., TEAEs, TRAEs, DHAEs, ILDs, and SAEs. For the purpose of this study, if an AE is reported as a partial date, then missing date imputations will be utilized (see section 7.1.1). Below is a descriptive list of AEs which will be reported for this study:

- A treatment-emergent adverse event (TEAE) is any AE that developed or worsened in severity during the on-treatment period (from the first dose of Test Article to 30 days after the last dose of Test Article).
- A treatment-related adverse event (TRAE) is defined as a TEAE that was classified by the investigator as related to Test Article exposure.
- A hypersensitivity AE is defined as a TEAE with an onset date occurring the same day or the day after exposure to Test Article from a pre-defined list of AE terms (see section 12.6.1.1).
- A drug hypersensitivity adverse event (DHAE) is any hypersensitivity AE accompanied by a positive titer for ADA observed in any sample on or subsequent to the onset of the AE (see section 12.6.1.2).
- Interstitial lung disease (ILD) AEs are defined using the MedDRA preferred terms and codes from the narrow search SMQ for ILD (see section 12.6.2). The ILD terms are used to identify pulmonary AEs.
- A serious adverse event (SAE) is defined as any AE that causes death, is life threatening, requires or prolongs hospitalization, leads to a persistent or significant disability, is a congenital anomaly or birth defect, or is classified by the investigator as an important medical event.

Adverse events will be summarized by incidence and listed by the MedDRA system organ class (SOC) and preferred term (PT), Common Terminology Criteria for Adverse Events (CTCAE) toxicity (severity) grade, and causal relationship to study drugs. In addition, separate summaries of interstitial lung disease (ILD), CTCAE grade 3 and 4 AEs, SAEs, treatment-related SAEs, TEAEs/TRAEs leading to death on study, and TEAEs/TRAEs leading to study drug discontinuation will be presented.

5.6.2 Laboratory Values

Actual values and changes from baseline in continuous laboratory parameters will be summarized using descriptive statistics by treatment group and time point.

Hematological and chemistry laboratory parameters will be graded according to the NCI CTCAE criteria v4.03, where applicable. Shift tables (comparing worst on-study grade versus baseline) will be used to summarize parameters where NCI-CTCAE criteria have been defined. When the

NCI CTCAE scale is not applicable for a parameter, analyses will be performed based on out-of-normal laboratory range values.

The frequency and percentage of subjects having degrees of serum liver function abnormalities (i.e. ≥ 3x-, 5x-, 10x-, or 20x-ULN for alanine aminotransferase (ALT) or aspartate aminotransferase (AST); >= 2x-ULN for bilirubin; >= 1.5x-ULN for ALP) will be summarized by treatment group. Serum liver function abnormalities will also be summarized using Hy's Law (AST or ALT>3xULN, bilirubin>2xULN, and ALP<= 1.5xULN).

All laboratory data will be presented in data listings and abnormal values will be noted. Categorical urinalysis data will be listed, but will not be tabulated.

5.6.3 Vital Signs

Physical examination dates will be listed for each subject.

5.6.4 Electrocardiograms

Shift in 12-lead ECG result from baseline to end-of-treatment will be summarized by treatment.

5.6.5 Other Safety Analyses

5.6.5.1 Human Anti-Drug Antibodies

Human Anti-Drug Antibody related summaries will be completed by the Sponsor Bioanalytical group.

The following endpoints will be summarized for the ADA Evaluable Population:

- ADA Positive Subjects - the number (%) of subjects with at least 1 treatment-induced or treatment-boosted ADA positive sample (see definitions below) at any time after the initial Test Article administration in the ADA evaluable population
- ADA Negative Subjects – the number (%) of subjects without a treatment-induced or treatment-boosted ADA positive sample at any time after the initial Test Article administration in the ADA evaluable population
- Baseline ADA Prevalence – the number of subjects with baseline ADA as a percentage of the total number of subjects tested at baseline for ADA
- Treatment-induced ADA – the number of subjects who were baseline ADA negative and developed an ADA response
- Treatment-boosted ADA – the number of subjects with pre-existing (baseline) ADA that was boosted to a higher titer any time after initial Test Article administration.
- ADA Incidence – the proportion of subjects with either treatment-induced ADA or treatment-boosted ADA
- Occurrence and titer of neutralizing antibodies

As appropriate, the kinetics of binding and neutralizing ADA responses will be analyzed. This includes onset, defined as the number of days from initial Test Article administration to the first instance of treatment induced ADA among baseline ADA negative subjects; and duration, defined as the number of days from the first instance of treatment-induced ADA to a subsequent instance of negative ADA among baseline ADA negative subjects. Persistent ADA responses are categorized by measurable ADA levels exceeding 16 weeks (approximately 5 half-lives for a typical IgG response).

5.7 Subgroup Analyses

Subgroup analyses will be conducted on the ITT population for the following subgroups:

- strata used in randomization
- age (<65 years, ≥65 years old)
- race (white, non-white)
- ECOG (0, 1/2)
- stage of disease at initial diagnosis [4 categories: I/II (combining IA, IB, IC, IIA, IIB, IIC), IIIA/B (combining IIIA, IIIB), IIIC, IV]
- baseline CA125 (≤1 ULN, >1 to ≤2 ULN, >2 to ≤3 ULN, >3 ULN)
- baseline albumin level (lower 10% of distribution, other)
- baseline total protein level (lower 10% of distribution, other)
- baseline liver and/or brain lesions (yes, no)

Forest plots will be generated for HR (and CI) for PFS and OS. The plots will be generated for overall and within subgroups defined by each stratification factor. The HR (and CI) in the Forest plots for the each of the two chemotherapy strata will be calculated using stratified Cox PH model in which it will be stratified only by the platinum-free-interval strata. Similarly, the HR (and CI) in the Forest plots for the each of the two platinum-free-interval strata will be calculated using stratified Cox PH model in which it will be stratified only by the chemotherapy strata.

Other subgroup analyses may be explored.

6 DATA MONITORING COMMITTEE AND INTERIM ANALYSIS

6.1 Data Monitoring Committee

The first DMC review of safety data will occur when the 15th subject completes Cycle 1 of the Combination Treatment Phase to assure that the tolerability of the modified farletuzumab dosing and chemotherapy combinations are acceptable. No formal statistical hypothesis testing is planned for the first DMC review; therefore no adjustments to the level of significance (α) are necessary.

The DMC will be composed of 3 voting members, all with oncology experience. An additional non-voting Syneos Health DMC support biostatistician will also be present to provide

consultation regarding the information presented. Following the first meeting, the DMC will conduct ongoing safety reviews at a minimum frequency of every 6 months.

Additional information regarding the DMC can be found in the Data Monitoring Committee Charter.

6.2 Interim Analysis

An interim analysis for OS will be performed to accompany the primary PFS analysis lock of the study (see section 5.4.2.1.1). Survival status reported up to the primary analysis cut-off date will be included in this analysis. Study follow-up for survival will continue after the interim OS analysis. The alpha allocation between the interim and final OS analyses will be determined based on the Lan-DeMets spending function with O'Brien-Fleming boundary.

7 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

7.1 Missing Data, Handling of Partial Adverse Event Start/Stop Dates

7.1.1 Adverse Events

The following algorithm should be used to estimate adverse event start dates for which only partial information is known:

- Missing day and month
  - If the year is the same as the year of first day on farletuzumab, then the day and month of the start date of drug will be assigned to the missing fields.
  - If the year is prior to the year of first day on farletuzumab, then December 31 will be assigned to the missing fields.
  - If the year is after the year of first day on farletuzumab, then January 1 will be assigned to the missing fields.
- Missing month only
  - Treat data as missing and replace both month and day according to the above procedure.
- Missing day only
  - If the month and year are the same as the month and year of the first day on drug, then the start date of farletuzumab will be assigned to the missing day.
  - If the month and year are before the month and year of the first day on farletuzumab, then the last day of the month will be assigned to the missing day.
  - If the month and year are after the month and year of the first day on farletuzumab, then the first day of the month will be assigned to the missing day.

If the resultant imputed start date is after the AE stop date (and the AE stop date is complete), the imputed start date will be reset to the AE stop date.

The following algorithm should be used to estimate adverse event stop dates, which are not ongoing at final visit, for which only partial information is known:

- Year is missing
  - Date left missing.
- Month is missing
  - Impute 'December'.
- Day is missing
  - Impute last date of that month.

If the resultant imputed stop date is after the last subject visit or death date, the imputed stop date will be reset to the last subject visit or death date.

7.1.2 Prior and Concomitant Therapy

The following algorithms should be used to estimate partial and missing start or stop dates:

- Missing start date where the stop date is recorded in full
  - If the stop date is before the date of first dose of Test Article, it will be considered a prior medication.
  - If the stop date is after the date of first dose of Test Article, it will be considered a concomitant medication.
- Missing stop date where the start date is recorded in full
  - If the start date is after the first dose of Test Article, it will be considered a concomitant medication.
- Partial start and stop dates
  - The month and year of the stop date will be used to assess whether the medication is prior or concomitant. For instance, if month and year exist for the stop date, this data will be compared with the first dose of Test Article and if the month or year show evidence of being after this date or on the same date (same month/year), the medication will be considered concomitant.
- Missing both the start and stop dates
  - These medications will be considered concomitant.

8 PROGRAMMING SPECIFICATIONS

The standard operating procedures (SOPs) of InVentiv Health Clinical will be followed in the creation and quality control of all tables, listings, and analyses.

Format of Output

1. Unless otherwise specified, all computer-generated output should be produced in landscape mode. Required margins: 1 inch on top and bottom and 1 inch on the left and right; required

font: Courier New; and required font size: 9. All outputs should have the following header line at the top of the page:

Eisai Protocol: MORAb-003-011 Page x of y

Each output has the following footer line at the bottom of the page:

```
Program:\...\...\<program name>.sas      Data Cutoff: ddMMMyyyy      ddMMMyyyy HH:mm
```

All output should have date (date output was generated) and page number. Tables/listings/figures should be internally paginated in relation to total length (i.e., page number should appear sequentially as page n of N, where N is the total number of pages in the table).

2. Each output should be identified by a numeral, and the output designation (e.g., Table 1) should be listed on the same line, before the title. A decimal system (x.y and x.y.z) should be used to identify tables and listings with related contents. The title is centered in initial capital characters.

Table No.
Table Title
Study Population

The study population should be identified immediately following the title.

3. Column headings should be in initial upper-case characters.
4. For numeric variables, include "unit" in column or row headings when appropriate.
5. Footnotes should be single spaced, but separated by at least a double space from the bottom line of the table. The notes are aligned vertically by the left vertical border of the table.
6. If the categories are not ordered (e.g., race), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
7. An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
8. Listings should be sorted by treatment, subject number, and study visit, unless otherwise specified.
9. In a listing, display the subject number only once for the subject with multiple records. If a subject's records run across multiple pages, display the subject number once for every page.

Data format

1. Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the individual units of measurement and the standard deviation for a set of values should be printed out to 2 more significant digits than

the individual units of measurement. The minimum and maximum should report the same significant digits as the original values. For example, for age (with raw data in whole years):

n	XX
Mean (STD)	XX.X (XX.XX)
Median	XX.X
Min, Max	XX, XX

2. Unless otherwise specified, data in columns of a table should be formatted as follows:
   - Alphanumeric values are left-justified.
   - Whole numbers (e.g., counts) are right-justified.
   - Numbers containing fractional portions are decimal aligned.
3. Unless otherwise specified, percentage values should be printed with 1 digit to the right of the decimal point (e.g., 12.8%, 5.4%). Less-than-signs "<0.1%" should be printed when values are >0.0 and <0.1% (not 0.0%).
4. Unless otherwise specified, missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A," with the footnote "N/A = not applicable," whichever is appropriate.
5. Dates should be printed in SAS® DATE9.format ("DDMMMYYYY": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

Unless otherwise specified, time should be printed in SAS® TIME5.format ("HH:MM": 17:30). Missing portions of time should be represented on subject listings as dashes (--:30). Times that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

9 STATISTICAL SOFTWARE

Unless otherwise specified, all statistical analyses will be performed using SAS® version 9.3 or greater.

10 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs.

11 REFERENCES

Agresti, Alan. Categorical Data Analysis. 2nd Edition, 2002.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guidance (version 1.1). Eur J Cancer. 2009;45:228-47.

FDA (2009). Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER), July 2009.

Kleinbaum , D.G. and Klein, M. Survival Analysis. A self-learning text. 2005.

12 APPENDICES

12.1 Schedule of Procedures/Assessments for PLD/Carboplatin Chemotherapy Arm

Schedule for PLD/Carboplatin Chemotherapy Arm

Evaluations	Screen Phase[a]	Combination Treatment Phase								Maintenance Treatment Phase			Test Article Admin Only Visits	EOT Visit[b]	Follow-up Phase[c]		
		Cycle 1[b]				Cycles 2 – 6[b]				Cycle(s) 1 – X[b]							
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3			30-Day Safety Visit	60-Day Visit	Follow-up Phone Call
	Day -30 to Rand.	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15					
IC, demography, eligibility	X																
Medical and cancer history	X																
Tumor histology, disease staging	X																
Physical examination[d]	X	X				X				X				X			
Height/BSA/weight[e]	X	X				X				X				X			
ECOG assessment	X	X				X				X				X			
RECIST imaging—CT or MRI[f]	X						X[f]		X[f]			X[f]		X			
12-lead ECG[g]	X													X			
Archived tumor block[h]	X																
Hematology and Chemistry[i]	X	X				X				X				X			
Serum CA125[j]	X	X				X				X[j]				X			
Pregnancy test (serum, urine)[k]	X	X				X				X				X	X	X	
Biomarker blood sample[l]	X	X				X				X[l]				X			
Biomarker urine sample[l]	X																
Serum farletuzumab sample[m]		X				X				X[m]				X	X	X	
Serum ADA sample[n]		X				X				X[n]				X	X	X	
Premedication (required)[o]		X	X	X	X	X	X	X	X	X	X	X	X				
Test Article administration[p]		X	X	X	X	X	X	X	X	X	X	X	X				
Carbo + PLD administration		X				X											

Schedule for PLD/Carboplatin Chemotherapy Arm

Concomitant medications[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Survival contact, anticancer treatment															X	X	X

ADA = human anti-drug antibody; AE = adverse event; BSA = body surface area; CA125 = cancer antigen 125; Carbo = carboplatin; CT =computerized tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; hCG = human chorionic gonadotropin; IC = Informed Consent; IV = intravenous; MRI = magnetic resonance imaging; PE = physical examination; PLD = pegylated liposomal doxorubicin; Rand. = Randomization; RECIST = Response Evaluation Criteria In Solid Tumors.

a: All Screening procedures are to be completed within 30 days prior to and including the date of Randomization unless otherwise specified. Procedures for the Cycle 1 Week 1 Visit do not need to be repeated if they were conducted within 14 days of Randomization.

b: All visits should be scheduled to occur within ±2 days of the target visit date, unless otherwise specified. The EOT Visit must be performed within 7 days of the last infusion of Test Article (farletuzumab or placebo), unless the subject's medical management warrants otherwise. Scans performed within 2 week of the last infusion of Test Article do not need to be repeated.

c: Follow-up visits will be performed at 30 and 60 days (within ±7 days) after the date of last Test Article administration. Thereafter, subjects will be contacted by phone monthly for the next 7 months and then every other month until death or the end of the study. During these visits and calls, anticancer therapy treatments will be collected and recorded. Subjects who discontinue treatment for reasons other than disease progression (radiographic) will be followed radiographically until disease progression or initiation of another anticancer therapy, on the same schedule as the Maintenance Treatment Phase (ie, every 9 weeks), where possible.

d: Comprehensive PEs will be conducted during Screening and at the EOT Visit. Abbreviated PEs (including follow-up of interval complaints and review of the cardiorespiratory system) will be conducted at Week 1 of each cycle during the Combination Treatment Phase and Week 1 of every third cycle during the Maintenance Treatment Phase (beginning with Maintenance Cycle 3).

e: Height will be collected during Screening only. Body weight will be measured during Screening, prior to Test Article administration on Week 1 of each cycle, and at the EOT Visit. BSA should only be recalculated for the purpose of chemotherapy dose modification if the subject experiences a $\geq$ 10% change in body weight.

f: RECIST 1.1 will be used for this study. CT or MRI scans may be obtained any time during the week prior to the next scheduled visit. Scans will be performed during Screening; every 6 weeks during Combination Treatment Phase (eg, Cycle 2 Week 2, Cycle 3 Week 4, Cycle 5 Week 2, and Cycle 6 Week 4); every 9 weeks during the Maintenance Treatment Phase (Week 3 of every third cycle beginning with Maintenance Cycle 3), and at the EOT Visit. Subjects who discontinue treatment for reasons other than disease progression (radiographic) will be followed radiographically until disease progression or initiation of another anticancer therapy, on the same schedule as the Maintenance Treatment Phase (ie, every 9 weeks), where possible. Scans performed within 2 weeks of the last Test Article administration do not need to be repeated.

g: 12-lead ECG will be performed during Screening and at the EOT Visit.

h: At Screening, the archival tumor tissue sample (taken at the time of initial diagnosis of ovarian cancer) will be collected for central histology confirmation and exploratory analyses of potential biomarkers. In the absence of the original primary tumor block, 15 to 20 unstained slides are required. If a minimum of 15 slides are not available, contact the CRA to discuss.

i: Hematology and Chemistry will be obtained during Screening, prior to Test Article infusion on Week 1 of every cycle during the Combination Treatment Phase, Week 1 of every third cycle during the Maintenance Treatment Phase (beginning with Maintenance Cycle 3), and at the EOT Visit. Hematology and Chemistry for the Combination Treatment Phase Cycle 1 Week 1 visit do not need to be repeated if the Screening samples were obtained within 14 days of Cycle 1 Day 1

j: Screening CA125 must be assessed by the central laboratory within 2 weeks prior to randomization. On-study CA125 samples will be obtained at Week 1 of every cycle during the Combination Treatment Phase, at Week 1 of every third cycle during the Maintenance Treatment Phase (beginning with Maintenance Cycle 3), and at the EOT Visit.

k: Only for female subjects of childbearing potential. At Screening, a serum pregnancy test (hCG) is to be conducted, which will be analyzed by the central laboratory from the same vial of blood drawn for the chemistry panel. Prior to Test Article administration at the following timepoints, a highly-sensitive urine pregnancy test (hCG) will be

Schedule for PLD/Carboplatin Chemotherapy Arm

conducted locally at the site: Cycle 1 Day 1, Week 1 of all Combination and Maintenance Treatment cycles, the EOT Visit, and at the 30- and 60-Day Follow-up visits.

l: Blood samples for biomarker analysis will be collected during Screening within 2 weeks prior to Randomization, at Week 1 of every cycle during the Combination Treatment Phase, at Week 1 of every third cycle during the Maintenance Treatment Phase (beginning with Maintenance Cycle 3), and at the EOT visit. Urine samples will be collected at the Screening visit only, within 2 weeks prior to Randomization. Details for sample collection and handling are provided in the laboratory manual.

m: Serum farletuzumab samples are to be drawn pre- and postinfusion (within 1 hour after the completion of the infusion) of Test Article at Week 1 of each cycle during the Combination Treatment Phase, at Week 1 of every third cycle during the Maintenance Treatment Phase (beginning with Maintenance Cycle 3), at the EOT Visit, and at the 30- and 60-Day Follow-up Phase visits.

n: Serum ADA samples are to be drawn prior to infusion of Test Article at Week 1 of each cycle during the Combination Treatment Phase, at Week 1 of every sixth cycle during the Maintenance Treatment Phase (beginning with Maintenance Cycle 3), at the EOT Visit, and at the 30- and 60-Day Follow-up visits.

o: All subjects must be premedicated within 4 hours prior to each infusion of Test Article with acetaminophen 650 mg, or the local equivalent. Premedications for carboplatin should be given according to country-specific labeling. All premedications must be recorded on the Premedications eCRF page.

p: The first dose of Test Article should be administered as close to the day of Randomization as possible but no more than 7 days following randomization; otherwise, medical monitor approval is required. Test Article will be administered IV once weekly prior to chemotherapy during the Combination Treatment Phase and once weekly during the Maintenance Treatment Phase. All subjects will receive a loading dose for the first 2 weeks (Cycle 1, Weeks 1 and 2) of farletuzumab (or placebo) 10 mg/kg, followed by 5 mg/kg weekly until disease progression or discontinuation of Test Article.

q: Concomitant medications are any new, discontinued, or ongoing medications (excluding protocol-required premedications) that have been taken within 30 days prior to the first dose of Test Article until 30 days after the last dose of Test Article (first follow-up visit).

r: All AEs occurring after the subject signs the IC form and continuing through 30 days after the last infusion of Test Article should be recorded. Serious AEs that are ongoing at the time of discontinuation of Test Article will be followed until resolution (or until stable if resolution is not expected).

12.2 Schedule of Procedures/Assessments for Paclitaxel/Carboplatin Chemotherapy Arm

Schedule for Paclitaxel/Carboplatin Chemotherapy Arm

Evaluations	Screen Phase[a]	Combination Treatment Phase						Maintenance Treatment Phase			Test Article Admin Only Visits	EOT Visit[b]	Follow-up Phase[c]		
		Cycle 1[b]			Cycles 2 – 6[b]			Cycle(s) 1 – X[b]							
		Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3			30-Day Safety Visit	60-Day Visit	Follow-up Phone Call
	Day -30 to Rand.	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15					
IC, demography, eligibility	X														
Medical and cancer history	X														
Tumor histology, disease staging	X														
Physical examination[d]	X	X			X			X				X			
Height/BSA/weight[e]	X	X			X			X				X			
ECOG assessment	X	X			X			X				X			
RECIST imaging—CT or MRI[f]	X						X[f]			X[f]		X			
12-lead ECG[g]	X											X			
Archived tumor block[h]	X														
Hematology and Chemistry[i]	X	X			X			X				X			
Serum CA125[j]	X	X			X[j]			X[j]				X			
Pregnancy test (serum, urine)[k]	X	X			X			X				X	X	X	
Biomarker blood sample[l]	X	X			X			X[l]				X			
Biomarker urine sample[l]	X														
Serum farletuzumab sample[m]		X			X			X[m]				X	X	X	
Serum ADA sample[n]		X			X			X[n]				X	X	X	
Premedication (required)[o]		X	X	X	X	X	X	X	X	X	X				
Test Article administration[p]		X	X	X	X	X	X	X	X	X	X				
Carbo + Pacli administration		X			X										
Concomitant medications[q]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events[r]	X	X	X	X	X	X	X	X	X	X	X	X	X		

Schedule for Paclitaxel/Carboplatin Chemotherapy Arm

Survival contact, anticancer treatment												X	X	X

ADA = human anti-drug antibody; AE = adverse event; BSA = body surface area; CA125 = cancer antigen 125; Carbo = carboplatin; CT =computerized tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; hCG = uman chorionic gonadotropin; IC = informed consent; IV = intravenous; MRI = magnetic resonance imaging; Pacli = paclitaxel; PE = physical examination; Rand. = Randomization; RECIST = Response Evaluation Criteria In Solid Tumors.

a: All Screening procedures are to be completed within 30 days prior to and including Randomization unless otherwise specified. Procedures for the Cycle 1 Week 1 Visit do not need to be repeated if they were conducted within 14 days of Randomization.

b: All visits should be scheduled to occur within ±2 days of the target visit date, unless otherwise specified. The EOT Visit must be performed within 7 days of the last infusion of Test Article (farletuzumab or placebo), unless the subject's medical management warrants otherwise. Scans performed within 2 week of the last infusion of Test Article do not need to be repeated.

c: Follow-up visits will be performed at 30 and 60 days (within ±7 days) after the date of last Test Article administration. Thereafter, subjects will be contacted by phone monthly for the next 7 months and then every other month until death or the end of the study. During these visits and calls, anticancer therapy treatments will be collected and recorded. Subjects who discontinue treatment for reasons other than disease progression (radiographic) will be followed radiographically until disease progression or initiation of another anticancer therapy, on the same schedule as the Maintenance Treatment Phase (ie, every 9 weeks), where possible.

d: Comprehensive PEs will be conducted during Screening and at the EOT Visit. Abbreviated PEs (including follow-up of interval complaints and review of the cardiorespiratory system) will be conducted at Week 1 of each cycle during the Combination Treatment Phase and at Week 1 of every third cycle during the Maintenance Treatment Phase (beginning with Maintenance Cycle 3).

e: Height will be collected during Screening only. Body weight will be measured during Screening, prior to Test Article administration on Week 1 of each cycle, and at the EOT Visit. BSA should only be recalculated for the purpose of chemotherapy dose modification if the subject experiences a $\geq$ 10% change in body weight.

f: RECIST 1.1 will be used for this study. CT or MRI scans may be obtained any time during the week prior to the next scheduled visit. Scans will be performed during Screening; every 6 weeks during the Combination Treatment Phase (Week 3 of every second cycle); and then every 9 weeks (Week 3 of every third cycle beginning with Maintenance Cycle 3) thereafter during the Maintenance Treatment Phase, and at the EOT Visit. Subjects who discontinue treatment for reasons other than disease progression (radiographic) will be followed radiographically until disease progression or initiation of another anticancer therapy, on the same schedule as the Maintenance Treatment Phase (ie, every 9 weeks), where possible. Scans performed within 2 weeks of the last Test Article administration do not need to be repeated.

g: 12-lead ECG will be performed during Screening and at the EOT Visit.

h: At Screening, the archival tumor tissue sample (taken at the time of initial diagnosis of ovarian cancer) will be collected for central histology confirmation and exploratory analyses of potential biomarkers. In the absence of the original primary tumor block, 15 to 20 unstained slides are required. If a minimum of 15 slides are not available, contact the CRA to discuss.

i: Hematology and Chemistry will be obtained during Screening, prior to Test Article infusion at Week 1 of every cycle during the Combination Treatment Phase, Week 1 of every third cycle during the Maintenance Treatment Phase (beginning with Maintenance Cycle 3), and at the EOT Visit. Hematology and Chemistry for the Combination Treatment Phase Cycle 1 Week 1 visit do not need to be repeated if the Screening samples were obtained within 14 days of Cycle 1 Day 1.

j: Screening CA125 must be assessed by the central laboratory within 2 weeks prior to randomization. On-study CA125 samples will be obtained at Week 1 of every cycle during the Combination Treatment Phase; at Week 1 of every third cycle during the Maintenance Treatment Phase (beginning with Maintenance Cycle 3), and at the EOT Visit.

k: Only for female subjects of childbearing potential. At Screening, a serum pregnancy test (hCG) is to be conducted, which will be analyzed by the central laboratory from the same vial of blood drawn for the chemistry panel. Prior to Test Article administration at the following timepoints, a highly-sensitive urine pregnancy test (hCG) will be

Schedule for Paclitaxel/Carboplatin Chemotherapy Arm

conducted locally at the site: Cycle 1 Day 1, Week 1 of all Combination and Maintenance Treatment cycles, the EOT Visit, and at the 30- and 60-Day Follow-up visits.

l: Blood samples for biomarker analysis will be collected during Screening within 2 weeks prior to randomization, at Week 1 of every cycle during the Combination Treatment Phase; at Week 1 of every third cycle during the Maintenance Treatment Phase (beginning with Maintenance Cycle 3); and at the EOT visit. Urine samples will be collected at the Screening visit only, within 2 weeks prior to Randomization. Details for sample collection and handling are provided in the laboratory manual.

m: Serum farletuzumab samples are to be drawn pre- and postinfusion (within 1 hour after the completion of the infusion) of Test Article on Week 1 of each cycle during the Combination Treatment Phase, on Week 1 of every third cycle during the Maintenance Treatment Phase (beginning with Maintenance Cycle 3), at the EOT Visit, and at the 30- and 60-Day Follow-up Phase visits.

n: Serum ADA samples are to be drawn prior to infusion of Test Article on Week 1 of each cycle during the Combination Treatment Phase, on Week 1 of every sixth cycle during the Maintenance Treatment Phase (beginning with Maintenance Cycle 3), at the EOT Visit, and at the 30- and 60-Day Follow-up visits.

o: All subjects must be premedicated within 4 hours prior to each infusion of Test Article with acetaminophen 650 mg, or the local equivalent. Premedications for carboplatin and paclitaxel should be given according to country-specific labeling. All premedications must be recorded on the Premedications eCRF page.

p: The first dose of Test Article should be administered as close to the day of Randomization as possible but no more than 7 days following randomization; otherwise, medical monitor approval is required. Test Article will be administered IV once weekly prior to chemotherapy during the Combination Treatment Phase and once weekly during the Maintenance Treatment Phase. All subjects will receive a loading dose for the first 2 weeks (Cycle 1, Weeks 1 and 2) of farletuzumab (or placebo) 10 mg/kg, followed by 5 mg/kg weekly until disease progression or discontinuation of Test Article.

q: Concomitant medications are any new, discontinued, or ongoing medications (excluding protocol-required premedications) that have been taken within 30 days prior to the first dose of Test Article until 30 days after the last dose of Test Article (first follow-up visit).

r: All AEs occurring after the subject signs the IC form and continuing through 30 days after the last infusion of Test Article should be recorded. Serious AEs that are ongoing at the time of discontinuation of Test Article will be followed until resolution (or until stable if resolution is not expected).

12.3 Quick Reference for Protocol-Specific Response Criteria

The following protocol-specific response criteria (copied from Appendix 4 of the study protocol) are based on RECIST (version 1.1) criteria.

Methods of Measurement

- As part of the disease assessment by RECIST 1.1 criteria, Computer Tomography (CT) with IV and oral contrast of the chest, abdomen and pelvis will be performed. Following baseline, subsequent chest CT is only required if a lesion is identified in the chest or metastasis to the chest is suspected at any point during the study.

- In subjects who have been followed previously by Magnetic Resonance Imaging (MRI), those who are intolerant of CT contrast media, or where there is a preference for MRI, MRI is acceptable. If MRI of the chest, abdomen, and pelvis is performed, CT of the chest without contrast must also be performed at baseline. Following baseline, subsequent non-contrast CT of the chest is only required if a target lesion is identified in the chest or metastasis to the chest is suspected at any point during the study.

- This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung

- When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and progressive disease (PD)

- All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and within 4 weeks of the randomization

- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Evaluable disease

An evaluable disease includes lesions that meet criteria for measurable disease per RECIST 1.1 or radiographically visible and evaluable lesions. Examples of evaluable but not measurable lesion include:

- small liver lesions, omental implants, serosal bowel implants, pelvic masses, or skin lesion that do not meet criteria for the size of measurable (<1cm) but can be considered non-measurable evaluable lesions at eligibility/screening
- pathologic lymph nodes with a short axis measuring $\geq$ 10 mm and < 15 mm

Subjects with only ascites or pleural effusion are not considered eligible for this protocol.

Measurable disease

A measureable disease is defined as the presence of at least one measurable lesion.

Measurable lesions

A measurable lesion must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 15 mm in short axis for a lymph node when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm)

Baseline Documentation of "Target" and "Non-Target" Lesions

- For subjects without measurable disease, all evaluable lesions are considered as non-target lesions

- When more than one measurable lesion is present at Baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at Baseline. (This means in instances where subjects have only one or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded.)

- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements

- Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed

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

- All other lesions (or sites of disease) should be identified as *non-target lesions* and should also be recorded at baseline. Measurements of these lesions are not required, but they should be followed as 'present', 'absent', or 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases')

Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target and non-target lesions.

Evaluation of Target Lesions:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters 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.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

NOTE: For Special notes on the assessment of target lesions that are lymph nodes, target lesions that become 'too small to measure,' and lesions that split or coalesce on treatment, please refer to the RECIST 1.1 guidelines (Eisenhauer, et al., 2009).

Evaluation of Non-Target Lesions:

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

NOTE: For special notes on the assessment of progression of non-target disease, as well as new lesions, please refer to the RECIST 1.1 guidelines (Eisenhauer, et al., 2009).

Evaluation of Time Point Response

The Time Point Response Table below provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

Time Point Response: Subjects with Target (+/– Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall
CR	CR	No	CR
CR	Non-CR / non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
CR = Complete Response; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease; NE = Not Evaluable			

12.4 Censoring Rules

12.4.1 Censoring Rules for Overall Survival

Situation	End Date	Censored
Death before or on data cut-off date	Date of Death	No
Death after data cut-off date	Date of data cut-off	Yes
Alive at data cut-off date	Date of data cut-off	Yes
Lost to follow-up prior to cut-off data	Last known date to be alive	Yes
Withdrawal of consent prior to cut-off	Last known date to be alive	Yes

12.4.2 Censoring Rules for Progression-Free Survival Based on Investigator Assessment

Situation	End Date	Censored
Investigator documented PD	Date of the first assessment of the series of the tests that determined PD	No
Death during the study before PD	Date of death	No
No baseline or post baseline tumor assessment	Date of randomization	Yes
No progression and no death at the time of data cutoff	Date of last adequate tumor assessment prior to data cutoff	Yes
Non-study anti-cancer treatment initiated before progression or death	Date of last adequate tumor assessment prior to initiation of non-study anti-cancer treatment	Yes
Death or progression after two or more missed tumor assessments	Date of last adequate tumor assessment prior to missed tumor assessment	Yes

General Considerations:

- Investigator-based PFS = (End Date – Randomization Date) + 1
- Tumor response assessments will be considered "adequate" for analysis if they are assigned as CR, PR, SD, PD, or Non-CR/Non-PD, and are not censored (e.g., obtained prior to initiation of nonstudy antitumor treatment).
- Tumor response assessment dates will be assigned based on the date the image was performed, not the date the image was assessed.
- Tumor response assessments obtained after initiation of nonstudy antitumor treatment will be considered "inadequate" for analysis, flagged in the data listings, and excluded from all tumor response based efficacy analyses. Tumor response assessments obtained the same day as initiation of nonstudy antitumor treatment will not be excluded.
- Two or more tumor response assessments will be considered missed if more than 13 weeks (during combination therapy), more than 19 weeks (during single-agent maintenance therapy), or more than 16 weeks (across combination therapy and single-agent maintenance therapy) have elapsed since the last tumor response assessment. If a subject develops progressive disease or dies after this interval, the tumor response assessment will be excluded from the analysis. However, if an adequate tumor response assessment assigned as CR, PR, or SD is obtained after this interval, then the tumor response assessment will not be excluded from the analysis.

Abbreviations: CR=Complete Response; NE=Not Evaluable; PD=Progressive Disease; SD=Stable Disease

12.5 General Considerations for Secondary Efficacy Endpoints: ORR, TTR, and Length of Remission

- Tumor response assessments will be considered "adequate" for analysis if they are assigned as CR, PR, SD, or PD and are not censored (e.g., obtained prior to initiation of nonstudy antitumor treatment).

- Tumor response assessment dates will be assigned based on the date the image was performed, not the date the image was assessed.

- Tumor response assessments obtained after initiation of nonstudy antitumor treatment will be considered "inadequate" for analysis, flagged in the data listings, and excluded from all tumor response based efficacy analyses. Tumor response assessments obtained the same day as initiation of nonstudy antitumor treatment will not be excluded.

- Two or more tumor response assessments will be considered missed if more than 13 weeks (during combination therapy), more than 19 weeks (during single-agent maintenance therapy), or more than 16 weeks (across combination therapy and single-agent maintenance therapy) have elapsed since the last tumor response assessment. If a subject develops progressive disease or dies after this interval, the tumor response assessment will be excluded from the analysis. However, if an adequate tumor response assessment assigned as CR, PR, or SD is obtained after this interval, then the tumor response assessment will not be excluded from the analysis.

12.6 Adverse Events of Interest (AEI)

12.6.1 Hypersensitivity AEs

12.6.1.1 Overall Hypersensitivity AEs

A Hypersensitivity AE is defined as a TEAE with an onset date occurring the same day or the day immediately after exposure to Test Article for a pre-specified list of terms. The terms include, but are not limited to, the following signs and symptoms:

- Cytokine Release Syndrome
- Flushing
- Fever
- Rigors/chills
- Sweating/diaphoresis
- Pruritus/itching
- Urticaria
- Bronchospasm/wheezing
- Bronchial edema

In order for an AE to be classified as hypersensitivity AE, the following criteria are simultaneously required:

1. The AE term must meet a pre-identified MedDRA term in a pre-defined group search basket for hypersensitivity AEs.
2. The AE term must be a TEAE.
3. The AE must follow the 2-day rule; that is, the AE must have an onset date occurring the same day or the day after exposure to Test Article.

12.6.1.2 Hypersensitivity AEs with Positive ADA (DHAEs)

For farletuzumab, a DHAE is a hypersensitivity AE (programmably identified as specified in 12.6.1.1) accompanied by a positive titer for ADA. The determination of DHAE status for each hypersensitivity AE is dependent on the ADA sample results obtained on or subsequent to the onset date of the AEI. There could be multiple subsequent ADA samples. If the ADA results are positive for at least one of these samples, the hypersensitivity AE will be considered a DHAE.

12.6.2 Interstitial Lung Disease (ILD)

A separate excel spreadsheet containing a group search basket for Interstitial Lung Disease, using MedDRA query narrow search SMQ, will be used to identify ILD AEs. ILD AEs will include, but not limited to the following terms:

- Interstitial lung disease
- Pulmonary fibrosis
- Pneumonitis

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