1 TITLE PAGE

Clinical Study Protocol

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
Sponsor:	.Eisai Inc. 155 Tice Boulevard Woodcliff Lake, NJ 07677 USA Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112-8088 Japan Eisai , Ltd European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK
Investigational Product Name:	Farletuzumab (MORAb-003)
Indication:	Platinum-sensitive Ovarian Cancer
Phase:	2
Approval Date(s):	V1.0 10 Nov 2014 (Original Protocol) V2.0 12 Feb 2015 (Amendment 01) V3.0 18 Dec 2017 (Amendment 02) V4.0 06 Nov 2018 (Amendment 03)
IND Number:	BB12219
EudraCT Number:	2014-003812-36
ENGOT Number	ENGOT-ov27
BGOG Number	BGOG-ov18
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

REVISION HISTORY

Revisions to Version 4.0 (per Amendment 03)

Date: 06 Nov 2018

Change	Rationale	Affected Protocol Sections
Replaced "Morphotek" with "Eisai" where noted.	**Update of study ownership**	**Title page, Section 6, Section 9.1.3, Section 9.5.8, Section 9.6.1, Protocol Signature page, Document footers**

Revisions to Version 3.0 (per Amendment 02)

Date: 18 Dec 2017

Change	Rationale	Affected Protocol Sections
Removed the 1:1 target stratification ratio and the associated minimum enrollment of 105 subjects per stratum and the description of the required number progression-free survival (PFS) events	The cap of the 105 subjects to reach the 1:1 chemotherapy strata ratio has been removed. This change allows investigator discretion of chemotherapy with no impact to original primary PFS analysis of the combined strata. Revised accrual period based on current estimate. Made the median PFS and median OS in-between the medians of the 2 chemotherapy strata since 50-50% is no longer applicable. Since the 2 tests related to the 2 chemotherapy strata are removed, the sequential testing of PFS first and OS second became feasible now.	• Synopsis • Section 9.1 • Section 9.1.2 • Section 9.4.1 • Section 9.4.4
Removed the milestone (b) that at least 68 PFS events in each stratum were necessary for primary endpoint analysis		• Synopsis • Section 9.7.1.6.1
Sample size considerations are no longer based of the effect of farletuzumab on PFS in each of the 2 chemotherapy regimens. Removed the second comparison from the sample size rationale Accrual period changed to 38 months Changed assumption for median PFS to 11 months in the control arm Changed assumption for median overall survival (OS) to 32 months Sequential testing will also be employed for OS analysis		• Synopsis • Section 9.7.2
Removed the description of the PFS analysis to be conducted in both strata		• Section 9.7.1.6.1

Removed the description of the secondary efficacy analyses to be conducted in both strata Removed milestone (b) that at least 60 OS events in each strata were necessary for analysis; OS will be determined when there are at least 124 OS events		• Synopsis • Section 9.7.1.6.2
Added that the primary and secondary analyses (PFS, OS, objective response [OR], duration of response [DR]) in each strata were to be considered as exploratory analyses		• Section 9.7.1.6.3
Revised Figure 1 to remove target enrollments in each arm		• Section 9.1
Revised inclusion criteria 6 and 7	Clarification of intended eligibility to make consistent with other protocol sections.	• Synopsis • Section 9.3.1
Revised exclusion criteria 8 and 14		• Synopsis • Section 9.3.2
Added that 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	Because OS is in the sequential procedure, this is applicable now.	• Section 9.7.3

Revisions to Version 2.0 (per Amendment 01)

Date: 12 Feb 2015

Change	Rationale	Affected Protocol Sections
Provided method of randomization (central stratified block)	In order to provide additional clarity on protocol design.	• Synopsis • Section 9.1 • Section 9.1.2 • Section 9.4.4
Updated Inclusion Criteria #8 and Exclusion Criteria #13 to clarify that no medical contraindications may be present as outlined in the chemotherapy product labels for the selected regimen to be used in this study	In order to ensure consistency with chemotherapy prescribing information	• Synopsis • Section 9.3.1 • Section 9.3.2
Updated Inclusion Criteria #14 to state that subjects must continue to use a medically acceptable method of contraception throughout the entire study period and for **6 months** after the last dose of Test Article is administered, rather than **5 months**, which was the timeframe initially required.	In order to ensure consistency with chemotherapy prescribing information	• Synopsis • Section 9.3.1 • Section 9.5.4.2
Updated Exclusion Criteria #8 to state that subjects may not have had a known allergic reaction to the concomitant chemotherapies selected by the investigator for planned treatment in this study.	In order to ensure consistency with chemotherapy prescribing information	• Synopsis • Section 9.3.2
Clarified stopping rules for the study	In order to provide additional clarity on protocol conduct.	• Section 9.3.3
Added urine pregnancy testing (to be conducted locally) at Cycle 1 Day 1, Week 1 of every cycle in Combination and Maintenance Treatment periods, End of Treatment, and at the 30- and 60-Day Follow-up visits.	In order to ensure consistency with chemotherapy prescribing information, and provide additional guidance regarding contraception and pregnancy testing.	• Table 5 • Section 9.5.1.4.3 • Table 6 • Table 7
Specified that the censoring and handling rules on missing values will be detailed in the Statistical Analysis Plan (SAP), as well as potential sensitivity analyses with regard to missing values.	In order to provide additional clarity on statistical handling of data.	• Section 9.7.1

Updated quantities of blood to be drawn for bioanalytical sampling	In order to more closely align with central laboratory blood sample handling practices	• Synopsis • Section 9.5.1.3.2 • Appendix 1 • Appendix 2
The statement instructing sites to send images to Central Imaging Laboratory for rapid reads in the case of suspected disease progression was removed. In addition, text was corrected to note that the Central Imaging Laboratory will no longer contact sites directly with results but will contact sponsor instead.	Because it is anticipated that a limited number of sites will use the rapid read service, the statement was removed in order to eliminate the potential for bias that could be introduced by using a rapid read service.	• Section 9.5.1.2.1
Inserted a statement indicating that the dose of farletuzumab will be recalculated based on the weight taken at each protocol specified time point	To provide clarification that the dose should be adjusted according to changes in body weight throughout the treatment period and not based on weight at study baseline only	• Section 9.4.2.1
Removal of reference to subject initials on the IP accountability log as only subject number will be captured.	Subject initials will not be collected on the IP accountability logs.	• Section 11.8
Other editorial changes have been made throughout	To correct obvious errors and ensure accuracy of content	• Throughout

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: Farletuzumab (MORAb-003)

Name of Active Ingredient: MORAb-003

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

Investigators

List of investigators to be maintained separately by the sponsor

Sites

List of investigative sites to be maintained separately by the sponsor

Study Period and Phase of Development

Phase 2

Objectives

Primary:

The primary objective of the study is to demonstrate that farletuzumab has superior efficacy compared to placebo in improving progression-free survival (PFS) as determined by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 when added to 1 of 2 standard chemotherapy regimens (carboplatin plus paclitaxel or carboplatin plus PLD) in subjects with platinum-sensitive ovarian cancer in first relapse who have a cancer antigen 125 (CA125) ≤ 3x the upper limit of normal (ULN) (105 U/mL) at study entry.

Secondary:

- To assess the effect of farletuzumab on overall survival (OS) in this population
- 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 (OR) rate, time to response (TTR) and duration of response (DR) by RECIST 1.1 criteria
- To assess the safety and tolerability of farletuzumab
- To assess the pharmacokinetics and exposure-response relationships between farletuzumab and PFS and OS

Exploratory:

- To explore blood CA125 change pattern 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

Study Design

MORAb-003-011 is a global, multicenter, double-blind, randomized placebo-controlled study.

Subjects will be enrolled into 1 of 2 chemotherapy treatment arms at the investigator's discretion: carboplatin plus paclitaxel or carboplatin plus PLD, and then randomized in a 2:1 ratio to receive weekly farletuzumab 5 mg/kg or placebo (ie, Test Article) using a central stratified block randomization scheme. All subjects will receive a loading dose for the first 2 weeks of 10 mg/kg Test Article (farletuzumab or placebo). Subjects will be stratified at randomization by individual chemotherapy treatment regimen and platinum-free interval following first-line therapy (6-12 months vs >12-36 months).

All subjects must have CA125 ≤ 3 x ULN (105 U/mL) confirmed at Screening for study entry using a central laboratory designated by the sponsor to assure a standardized assay is used (Architect CA125 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.

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

An independent data monitoring committee (DMC) will be utilized to monitor the safety profile, and to enhance safety oversight.

Number of Subjects

A total of 210 subjects are planned for enrollment, including 140 subjects in the farletuzumab arm, and 70 subjects in the placebo arm.

Inclusion Criteria

1. Female subjects who are at least 18 years of age at the time of informed consent
2. CA125 ≤ 3 x ULN (105 U/mL) confirmed within 2 weeks of randomization using a centralized laboratory assay
3. A histologically confirmed diagnosis of high-grade serous epithelial ovarian cancer including primary peritoneal and fallopian tube malignancies; all other histologies, including mixed histology, are excluded
4. Have been treated with debulking surgery and a first–line platinum based chemotherapy regimen
5. Maintenance therapy during the first platinum-free interval is allowed; however, the last dose must have been at least 21 days prior to Randomization.
6. Must be in a first relapse and have evaluable disease by computed tomography (CT) or magnetic resonance imaging (MRI) scan, according to RECIST 1.1 (subjects with measurable disease per RECIST 1.1 or radiographically visible and evaluable disease). Subjects with only ascites or pleural effusion are excluded.
7. Must have relapsed radiographically within ≥6 months and ≤36 months of completion of first-line platinum chemotherapy
8. Must be a candidate for treatment with either carboplatin plus paclitaxel or carboplatin plus PLD with no medical contraindications present as outlined in the product labels for the selected regimen to be used in this study
9. Have a life expectancy of at least 6 months, as estimated by the investigator

10. Other significant medical conditions must be well-controlled and stable in the opinion of the investigator for at least 30 days prior to Randomization
11. Have an Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2
12. Subjects being enrolled to receive paclitaxel plus carboplatin treatment must have neuropathic function (sensory and motor) ≤ Grade 2 according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03
13. Laboratory results within the 2 weeks prior to Randomization must be as follows:
    - Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3
    - Platelet count ≥ 100,000 cells/mm^3
    - Hemoglobin ≥ 9 g/dL
    - Creatinine < 1.5 x ULN (CTCAE Grade 1)
    - Bilirubin < 1.5 x ULN (CTCAE Grade 1)
    - Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) < 3 x ULN (CTCAE Grade 1)
    - Alkaline Phosphatase < 2.5 x ULN (CTCAE Grade 1)
    - Baseline albumin ≥ Lower Limit of Normal
14. Subjects of childbearing potential must be surgically sterile or consent to use a medically acceptable method of contraception throughout the study period. All females will be considered to be of childbearing potential unless they are postmenopausal (eg, amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing). If a patient of childbearing potential is neither surgically sterile nor postmenopausal, a highly-effective contraceptive method (ie, a method that can achieve a failure rate of less than 1% per year when used consistently and correctly) must start either before or at Screening and continue throughout the entire study period and for 6 months after the last dose of Test Article is administered. Pregnant and/or lactating females are excluded
15. Subjects must provide written informed consent and be willing and able to comply with all aspects of the protocol

Exclusion Criteria

1. Known central nervous system (CNS) tumor involvement
2. Evidence of other active invasive malignancy requiring treatment other than surgery in the past 3 years
3. Clinically significant heart disease (eg, congestive heart failure of New York Heart Association Class 3 or 4, angina not well controlled by medication, or myocardial infarction within 6 months)
4. Electrocardiogram (ECG) demonstrating clinically significant arrhythmias that are not adequately medically managed (Note: subjects with chronic atrial arrhythmia, ie, atrial fibrillation or paroxysmal supraventricular tachycardia [SVT], are eligible)
5. Active serious systemic disease, including active bacterial or fungal infection
6. Active viral hepatitis or active human immunodeficiency virus (HIV) infection. Asymptomatic positive serology is not exclusionary
7. Other concurrent immunotherapy (eg, immunosuppressants or chronic use of systemic corticosteroids with the exception that low-dose corticosteroids [50 mg/day prednisone or equivalent corticosteroid] are allowed; these should be discussed with the Medical Monitor)
8. Known allergic reaction to a prior monoclonal antibody therapy or have any documented Anti-Drug Antibody (ADA) response; additionally known allergic reaction to the concomitant

chemotherapies selected by the investigator for planned treatment in this study unless desensitization is planned. 9. Previous treatment with farletuzumab or other folate receptor targeting agents 10. Previous treatment with cancer vaccine therapy 11. For subjects being enrolled to receive PLD plus carboplatin, prior treatment with anthracyclines or anthracenodiones 12. Breast-feeding, pregnant, or likely to become pregnant during the study 13. Any medical or other condition that, in the opinion of the investigator, would preclude the subject's participation in a clinical study including medical contraindications as outlined in the product labels for the chemotherapies selected by the investigator for planned treatment in this study 14. Patients who have had secondary debulking surgery or any second line therapy 15. Currently enrolled in another clinical study or used any investigational drug or device within 30 days (or 5 x half-life for investigational drugs where the half-life is known) preceding informed consent
Study Treatments The Test Article (farletuzumab or placebo) will be administered intravenously (IV) weekly. All subjects will receive a loading dose for the first 2 weeks of 10 mg/kg farletuzumab (or placebo), followed by 5 mg/kg weekly.
Duration of Treatment The duration of participation for individual subjects is expected to be approximately 46 months. This includes a maximum screening period of 30 days, an estimated median Test Article treatment period of 15 months, and an additional estimated survival follow-up period of 30 months. Subjects may discontinue for intolerable toxicity or may withdraw consent for any other reason at any time. Subjects who choose to discontinue Test Article but agree to continue in the study should still be followed for disease progression and OS.
Concomitant Drug/Therapy In addition to Test Article, all subjects will receive 6 cycles of chemotherapy: either carboplatin (area under the curve [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).
Assessments **Primary Efficacy:**

- PFS based on radiographic assessments utilizing RECIST 1.1 criteria

Secondary Efficacy:
- Overall Survival
- Length of first versus second platinum-free interval
- Tumor Response (OR, TTR, DR per RECIST 1.1)

Biomarkers:
- CA125 levels in blood and tissue
- Folate receptor alpha levels in blood, tissue, and urine
- Other exploratory biomarkers

Pharmacokinetics/Pharmacodynamics:
- Determination of farletuzumab serum concentration
- Exposure-response

Safety:
- Adverse Events (AEs) (including drug hypersensitivity AEs)
- Clinical laboratory tests (serum chemistry and hematology)
- Tolerability (discontinuations, treatment delays, dose reductions)
- ECGs
- Physical examinations
- ECOG Performance Status
- ADA

Standard safety monitoring and grading will be assessed using the NCI CTCAE.

Bioanalytical Methods

Serum samples will be analyzed to measure circulating farletuzumab concentrations using a validated quantitative assay. Similarly, a tiered analysis approach will be used to identify, confirm, and titer potential ADA responses in serum samples using validated assays. A blood sample (5.0 mL) will be collected for each test at Screening and at various time points throughout the study. Complete instructions for processing and shipping samples will be located in the laboratory manual, and bioanalytical method descriptions for serum farletuzumab and ADA are included as appendices to the protocol.

Statistical Methods

Analysis Populations:

- Intent-to-Treat Population (ITT), defined as all randomized subjects according to the treatment assigned by interactive response technology (IRT). This is the primary analysis population for all efficacy endpoints.
- Safety Analysis Set (SAS), 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, analyzed by the treatment received. All safety endpoints will be analyzed using this set of subjects.
- Evaluable Populations, 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 assessment performed. They will be

used to evaluate tumor response, farletuzumab serum drug levels, and other biomarker defined populations.

Primary Efficacy Endpoint Evaluation:

PFS is defined as the time (in months) from the date of randomization 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. The cut-off date for PFS will be based on the following milestone: a) at least a total number of 143 PFS events, or b) a minimum of 6 months PFS follow-up from last subject enrolled, whichever occurs later. The cut-off date for PFS will be used for secondary efficacy variables, as well as survival data supporting the interim survival analysis.

The stratified log rank test will be utilized 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 vs. carboplatin plus PLD), and (2) length of platinum-free interval following first line therapy (6-12 months vs. >12-36 months). The hazard ratio (HR) will be estimated based on Cox's proportional hazards model stratified by the same two factors.

Key Secondary Efficacy Endpoint Evaluation:

OS is defined as the time from the date of randomization to the date of death, due to all causes. 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. OS will be analyzed using methods similar to the PFS analyses.

Interim Analyses

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.

An interim analysis for OS will be performed to accompany the primary PFS analysis of the study. 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.

Sample Size Rationale

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 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, and 11.3 months for carboplatin plus PLD) 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 patients 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.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
1st Cmin	trough concentration at Cycle 2 Day 1
ADA	Anti-drug Antibody
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase (SGOT)
ATC4	Anatomical Therapeutic Chemical Class 4
AUC	area under the curve
BGOG	Belgian Gynecological Oncology Group
BLQ	below limit of quantitation
BSA	body surface area
CA	Competent Authority
CA125	cancer antigen 125
CALYPSO	Caelyx in Platinum Sensitive Ovarian patients
Carbo	carboplatin
CDR	complementarity determining region
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
C_{min}	minimum or “trough” concentration
$C_{min,av}$	average trough concentration from the final 3 visits
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CRA	clinical research associate
CRO	contract research organization
CSR	clinical study report

Abbreviation	Term
CT	computed tomography
CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
DHAE	drug hypersensitivity adverse event
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ENGOT	European Network of Gynecological Oncology Trials groups
EOS	end of study
EOT	end of treatment
EU	European Union
FAR	farletuzumab
FDA	United States Food and Drug Administration
FRA	folate receptor alpha
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HR	hazard ratio
IC	informed consent
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILD	interstitial lung disease
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology (web or voice randomization system)
ITT	intent-to-treat

Abbreviation	Term
IV	intravenous
LV	left ventricular
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	microRNA
MRI	magnetic resonance imaging
NE	not evaluable
OR	objective response
OS	overall survival
Pacli	paclitaxel
PCR	polymerase chain reaction
PD	progressive disease
PE	physical examination
PET	positron emission tomography
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetics
PLD	pegylated liposomal doxorubicin
PPE	palmar-plantar erythrodysesthesia
PR	partial response
RBC	red blood cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SOC	system organ class

Abbreviation	Term
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SVT	supraventricular tachycardia
TEAE	treatment-emergent adverse event
TMF	trial master file
TRAE	Treatment-related adverse event
TTR	time to response
ULN	upper limit of normal
US	United States
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

Documentation of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigators (or the sponsor) will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) per local requirements. The sponsor should also provide the IRB/IEC with a summary of the study's outcome, where required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

The definition for end of the study, as required by certain regulatory agencies, is the time of data cut-off for the final analysis or the time of last subject/last treatment, whichever occurs later. The estimated study end date is July 2019.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki October, 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 90 investigational sites in North America, Europe and Japan.

The name, telephone, fax number, and email address of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) will be provided on the Study Contact Sheet within the Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

The indication under study is platinum-sensitive ovarian cancer in first relapse with a cancer antigen 125 (CA125) level ≤ 3x the upper limit of normal (ULN).

7.1.1 Current Therapeutic Options

The standard first-line therapy for advanced ovarian cancer, following maximal cytoreductive surgery, is platinum-based chemotherapy. In 2004 the Ovarian Cancer Consensus Conference statements indicated carboplatin–paclitaxel as standard first-line therapy, and this regimen has been adopted as the control arm in the next generation studies (Guarneri, et al., 2010; Ledermann and Kristeleit, 2010). According to DeVita, et al., in women treated with platinum and taxane combinations as first-line therapy, the response rate (RR) ranges from 70% to over 80% (2011). Even if chemotherapy results in a complete clinical response (ie, normal physical examination [PE], normal serum CA125, and negative computed tomography [CT] scan of the abdomen and pelvis), about 50% of patients with Stage III or IV cancer have residual tumor. Most patients (≈75%) respond to initial treatment for ovarian cancer, although most will eventually experience relapse (Morgan, et al., 2012). Of patients with persistent elevation of CA125, 90 to 95% have residual tumor, and the recurrence rate in patients with a clinical complete response after initial chemotherapy (6 courses of carboplatin and paclitaxel) is 60 to 70% (Gershenson and Ramirez, 2013). The majority of patients eventually die of disease persistence or recurrence; long-term survival remains low, with a 5-year US relative survival rate of 44% across all stages (American Cancer Society, 2014).

Results of the randomized, multicenter, Phase 3 study CALYPSO (Caelyx in Platinum Sensitive Ovarian patients), which enrolled 976 patients in relapsed/recurrent ovarian cancer, were published by Pujade-Lauraine, et al., in 2010. Patients with histologically proven ovarian cancer with recurrence more than 6 months after first- or second-line platinum and taxane-based therapies were randomly assigned by stratified blocks to either carboplatin/pegylated liposomal doxorubicin (PLD) (carboplatin area under the curve [AUC] 5 plus PLD 30 mg/m^2) (Carbo/PLD) every 4 weeks or carboplatin/paclitaxel (carboplatin AUC 5 plus paclitaxel 175 mg/m^2) (Carbo/Pacli) every 3 weeks for at least 6 cycles. With median follow-up of 22 months, progression-free survival (PFS) for the Carbo/PLD arm was statistically superior to the Carbo/Pacli arm (hazard ratio [HR], 0.821; 95% confidence interval [CI], 0.72 to 0.94; *P*=0.005); median PFS was 11.3 versus 9.4 months, respectively.

In light of the CALYPSO trial data, PLD has been proven to be a highly active partnering agent for carboplatin in platinum-sensitive ovarian cancer; therefore, both chemotherapy combinations are deemed suitable standard of care options for use as study controls in ovarian cancer.

7.1.2 MORAb-003 (Farletuzumab)

7.1.2.1 Mechanism of Action

Farletuzumab is a humanized monoclonal antibody that binds to the folate receptor alpha (FRA). The expression of FRA is known to relate to the malignant potential of the cancer. Farletuzumab's mechanism of action is thought to be mediated via both complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity (ADCC) (MORAb-003 Global Investigator's Brochure, 2014).

7.1.2.2 Clinical Experience With Farletuzumab

Farletuzumab has been studied in the treatment of ovarian cancer (epithelial, platinum sensitive, platinum resistant, first relapse, and refractory relapsed), non-small cell lung cancer, and solid tumors. Farletuzumab is delivered by intravenous (IV) infusion. Eight clinical studies have been conducted to-date: 3 Phase 1 studies (MORAb-003-001, MORAb-003-005, MORAb-003-J081-102), 4 Phase 2 studies (MORAb-003-003, MORAb-003-009, MORAb-003-002, and long-term follow-up study MORAb-003-002A), and 1 Phase 3 study (MORAb-003-004). Across all studies, a total of 1192 subjects have been exposed to farletuzumab: 56 subjects in Phase 1 studies, 397 subjects in Phase 2 studies, and 739 subjects in Phase 3 studies (MORAb-003 Global Investigator's Brochure, 2014).

In study MORAb-003-001, 25 subjects received different dose levels of farletuzumab. Among them, 3 subjects were treated at a dose level of 200 mg/m^2, and 7 subjects were treated at a dose level of 400 mg/m^2, which are approximately equivalent to 5 mg/kg and 10 mg/kg, respectively. There were no drug-related AEs of Grade 3, 4, or 5.

Fifteen ovarian cancer patients received farletuzumab plus Carbo/PLD in study MORAb-003-005. Farletuzumab in combination with Carbo/PLD appears to be generally well-tolerated, and the safety profile of farletuzumab in combination with Carbo/PLD was consistent with that seen previously for the Carbo/PLD regimen. The clinical studies are summarized in the MORAb-003 Global Investigator Brochure (2014).

7.1.2.3 Common Serious Adverse Events Expected to Occur in the Study Population Even in the Absence of Study Drug Exposure

Since most patients with advanced ovarian cancer are treated as soon as possible, it can be very difficult to distinguish the symptoms related to the underlying disease from those related to the chemotherapy being administered. Generally, symptoms and serious adverse events (SAEs) associated with the natural course of disease can include ascites, abdominal pain, nausea, vomiting, diarrhea, gastrointestinal obstruction, back pain, urinary dysfunction, liver abnormalities due to metastatic disease, and thromboembolic complications. Those related to chemotherapy may include thrombocytopenia and neutropenia, nausea and vomiting and alopecia with most agents; and additionally those related to the specific chemotherapy being administered, such as cardiac toxicity and hand foot syndrome with PLD (DeVita and Rosenberg, 2006; DeVita, et al., 2011; Janssen, 2013).

7.2 Study Rationale

A Phase 3 study (MORAb-003-004) was performed to examine the efficacy, safety, and pharmacokinetics (PK) of farletuzumab (FAR) when added to carboplatin/taxane chemotherapy in subjects with platinum-sensitive ovarian cancer in first relapse. A total of 1100 subjects were randomized, and of these, 1091 received at least one dose of study drug (361 in the placebo + carboplatin/taxane group, 367 in the FAR 1.25 mg/kg + carboplatin/taxane group, and 363 in the FAR 2.5 mg/kg + carboplatin/taxane group). The primary analysis indicated that the study did not meet its primary endpoint for PFS (Data on file). Median PFS based on independent review in the intent to treat (ITT) population was 9.0, 9.5, and 9.7 months in the placebo, FAR 1.25 mg/kg, and FAR 2.5 mg/kg groups, respectively. Neither FAR group was different statistically from the placebo group for either PFS or overall survival (OS), however subgroup analysis on CA125 and farletuzumab exposure indicated positive results for PFS and OS that warrant further investigation (MORAb-003 Global Investigator's Brochure, 2014).

MORAb-003-004 Subgroup Analysis

CA125 has been used extensively as a serum biomarker to assess prognosis and recurrence in epithelial ovarian cancer. In the Phase 3 study (MORAb-003-004), CA125 serum levels were collected for subjects at screening, baseline, and at on-going intervals throughout the study. Due to the potential utility of CA125 as a biomarker of disease volume to supplement radiographic and clinical assessments, CA125 was pre-specified in the primary statistical analysis plan (SAP) as a covariate applied to subgroup efficacy analysis. A threshold of 3 x ULN was prespecified for these efficacy analyses. Previous literature has demonstrated that lower CA125 levels may be indicative of a less advanced state of disease and that rising

levels may correlate with disease progression (Markman, 1997; Markman, et al., 2006). This CA125 biomarker defined population of ≤3 x ULN includes subjects with normal CA125 levels and subjects with marginally elevated levels, therefore a patient population that may be associated with a lower overall disease burden or potentially less residual disease that may not be adequately captured radiographically. It is postulated that this disease environment characterized by less overall disease burden and less rapidly proliferating disease may be better suited to antibody treatment with farletuzumab, because farletuzumab exposure levels and tumor localization may take time to adequately accumulate based on the long half-life and to generate an associated immune response. It has also been suggested that CA125 (also known as MUC16) is implicated in the inhibition of target cell killing via ADCC by suppressing natural killer cell function, thereby reducing the efficacy of immunotherapeutic antibodies (Felder, et al., 2014).

The MORAb-003-004 subgroup analyses of primary data showed that subjects with baseline CA125 ≤ 3 x ULN (n=186) in the ITT population receiving high dose (2.5 mg/kg) farletuzumab versus those with baseline CA125 > 3 x ULN had a difference in median PFS of 13.6 months compared to 8.8 months in placebo (HR=0.49; *P*=0.0014). Subjects in the high dose >3 x ULN group had no difference in PFS (HR=0.97). The PFS clinical benefit was observed in further post-hoc analyses at several baseline and screening CA125 cut points with favorable HR at lower CA125 cut point levels but diminishing potential clinical effect as CA125 rises. An optimized CA125 cut point analysis was done as a supporting analysis of the CA125 subgroup efficacy analyses, and ≤ 3 x ULN was identified as the optimal cut point level. In addition, data from the final analysis indicated a positive benefit for OS (key secondary endpoint) for subjects with CA125 ≤ 3 x ULN in the 2.5 mg/kg FAR dose with a HR of 0.44 (*P*=0.0054).

In study MORAb-003-004, 77% of subjects were classified as serous histopathologic type and generally had better outcome across PFS and OS than other histology types including specifically clear cell. In the MORAb-003-004 study primary data subgroup of serous ovarian cancer subjects with screening CA125 ≤ 3 x ULN, the observed PFS difference was 14.3 months in 2.5 mg/kg farletuzumab versus 9.9 months in placebo (HR=0.52; *P*=0.0021). Serous tumors are associated with high target expression (94.4% expression of folate receptor alpha) and a more well-defined pattern of CA125 expression; therefore, subjects with serous tumors have been identified as an appropriate target population for the proposed proof-of-concept study (Data on file).

An exposure-response analysis of MORAb-003-004 found that PFS and OS in subjects with higher farletuzumab serum exposure levels was significantly longer compared with subjects with below-median farletuzumab levels and subjects receiving placebo treatment. Analyses were performed across various PK parameters including C_{min},av, 1st C_{min}, AUC, and steady-state C_{min} with similar results of potential observed benefit for higher exposure subjects.

Exposure-response analyses and PK simulation suggested that improved clinical benefit could potentially be obtained by increasing exposure of farletuzumab. PK concentration

simulations were performed based on the PK model to predict an optimal dosage regimen to achieve the target farletuzumab exposures. The results indicated that target 1st C_{min} (above 54 µg/mL) and steady-state C_{min} (above 120 µg/mL) can be reached and sustained in almost all patients following weekly dosing at 5 mg/kg. In addition, the 10-mg/kg loading dose given at the first and second treatments could bring the serum farletuzumab level to the targeted steady-state serum concentration within 2 weeks of start of treatment. (MORAb-003 Global Investigator's Brochure, 2014).

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to demonstrate that farletuzumab has superior efficacy compared with placebo in improving PFS, as determined by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 (Eisenhauer, et al., 2009), 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 ≤ 3 x ULN (105 U/mL) at study entry.

8.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the effect of farletuzumab on OS in this population
- 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 (OR) rate, time to response (TTR) and duration of response (DR) by RECIST 1.1 criteria (Appendix 4)
- To assess the safety and tolerability of farletuzumab
- To assess the PK and exposure-response relationships between farletuzumab and PFS and OS

8.3 Exploratory Objectives

The exploratory objectives of the study are:

- To explore blood CA125 change pattern 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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

MORAb-003-011 is a global, multicenter, double-blind, randomized placebo-controlled study in subjects with platinum-sensitive ovarian cancer in first relapse who have low CA125 (≤ 3 x ULN, or 105 U/mL).

Approximately 210 subjects will be 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 using a central stratified block randomization scheme. All subjects will receive a loading dose for the first 2 weeks of 10 mg/kg farletuzumab (or 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 vs >12-36 months). The randomization block will be defined in the IRT system.

All subjects must have CA125 ≤ 3 x ULN (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. Please refer to Section 9.5.8 for additional details on the DMC.

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.

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.

An overview of the study design is presented in Figure 1.

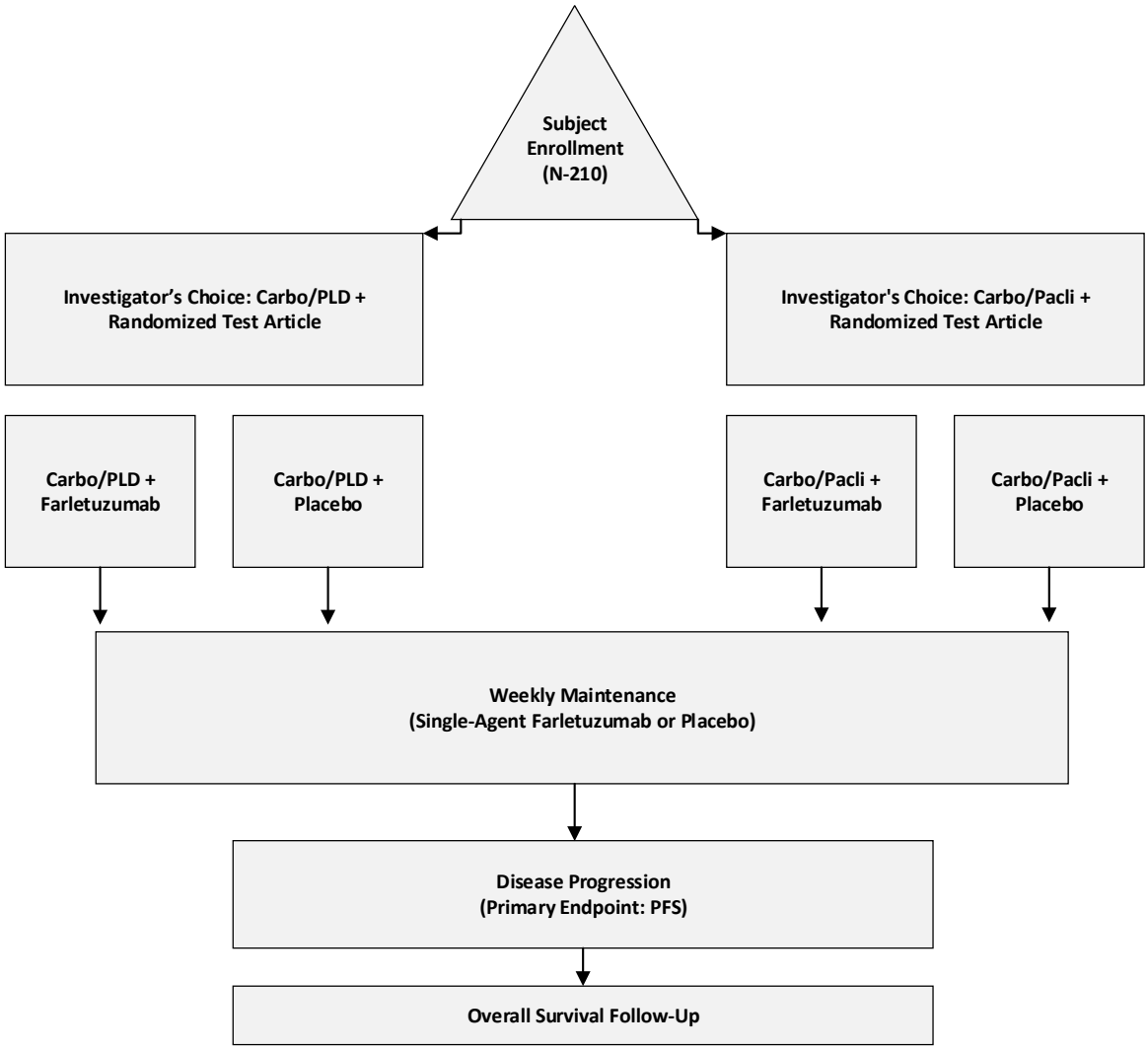

Figure 1 MORAb-003-011 Study Schema

9.1.1 Screening Phase

All Screening procedures must be completed within 30 days prior to and including the date of Randomization unless otherwise specified. The purpose of the Screening Phase is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any Screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

For specific details on the Screening Phase, refer to the Schedule of Procedures/Assessments (Table 6 and Table 7).

9.1.2 Randomization

Subjects who are eligible for this study will be enrolled into 1 of 2 chemotherapy treatment options 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 using a central stratified block randomization scheme and stratified by platinum-free interval following first-line therapy (6-12 months vs >12-36 months). The randomization block will be defined in the IRT system.

9.1.3 Combination Treatment Phase

The Combination Treatment Phase will extend from the start of Test Article administration until either disease progression is confirmed by radiographic assessment, or 6 cycles of chemotherapy are completed, whichever occurs first. Subjects are expected to initiate treatment with Test Article as close to the day of Randomization as possible but no later than 7 days following Randomization. If a delay in the start of Test Article beyond that timeframe is expected, the Eisai Medical Monitor must be contacted.

Subjects will receive the following treatments during the Combination Treatment Phase: 6 cycles of open-label treatment with 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) in combination with Test Article (either farletuzumab or placebo). All subjects will receive a loading dose for the first 2 weeks of 10 mg/kg farletuzumab (or placebo), followed by 5 mg/kg weekly thereafter.

Up to 2 additional cycles of Combination Treatment (to a maximum of 8 cycles) may be administered at the investigator's discretion.

Subjects who experience intolerable toxicity to chemotherapy and cannot complete 6 cycles of treatment should continue on to Maintenance Treatment with farletuzumab or placebo.

During the Combination Treatment Phase, computed tomography (CT) or magnetic resonance imaging (MRI) scans will be conducted every 6 weeks until documentation of disease progression.

For specific details on the Combination Treatment Phase, refer to the Schedule of Procedures/Assessments (Table 6 and Table 7).

9.1.4 Maintenance Treatment Phase

All subjects who complete the Combination Treatment Phase (as outlined in Section 9.1.3) will be eligible to receive Maintenance Treatment with farletuzumab (or placebo) 5 mg/kg weekly. The assessments to be completed during this phase are detailed in the Schedule of Procedures/Assessments (Table 6 and Table 7). Maintenance treatment will continue until disease progression is confirmed by radiographic assessment, or until the subject

discontinues treatment with Test Article for any other reason. During this phase, CTs or MRIs (see Section 9.5.1.2.1) will be conducted every 9 weeks (3 cycles) until documentation of disease progression.

9.1.5 End of Treatment

All subjects who discontinue treatment with Test Article at any time and for any reason will have an End of Treatment (EOT) Visit conducted. The assessments to be conducted at this visit are detailed in the Schedule of Procedures/Assessments (Table 6 and Table 7).

All EOT visit procedures should be conducted within 1 week following the last infusion of Test Article, unless the subject's medical management warrants otherwise.

9.1.6 Follow-Up Phase

The Follow-Up Phase for each subject will begin immediately after the EOT assessments have been completed and will continue as long as the study subject is alive or until the study subject withdraws consent or the sponsor chooses to discontinue the study. The assessments to be conducted during this phase are detailed in the Schedule of Procedures/Assessments (Table 6 and Table 7). Subjects who discontinue treatment with Test Article before disease progression will continue to undergo tumor response assessment by CT or MRI every 9 weeks until documentation of disease progression or start of another anticancer therapy. New anticancer therapies initiated during the Follow-up Phase will also be collected for these subjects.

9.1.7 End of Study

Following completion of all study-related assessments (eg, as a result of completion of survival follow-up), the End of Study (EOS) electronic case report form (eCRF) page should be completed. Refer to Section 9.5.5 for the definition of End of Study.

9.2 Discussion of Study Design, Including Choice of Control Groups

See Section 7.2 for a discussion of the study design.

9.3 Selection of Study Population

Approximately 210 subjects with low CA125 (≤3 x ULN or 105 U/mL) platinum-sensitive ovarian cancer in first relapse will be randomized at approximately 90 sites in regions that include North America, Europe, and Japan. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be enrolled into the study.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Female subjects who are at least 18 years of age at the time of informed consent
2. CA125 ≤3 x ULN (105 U/mL) confirmed within 2 weeks of randomization using a centralized laboratory assay
3. A histologically confirmed diagnosis of high-grade serous epithelial ovarian cancer including primary peritoneal and fallopian tube malignancies; all other histologies, including mixed histology, are excluded
4. Have been treated with debulking surgery and a first-line platinum-based chemotherapy regimen
5. Maintenance therapy during the first platinum-free interval is allowed; however, the last dose must have been at least 21 days prior to Randomization.
6. Must be in a first relapse and have evaluable disease by CT or MRI scan, according to RECIST 1.1 (subjects with measurable disease per RECIST 1.1 or radiographically visible and evaluable disease). Subjects with only ascites or pleural effusion are excluded. See Appendix 4.
7. Must have relapsed radiographically within ≥6 months and ≤36 months of completion of first-line platinum chemotherapy
8. Must be a candidate for treatment with either carboplatin plus paclitaxel or carboplatin plus PLD with no medical contraindications present as outlined in the product labels for the selected regimen to be used in this study
9. Have a life expectancy of at least 6 months, as estimated by the investigator
10. Other significant medical conditions must be well-controlled and stable in the opinion of the investigator for at least 30 days prior to Randomization
11. Have an Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2
12. Subjects being enrolled to receive paclitaxel plus carboplatin treatment must have neuropathic function (sensory and motor) ≤ Grade 2 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (National Cancer Institute, 2010)
13. Laboratory results within the 2 weeks prior to Randomization must be as follows:

    -Absolute neutrophil count (ANC) ≥1,500 cells/mm^3

    -Platelet count ≥100,000 cells/mm^3

    -Hemoglobin ≥9 g/dL

    -Creatinine <1.5 x ULN (CTCAE Grade 1)

    -Bilirubin <1.5 x ULN (CTCAE Grade 1)

    -Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) <3 x ULN (CTCAE Grade 1)

    -Alkaline Phosphatase <2.5 x ULN (CTCAE Grade 1)

    -Baseline albumin ≥ Lower Limit of Normal
14. Subjects of childbearing potential must be surgically sterile or consent to use a medically acceptable method of contraception throughout the study period. All females will be considered to be of childbearing potential unless they are postmenopausal (eg,

amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing). If a patient of childbearing potential is neither surgically sterile nor postmenopausal, a highly-effective contraceptive method (ie, a method that can achieve a failure rate of less than 1% per year when used consistently and correctly) must start either prior to or at Screening and continue throughout the entire study period and for 6 months after the last dose of Test Article is administered. Pregnant and/or lactating females are excluded

15. Subject must provide written informed consent and be willing and able to comply with all aspects of the protocol

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Known central nervous system (CNS) tumor involvement
2. Evidence of other active invasive malignancy requiring treatment other than surgery in the past 3 years
3. Clinically significant heart disease (eg, congestive heart failure of New York Heart Association Class 3 or 4, angina not well controlled by medication, or myocardial infarction within 6 months)
4. Electrocardiogram (ECG) demonstrating clinically significant arrhythmias that are not adequately medically managed (Note: subjects with chronic atrial arrhythmia, ie, atrial fibrillation or paroxysmal supraventricular tachycardia [SVT], are eligible)
5. Active serious systemic disease, including active bacterial or fungal infection
6. Active viral hepatitis or active human immunodeficiency virus (HIV) infection. Asymptomatic positive serology is not exclusionary.
7. Other concurrent immunotherapy (eg, immunosuppressants or chronic use of systemic corticosteroids, with the exception that low-dose corticosteroids [50 mg/day prednisone or equivalent corticosteroid] are allowed; these should be discussed with the Medical Monitor)
8. Known allergic reaction to a prior monoclonal antibody therapy or have any documented Anti-Drug Antibody (ADA) response; additionally known allergic reaction to the concomitant chemotherapies selected by the investigator for planned treatment in this study unless desensitization is planned
9. Previous treatment with farletuzumab or other folate receptor targeting agents
10. Previous treatment with cancer vaccine therapy
11. For subjects being enrolled to receive carboplatin plus PLD, prior treatment with anthracyclines or anthracenodiones
12. Breast-feeding, pregnant, or likely to become pregnant during the study

13. Any medical or other condition that, in the opinion of the investigator, would preclude the subject's participation in a clinical study including medical contraindications as outlined in the product labels for the chemotherapies selected by the investigator for planned treatment in this study
14. Patients who have had secondary debulking surgery or any second line therapy
15. Currently enrolled in another clinical study or used any investigational drug or device within 30 days (or 5 x half-life for investigational drugs where the half-life is known) preceding informed consent

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator will discontinue a subject's study treatment (chemotherapies and/or Test Article) or withdraw the subject from the study if any of the following circumstances occur at any time during the subject's study participation:

- The subject's continued participation, in the investigator's judgment, would be detrimental to her health
- The subject withdraws consent for continued participation or refuses further treatment with the study agent(s)
- The subject experiences an intolerable toxicity to chemotherapy not ameliorable by symptomatic treatment or dose schedule modification
- The subject has objective evidence of disease progression
- The Test Article is held for more than 28 days
- The subject experiences a hypersensitivity AE to Test Article of CTCAE Grade 3 that cannot be medically managed to a level of Grade 2 or a reaction of Grade 4 (see Section 9.5.1.4.7)
- The subject receives other anticancer therapy (eg, chemotherapy or radiotherapy) during the Combination Treatment Phase or Maintenance Treatment Phase
- The subject becomes pregnant

The investigator should confirm whether a subject will discontinue Test Article but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented.

The reason for discontinuation will be documented. If a subject discontinues treatment with Test Article and agrees to continue in the study, the subject will enter the Follow-Up Phase and complete protocol-specified EOT visits, procedures, and survival follow-up. 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.

All subjects will be followed for survival until death, except where a subject withdraws consent or the sponsor chooses to discontinue the study.

At the time of the completion of the study by the sponsor, provisions will be made to allow for continued treatment of subjects who have not yet experienced disease progression and are receiving Test Article as long as the efficacy endpoints of the trial have been met. In the event the study is terminated and the efficacy endpoints have not been met, all subjects will be required to discontinue Test Article administration.

9.4 Treatments

"Test Article" refers to the experimental drug being tested. The Test Article in this study is farletuzumab (or placebo). "Study Drug" refers to any drug(s) or formulations under evaluation in the study, including the Test Article and background chemotherapies. The Study Drugs in this study are farletuzumab, placebo, carboplatin, paclitaxel and PLD.

9.4.1 Treatments Administered

At the end of the Screening Phase, all eligible subjects will be 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 Test Article (farletuzumab or placebo). Subjects will receive a 10 mg/kg loading dose of Test Article for 2 weeks, followed by 5 mg/kg weekly. Combination Treatment will be administered by qualified personnel in the clinic for 6 cycles. Up to 2 additional cycles of Combination Treatment (to a maximum of 8 cycles) may be administered at the investigator's discretion. Subjects who experience intolerable toxicity to chemotherapy and cannot complete 6 cycles of treatment should continue on to Maintenance Treatment with farletuzumab or placebo.

On Day 1 of each cycle, the Test Article will be administered prior to chemotherapy (carboplatin plus paclitaxel or carboplatin plus PLD).

9.4.1.1 Farletuzumab

For subjects assigned to receive farletuzumab, the unblinded pharmacist or other appropriately qualified unblinded investigational site personnel (hereafter referred to as "unblinded pharmacist") will prepare the required volume of farletuzumab in an infusion bag. The remaining farletuzumab left in a vial after withdrawing the subject's assigned dose is not to be used for subsequent doses.

9.4.1.2 Placebo

For subjects assigned to receive placebo, the unblinded pharmacist will prepare an infusion bag identical to that used for farletuzumab administration. For the placebo infusion, the

amount of 0.9% sodium chloride administered should equal the volume which would be used if the subject was randomized to farletuzumab.

9.4.1.3 Administration of Test Article

The unblinded pharmacist (or designee) will document the time of drug preparation and then provide the prepared Test Article to blinded site personnel in a blinded manner for administration. Only appropriately trained blinded investigational site personnel are permitted to administer Test Article to study subjects.

Dilution of farletuzumab in normal saline is not necessary, however if institutional guidelines require dilution of monoclonal antibodies, farletuzumab may be diluted in a 1:1 ratio with normal saline.

For subjects randomized to receive placebo, the unblinded pharmacist should calculate the volume of farletuzumab that would have be given if the subject had been randomized to farletuzumab and then prepare saline equal to that volume in order to maintain the blind.

Test Article will be administered IV using an in-line 0.20 or 0.22 micron filter. The initial infusion will be delivered at 1 mL/min and the rate progressed as tolerated to 10 mL/min. If 10 mL/min is well-tolerated, subsequent infusions may begin at that rate. If infusion-related adverse effects are encountered, the infusion rate should be decreased by at least 50%, and then advanced back to the highest rate that was well-tolerated. (See Section 9.5.1.4.7 for the assessment and treatment of infusion-related adverse effects).

If an indwelling venous access device is used, Test Article will be administered via a different lumen than that used for blood collections whenever possible. Test Article should be administered via the most distal lumen of a multi-lumen catheter to reduce the possibility of confounding drug level analyses.

To ensure that the subject receives the full dose of Test Article, the tubing should be flushed with a volume of normal saline sufficient to deliver the Test Article remaining in the tubing.

Additional details on procedures for preparation of Test Article for administration are outlined in the Pharmacy Manual.

The following treatments will be administered to subjects in this study (Table 1).

Table 1 Treatments Administered

Drug Name	Dose	Dose Form/Route of Administration	Dose Schedule
Farletuzumab (MORAb-003)	10 mg/kg (Loading Dose)	Solution, delivered by IV infusion	Once weekly for the first 2 weeks of treatment
Farletuzumab (MORAb-003)	5 mg/kg	Solution, delivered by IV infusion	Once weekly, starting at Cycle 1/Week 3 and continuing until disease progression
-Or-			
Placebo	Same volume as farletuzumab	Farletuzumab-matched solution (normal saline), delivered by IV infusion	Same as above for farletuzumab
-And-			
Carboplatin	AUC 5	Solution, delivered by IV infusion	Every 3 weeks for 6 Cycles
Paclitaxel	175 mg/m^2	Solution, delivered by IV infusion	Every 3 weeks for 6 Cycles
-Or-			
Carboplatin	AUC 5	Solution, delivered by IV infusion	Every 4 weeks for 6 Cycles
PLD	30 mg/m^2	Solution, delivered by IV infusion	Every 4 weeks for 6 Cycles

AUC = area under the curve; IV = intravenous; PLD = pegylated liposomal doxorubicin

9.4.2 Dose Modification

9.4.2.1 Test Article (Farletuzumab or Placebo)

The dose of Farletuzumab will be calculated based on the weight taken at each protocol specified time point.

If Test Article is delayed more than 28 days, the subject must be discontinued from Test Article and should complete EOT procedures and continue to the Follow-Up Phase of the study.

Reasonable efforts will be taken to maintain a weekly dosing schedule of the Test Article. In the event of a delay in dosing with chemotherapy (carboplatin plus paclitaxel or carboplatin plus PLD), the dose of Test Article will be administered as planned. These will be considered "Test Article Administration Only" visits, as noted in the Schedule of Procedures/Assessments (Table 6 and Table 7). If chemotherapy must be held longer than 4 weeks within a given cycle, the subject should discontinue the Combination Treatment Phase and may move to the Maintenance Treatment Phase of the study.

9.4.2.2 Chemotherapy

The chosen regimen of chemotherapy (carboplatin plus paclitaxel or carboplatin plus PLD) must not change after randomization.

If there is toxicity due to chemotherapy (carboplatin plus paclitaxel or carboplatin plus PLD) during the first 6 cycles, doses may be reduced. Dose reductions of paclitaxel, PLD, or carboplatin should be made according to the schedules provided in Section 9.4.2.2.1, Section 9.4.2.2.2, and Section 9.4.2.2.3, respectively. Dose reductions for toxicities not listed in these sections can be made per package insert. In case the chemotherapy is discontinued due to intolerable toxicity, the subject will move into the Maintenance Treatment Phase and continue treatment with Test Article (farletuzumab or placebo) until confirmation of disease progression.

If there is a change of >10% of body weight, or as per study site guidelines, doses of carboplatin, paclitaxel, and PLD should be recalculated. Detailed instructions on dose modifications will be provided in the Pharmacy Manual.

The sponsor's Medical Monitor may be consulted for any issues related to dose modifications.

If there is a delay in dosing with chemotherapy, a "Test Article Administration Only" visit will be conducted (see Table 6 and Table 7). At the time of resuming chemotherapy administration, the administration cycle will reset. For example, the first day of carboplatin plus paclitaxel or carboplatin plus PLD administration will be on Week 1 Day 1 of the appropriate cycle. The protocol schedule of evaluations will be driven by the day and number of chemotherapy cycles (carboplatin plus paclitaxel or carboplatin plus PLD).

9.4.2.2.1 PACLITAXEL

Neutropenia or thrombocytopenia

- Paclitaxel should not be administered until:
  - the neutrophil count is at least 1,500 cells/mm^3, and
  - the platelet count is at least 100,000 cells/mm^3
- Subjects who experience severe neutropenia (neutrophil < 500 cells/mm^3 for a week or longer) during paclitaxel therapy should have the dose reduced by 20% for subsequent courses of paclitaxel.

Peripheral neuropathy

Grade 2 peripheral neuropathy during paclitaxel therapy should have the dose reduced by 20% for subsequent courses of paclitaxel.

9.4.2.2.2 PEGYLATED LIPOSOMAL DOXORUBICIN (PLD)

If the subject experiences early symptoms or signs of infusion reaction, immediately discontinue the infusion, give appropriate premedications (antihistamine and/or short acting corticosteroid) and restart at a slower rate.

To manage adverse events such as palmar-plantar erythrodysesthesia (PPE), stomatitis or hematological toxicity, the dose may be reduced or delayed. Guidelines for dose modification secondary to these adverse effects (as detailed in the CAELYX® Product Information sheet [2013]) are provided below (Table 2, Table 3, and Table 4). The toxicity grading in these tables is based on the CTCAE criteria.

The tables for PPE and stomatitis provide the schedule followed for dose modification in clinical trials in the treatment of breast or ovarian cancer (modification of the recommended 4 week treatment cycle).

Table 2 PLD Toxicity—Hematological (ANC or Platelets)

GRADE	ANC (cells/mm^3)	PLATELETS (cells/mm^3)	MODIFICATION
Grade 1	1,500 – 1,900	75,000 – 150,000	Resume treatment with no dose reduction
Grade 2	1,000 - <1,500	50,000 - <75,000	Wait until ANC ≥1,500 cells/mm^3 and platelets ≥75,000 cells/mm^3; redose with no dose reduction
Grade 3	500 - <1,000	25,000- <50,000	Wait until ANC ≥1,500 cells/mm^3 and platelets ≥75,000 cells/mm^3; redose with no dose reduction
Grade 4	<500	<25,000	Wait until ANC ≥1,500 cells/mm^3 and platelets ≥75,000 cells/mm^3; decrease dose by 25% or continue full dose with growth factor support.

ANC = absolute neutrophil count; PLD = pegylated liposomal doxorubicin

Table 3 PLD Toxicity—Palmar-Plantar Erythrodysesthesia

Toxicity Grade at Current Assessment	Week After Prior Dose		
	Week 4	Week 5	Week 6
Grade 1: mild erythema, swelling, or desquamation not interfering with daily activities	**Redose unless** subject has experienced a previous Grade 3 or 4 skin toxicity, in which case wait an additional week	**Redose unless** subject has experienced a previous Grade 3 or 4 skin toxicity, in which case wait an additional week	**Decrease dose by 25%; return to 4 week interval**
Grade 2: erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter	**Wait an additional week**	**Wait an additional week**	**Decrease dose by 25%; return to 4 week interval**
Grade 3: blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing	**Wait an additional week**	**Wait an additional week**	**Withdraw subject**
Grade 4: diffuse or local process causing infectious complications, or a bedridden state or hospitalization	**Wait an additional week**	**Wait an additional week**	**Withdraw subject**

Table 4 PLD Toxicity—Stomatitis

Toxicity Grade at Current Assessment	Week After Prior Dose		
	Week 4	Week 5	Week 6
Grade 1: painless ulcers, erythema, or mild soreness	**Redose unless** subject has experienced a previous Grade 3 or 4 stomatitis in which case wait an additional week	**Redose unless** subject has experienced a previous Grade 3 or 4 stomatitis in which case wait an additional week	**Decrease dose by 25%; return to 4 week interval** or withdraw subject per physician's assessment
Grade 2: painful erythema, oedema, or ulcers, but can eat	**Wait an additional week**	**Wait an additional week**	**Decrease dose by 25%; return to 4 week interval** or withdraw subject per physician's assessment
Grade 3: painful erythema, oedema, or ulcers, but cannot eat	**Wait an additional week**	**Wait an additional week**	**Withdraw subject**
Grade 4: requires parenteral or enteral support	**Wait an additional week**	**Wait an additional week**	**Withdraw subject**

Subjects on this study will typically receive a cumulative anthracycline dose significantly below 450 mg/m^2, and thus will not require routine monitoring of left ventricular (LV) cardiac function. Should the above dose be exceeded in a rare subject, or should there be clinical evidence of deterioration of LV function at any dose, monitoring of LV function (typically by echocardiogram or multigated acquisition scan) should be instituted and no further anthracycline should be administered if there is evidence of impaired LV function.

9.4.2.2.3 CARBOPLATIN

Neutropenia or thrombocytopenia

Carboplatin should not be repeated until the neutrophil count is at least 1500 cells/mm^3 and the platelet count is at least 100, 000 cells/mm^3.

For renal toxicity of carboplatin the dose in mg will be modified per institutional procedures to maintain AUC 5.

In the event of an allergic reaction to carboplatin, the subject may undergo a desensitization procedure at the discretion of the investigator. The standard protocol in use at the investigative site should be used. The subject may remain on the study if, after completion of the desensitization procedure, they are a candidate to remain on carboplatin plus paclitaxel or carboplatin plus PLD therapy at the planned dose and schedule.

9.4.3 Identity of Investigational Products

Farletuzumab will be supplied to the clinical site by a third-party drug distribution vendor.

Farletuzumab is packaged in single-use vials. The dose of farletuzumab required for a subject is to be taken from as many vials as required. Any farletuzumab remaining in a vial after withdrawing the subject's assigned dose is not to be used for subsequent doses.

Saline for placebo will be provided by the site and delivered to the blinded study team in a manner that will preserve the blind.

9.4.3.1 Farletuzumab

Farletuzumab (Chemical Name: MORAb-003) is a humanized IgG1/κ monoclonal antibody that binds to the human FRA. The MORAb-003 antibody is produced by a transfected Chinese hamster ovary K1 cell line and has been constructed by grafting murine complementarity-determining (humanized) regions into a human IgG1/κ backbone. Farletuzumab is formulated as 5.0 mg/mL (± 0.5 mg/mL) in phosphate buffered physiological saline (pH 7.2) (MORAb-003 Global Investigator's Brochure, 2014). No animal-derived materials, except production cells, are used in any step of the cultivation and purification processes for MORAb-003 production.

The formulations to be used in this clinical study are presented below:

Study product:	Farletuzumab
Formulation:	Phosphate buffered saline with 0.01% Tween 80
Strength:	5 mg/mL
Route of administration:	IV infusion

Farletuzumab as an investigational product is available for IV administration in single-use vials (5 mL and 20 mL) of sterile drug product (5 mg/mL farletuzumab in phosphate-buffered saline with 0.01% Tween 80).

Additional details of the farletuzumab drug substance and drug product are provided in the MORAb-003 Global Investigator's Brochure (2014).

9.4.3.2 Placebo

Normal saline will be used as placebo and will be supplied by the investigational site unless prohibited by local regulations or institutional policy.

9.4.3.3 Chemotherapies

The chemotherapies administered during the study (carboplatin, paclitaxel, and PLD) will be supplied by the investigational site unless prohibited by local regulations or institutional policy. All chemotherapeutic agents used in this clinical trial will meet the applicable US Food and Drug Administration (FDA), European Medicines Agency, or local regulatory standards.

9.4.3.4 Chemical Name, Structural Formula of Investigational Product

MORAb-003

9.4.3.5 Comparator Drug

Placebo is used as a comparator in this randomized, double blind study. (Refer to Section 9.4.3.2 for details.)

9.4.3.6 Labeling for Test Article

Farletuzumab will be labeled as investigational product per local regulations, and supplied to the clinical site by a third-party drug distribution vendor.

9.4.3.7 Storage Conditions

The chemotherapies (carboplatin, paclitaxel, and PLD) must be stored as instructed on their associated labels.

Farletuzumab must be kept in a secure location at the study site, stored at 2°C to 8°C in its original container, and protected from light. Note that all relevant site-specific guidelines and country-specific labeling requirements must be followed. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

Additional details on the storage, handling, and inventory of farletuzumab will be provided in the study Pharmacy Manual and MORAb-003 Global Investigator's Brochure (2014).

9.4.4 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. All investigational sites will receive training during their initiation visits regarding procedures to enroll subjects.

After the Screening Phase, subjects who qualify for the study will be randomized in a 2:1 ratio to the following treatment groups: either farletuzumab or placebo weekly.

Central stratified block randomization will be used, which will be performed by interactive response technology (IRT). The IRT system will generate the randomized identification numbers.

Randomization will be stratified as follows:

1. Carboplatin/paclitaxel versus carboplatin/PLD
2. By platinum-free interval following first-line therapy (6-12 months vs >12-36 months)

9.4.5 Selection of Doses in the Study

The results of the exposure-response analysis of MORAb-003-004 and subsequent PK modeling suggests that target exposure levels can be reached and sustained in almost all subjects following weekly dosing at 5 mg/kg, with 2 loading doses of 10 mg/kg for the first 2 weeks of treatment to facilitate rapid serum farletuzumab concentration levels (Data on file; MORAb-003 Global Investigator's Brochure, 2014).

9.4.6 Selection and Timing of Dose for Each Subject

Refer to Section 9.4.1 for details on selection and timing of doses for individual subjects.

9.4.7 Blinding

This study is randomized and double-blinded. A master list of all treatments and the subject numbers associated with them will be maintained by the IRT vendor. In the event that emergency conditions require knowledge of the Test Article given, the blind may be broken through the IRT system. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study will be blinded to the treatment codes, including investigators, site personnel, and sponsor staff, unless specifically designated as unblinded and independent from the study team. Such independent, unblinded study personnel may include: drug distribution, interactive web or voice response system (IRT) vendor staff, an independent site monitor for each site for drug accountability and pharmacy oversight, DMC members, and an independent statistician who generates outputs for DMC review. Pharmacovigilance staff will be unblinded as necessary for reporting to regulatory authorities, with appropriate controls to assure that access to any unblinded information is restricted to the safety reporting staff. The sponsor will maintain a list of any designated individuals at the investigative site, sponsor, and select vendors (where appropriate) that are designated as unblinded.

Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety, DMC) until the time of unblinding, per standard operating procedure.

Best practices within the site should be exercised to maintain the blinding of investigators, subjects, study coordinators and all study staff. Unblinded site personnel will include a pharmacist or designee, who will prepare the Test Article (farletuzumab or placebo) and dispense it in a blinded fashion. All relevant site personnel will receive training during site initiation visits on blinding and unblinding procedures.

The primary site monitor will be blinded; hence, a separate unblinded monitor will be assigned specifically for drug accountability and monitoring of pharmacy procedures. Data collection and management staff will maintain blinding of data until a formal unblinding notification is provided by the sponsor for final analysis of the primary efficacy endpoint. All unblinded data maintained during the study until final unblinding authorized for analysis, including safety data required for the DMC or as requested by regulatory agencies, will be maintained in a secure, restricted-access data file system.

The study will be unblinded for analysis purposes at the time of the primary PFS analysis; however, no subject-level unblinding information will be communicated to the sites until the final OS analysis has been completed.

Each investigator will ensure that the blind is broken only in accordance with the protocol conditions for unblinding due to medical necessity or for safety reasons. Individual subject unblinding by the investigator should only be performed in the case of a medical emergency requiring knowledge of the treatment assignment. Premature unblinding must be reported to the medical monitor immediately and must be documented with an explanation (eg, due to an SAE).

Specific details for blinding and pharmacy procedures will be outlined in the site's blinding plan and/or the Pharmacy Manual, and all pharmacy-related questions should be directed to the unblinded monitor. All other study-related questions should be directed to the sponsor medical monitor or other sponsor personnel (or designee), as appropriate.

9.4.8 Prior and Concomitant Therapy

All prior medications (including over-the-counter medications) administered 30 days before the first dose of Test Article and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 30 days after the final dose of Test Article will be recorded.

Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with farletuzumab or other study treatments may be continued during the study.

Aspirin, nonsteroidal antiinflammatory drugs, and low-molecular-weight heparin are permissible but should be used with caution. Granulocyte colony-stimulating factor or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines, but the subject should be carefully monitored for increases in red blood cell (RBC) counts.

9.4.8.1 Premedications

All premedications for Test Article and chemotherapy must be reported in the eCRF.

9.4.8.1.1 Premedications for Test Article

All subjects must be premedicated within 4 hours prior to Test Article (farletuzumab or placebo) infusion with acetaminophen 650 mg by mouth or clinical equivalent per clinic routine and country availability.

In the event of a hypersensitivity AE believed to be associated with Test Article (farletuzumab or placebo) infusion, subjects should be premedicated for subsequent infusions with antipyretic and histamine receptor blocking medications (eg, diphenhydramine, ranitidine, etc.), per the clinic routine, in order to reduce the incidence/severity of fluid retention and/or hypersensitivity reactions. These medications will be reported in the eCRF.

Refer to Section 9.5.1.4.7 for additional details regarding the administration of secondary prophylaxis for treatment of hypersensitivity AEs.

9.4.8.1.2 PREMEDICATIONS FOR CHEMOTHERAPY

Antiemetics may be given with chemotherapy at the discretion of the investigator. Premedications for carboplatin and paclitaxel should be given according to country-specific labeling.

Carboplatin

Anaphylactic-like reactions to carboplatin have been reported and may occur within minutes of carboplatin administration. Epinephrine, corticosteroids and antihistamines may be employed to alleviate symptoms.

Paclitaxel

All subjects must be premedicated with corticosteroids prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. A typical regimen is dexamethasone 20 mg orally, administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel administration.

Pegylated Liposomal Doxorubicin (PLD)

No premedication is required for use with PLD. Serious and sometimes life-threatening infusion reactions to PLD, which are characterized by allergic-like or anaphylactoid-like reactions, may occur within minutes of starting the infusion. Medications to treat these symptoms (eg, antihistamines, corticosteroids, adrenaline, and anticonvulsants), as well as emergency equipment, should be available for immediate use.

9.4.8.2 Drug-Drug Interactions

There are no known drug-drug interactions between any of the therapeutic or concomitant medications used in the study.

9.4.8.3 Prohibited Concomitant Therapies and Drugs

Subjects should not receive other anticancer therapies while on study. If subjects receive additional non-study anticancer therapies, such as chemotherapy, hormone therapy, or immunotherapy, this will be judged to represent evidence of disease progression, and Test Article will be discontinued. These subjects should complete all EOT assessments and continue to be followed for survival in the Follow-Up Phase.

9.4.9 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Unblinded CRAs will review treatment compliance during site pharmacy visits and at the completion of the study. Test Article is to be dispensed only to subjects enrolled in the clinical trial. Infusions of the study drugs are to be administered by appropriately trained and qualified personnel.

9.4.10 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the unblinded pharmacist until the following documentation has been received by the sponsor or CRO personnel:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by the investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the PI, and, where available, a copy of the PI's current medical license or medical registration number (preferably included on the curriculum vitae)
- A signed and dated clinical studies agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The unblinded pharmacist will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to ICH GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, reconciliation of unused study drugs that are

shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs that occurs at the site, where available. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The Test Article and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor (ie, unblinded CRA) or a representative of a health authority (eg, FDA, Medicines and Healthcare Products Regulatory Agency).

Drug accountability will be reviewed during site pharmacy visits and at the completion of the study by the unblinded CRA.

As permissible by site standards, all empty and partially used Test Article vials are to be destroyed by the site. Destruction will occur following the site's standard procedures and certificates of destruction will be maintained. If destruction on site is not allowed, arrangements can be made to return used vials to the depot.

At the conclusion of the study or by sponsor directive, and upon completion of drug accountability and reconciliation procedures by the site's unblinded personnel and review by the unblinded CRA, any unused vials of Test Article that were shipped to the site but not administered to subjects must be destroyed by the site or boxed, sealed, and shipped back to the sponsor's designated central or local depot, following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Screening Assessments

9.5.1.1.1 DEMOGRAPHY

Subject demography information will be collected during Screening. Demography information includes date of birth (or age), gender, and race/ethnicity. Subject initials will not be collected to protect subject confidentiality.

9.5.1.1.2 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. Relevant medical and surgical history must be noted in the eCRF.

PEs (comprehensive or abbreviated/symptom-directed) will be performed as designated in the Schedule of Procedures/Assessments (Table 6 and Table 7). Comprehensive PEs will be performed at Screening and at the EOT visit, and will include evaluations of the following systems: general appearance, HEENT, respiratory, cardiovascular, abdomen, musculoskeletal, neurological, extremities, lymph nodes, dermatologic, and vital signs. Abbreviated PEs will be conducted at all other time points, as indicated in Table 6 and Table 7. Abbreviated PEs will include follow-up of interval complaints and review of the cardiorespiratory system.

Documentation of the PE will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History eCRF. Changes from Screening PE findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

9.5.1.1.3 Body Weight, Height, and Body Surface Area

Body weight will be measured at Screening, and at the time points listed in the Schedule of Procedures/Assessments (Table 6 and Table 7). Body weight will always be collected prior to Test Article (farletuzumab or placebo) administration at the specified time points.

Height will be measured on all subjects only at the Screening visit.

9.5.1.1.4 Prior Cancer History

During Screening, disease stage and tumor histologic type at initial diagnosis for each subject's ovarian cancer will be collected.

Any prior cancer therapy will also be recorded.

Historical CA125 results will also be collected.

9.5.1.1.5 Performance Status (ECOG)

All subjects will be assessed for ECOG Performance Status (Appendix 3) at Screening and at the time points listed in the Schedule of Procedures/Assessments (Table 6 and Table 7).

9.5.1.1.6 Assessment of Cardiac Function

All subjects enrolled will have a 12-lead ECG conducted at Screening and at the EOT Visit.

9.5.1.2 Efficacy Assessments

9.5.1.2.1 RECIST 1.1 (CT or MRI)

As part of the disease assessment by RECIST 1.1 criteria (Appendix 4), 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 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.

Positron emission tomography (PET)/CT scans are generally not acceptable for study readings; however, if the CT portion meets criteria for an "optimized CT" as defined in the radiology charter, these CTs may be submitted. The same methods of assessment and same techniques (eg, CT scan, spiral CT scan, or MRI) should be used throughout the study to characterize each identified and reported lesion. Lossy compressed images should not be submitted as information is lost when image is compressed.

Radiographic assessments (CT or MRI) will be performed according to the Schedule of Procedures/Assessments (Table 6 and Table 7).

Subjects who discontinue treatment with Test Article for reason other than disease progression (eg, AE or intolerable toxicity) should be followed radiographically until documented progression or initiation of any new anticancer treatment. Where feasible, follow-up scans should be obtained at the same schedule as Maintenance Treatment (ie, every 9 weeks) until disease progression is confirmed or at study completion.

The investigators' objective measures of disease (CT or MRI scan), graded according to the RECIST 1.1 criteria (Appendix 4), will be used to determine PFS, the primary efficacy endpoint of the study. Subjects with measurable disease will be assigned to one of the categories of change in disease state, namely, "complete response (CR)," "partial response (PR)," "stable disease (SD)," "progressive disease (PD)," or "not evaluable (NE)." Subjects with evaluable only disease will be assigned to one of the categories of change in disease state, namely, "complete response (CR)," "stable disease (SD)," "progressive disease (PD)," or "not evaluable (NE)." The interpretation of the scan will be recorded on the eCRF.

Secondary efficacy endpoints involving assessment dates, date of response, and date of disease progression will also be based on data from the investigators' assessment of images using RECIST 1.1 criteria (eg, length of platinum-free interval, OR, TTR, and DR).

All CT or MRI scans will be sent by the study sites to an independent central imaging laboratory for quality control purpose. Refer to Section 9.6 for additional details.

9.5.1.2.2 CA125 ASSESSMENT

Assessment of CA125 levels will be used to determine eligibility and will be used for exploratory analysis, and will be measured at the time points specified in the Schedule of Procedures/Assessments (Table 6 and Table 7).

At Screening, CA125 levels will be analyzed by the Central Laboratory for confirmation of eligibility. Samples for this analysis must be provided within 2 weeks prior to Randomization.

9.5.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

Blood samples for the assessment of serum levels of farletuzumab are to be drawn before and after the infusion (ie, within 1 hour after the completion of the infusion) of Test Article as specified in the Schedule of Procedures/Assessments (Table 6 and Table 7). Quantities of blood to be drawn at each study time point are provided in Appendix 2. See Laboratory Manual for a description of collection, handling, and shipping procedures for PK samples.

Samples will be analyzed using a fluorescent immunoassay format that measures free forms of farletuzumab in human serum. This assay was validated for regression model fit, selectivity, accuracy/precision, minimum required dilution, range of quantification, dilutional linearity/prozone, sample stability, and robustness. See Appendix 1 for additional details on PK analyses.

Blood samples for the assessment of serum levels of farletuzumab are to be collected via an indwelling catheter or via venipuncture into tubes for serum collection provided by the Central Laboratory. If the samples are collected through a catheter, 1.0 mL of blood will be withdrawn and discarded to assure that the solution used to maintain catheter patency does not dilute the sample. If a multilumen catheter is used, samples should be drawn "upstream" or proximal to the Test Article delivery lumen, never from the same lumen that was used for Test Article delivery. If the Test Article is being administered by peripheral IV, do not withdraw the blood from the arm in which the Test Article is being given. The anatomical sites from which the samples are drawn and through which Test Article is administered must be documented in the medical record.

Logistical considerations may dictate a deviation from the protocol-specified sample collection time point. In each case, the actual time of sampling and actual start/stop times of infusions must be documented.

9.5.1.3.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Archived tumor tissue, blood, and urine samples will be collected from all consenting study subjects from both treatment groups for biomarker analyses. The objective of these analyses is the potential identification of biomarkers that either predict or determine clinical response

to farletuzumab, or that may be used to understand the pharmacology of farletuzumab in a subject. Samples will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 6 and Table 7). Instructions for the collection, processing, storage, and shipping of samples will be provided in a separate Laboratory Manual.

An archival tumor tissue sample (formalin-fixed, paraffin embedded block) taken at the time of initial diagnosis of ovarian cancer will be collected during Screening in order to assess tumor histology and for assessment of biomarkers. These analyses require either the original primary tumor block or 15-20 (4-5 micron) serial sections cut from the original primary tumor block. If a minimum of 15 slides are not available, contact the CRA to discuss.

Tissue biomarker samples from study subjects may be used to analyze deoxyribonucleic acid (DNA), ribonucleic acid (RNA), microRNA (miRNA), or proteins by any of a number of technologies including next generation sequencing, polymerase chain reaction (PCR), mutation analysis, immunohistochemistry, or other assays/methods.

A urine sample will be collected at Screening, within 2 weeks of Randomization, for biomarker analysis.

At Screening, within 2 weeks of Randomization, 22.0 mL of blood will be collected for biomarker and nucleic acid extraction and analysis (one 8.5-mL vial for DNA extraction, one 6.0-mL vial for plasma, one 5.0-mL vial for serum, and one 2.5-mL vial for RNA extraction).

At subsequent time points throughout the study (Table 6 and Table 7), 11 mL of blood will be collected for biomarker assessment (one 5.0-mL vial for serum, and one 6.0-mL vial for plasma).

Genomic (blood) DNA/RNA/miRNA extracted from whole blood from study subjects may be analyzed by any of a number of technologies including next generation sequencing, PCR, mutation analysis, or other assay/methods.

Serum, urine, and plasma biomarker samples from study subjects may be analyzed using any of a number of technologies including genomic, proteomic, metabolomic, lipidomic, or other assays/methods.

Samples (tissue, serum, plasma, urine, genomic nucleic acid) may be used for biomarker discovery and/or validation to identify biomarkers that may be useful to predict treatment response (efficacy, PD), and/or safety-related outcomes. Samples may also be used for the development of potential diagnostics for farletuzumab. The decision to perform exploratory biomarker analysis may be based on the clinical outcome of the study and/or the signals observed in other clinical studies.

9.5.1.4 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all CTCAE grades (for both increasing and decreasing severity), and SAEs; regular monitoring of hematology, and blood chemistry values; periodic measurement of ECGs; performance of PEs; assessment of ECOG scores; and assessment of survival status, as detailed in the Schedule of Procedures/Assessments (Table 6 and Table 7).

9.5.1.4.1 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the study drug(s).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product
- Any new disease or exacerbation of an existing disease; however, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (ie, prior to the first administration of study drug)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit and for 30 days after the subject's last dose of Test Article.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. The investigator is responsible for reviewing all laboratory findings in all subjects to determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Any ECG abnormality that the investigator considers to be an AE should be reported as such. All AEs must be followed for 30 days after the subject's last dose of Test Article, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study drug(s).

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to the CTCAE v4.03 (National Cancer Institute, 2010). Investigators will report CTCAE grades for all AEs.

Assessing Relationship to Study Drug(s)

Items to be considered when assessing the relationship of an AE to the study drug(s) are:

- Temporal relationship of the onset of the event to the initiation of the study drug
- The course of the event, especially the effect of discontinuation of study drug(s) or reintroduction of study drug(s), as applicable
- Whether the event is known to be associated with the study drug or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded in the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related)	A causal relationship between the study drug and the AE is a reasonable possibility.
No (not related)	A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.4.2 Serious Adverse Events and Other Events of Interest

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

Other events of interest include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events of interest are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with events of interest are to be reported in the eCRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations due to disease progression
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

Death due to disease progression is a study endpoint, and is therefore not considered an SAE in this study and does not need to be reported as such, unless required by local regulations.

9.5.1.4.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed for safety assessment, including hematology, chemistry, and pregnancy testing are summarized in Table 5. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 6 and Table 7) lists the visits and time points at which blood for clinical laboratory tests will be collected in the study.

Table 5 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and white blood cell count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	Albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), bilirubin (total, direct, and indirect), blood urea nitrogen, calcium, bicarbonate, chloride, cholesterol, creatinine, globulin, glucose, lactate dehydrogenase, magnesium, phosphorous, potassium, sodium, total protein, triglycerides, uric acid
Pregnancy Test (hCG)	Serum, urine (highly-sensitive)

ALT (SGPT) = alanine aminotransferase; AST (SGOT) = aspartate aminotransferase; hCG = human chorionic gonadotropin; RBC = red blood cell;

Clinical laboratory tests during the study will be performed by ICON Laboratories (with the exception of urine pregnancy tests, which will be performed locally). Eligibility will be determined by the central laboratory. All protocol-required blood samples (as noted in the Schedule of Procedures/Assessments [Table 6 and Table 7]) will be collected and sent to the central laboratory as specified in the laboratory manual.

In addition, local laboratories may be used for treatment decisions, safety evaluation, and for management of chemotherapy-related toxicity, as appropriate; however, local laboratory results will not be collected. All local hematology and blood chemistry samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle.

A laboratory abnormality reported by either the central laboratory or local laboratory may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.4.1 and the eCRF Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

For laboratory abnormalities meeting the criteria of SAEs (see Section 9.5.1.4.2), the site must fax or email the SAE report including the laboratory report (as regionally required) to the sponsor using the SAE form (see Section 9.5.4.1).

For women of childbearing potential (refer to Section 9.3.1 for details), pregnancy testing will be performed prior to and throughout the study period. At Screening, a single sample of blood will be taken for a serum human chorionic gonadotropin (hCG) pregnancy test, which will be submitted to the central laboratory for analysis. In addition, prior to Test Article administration, a highly-sensitive urine pregnancy test (hCG) will be administered locally at the timepoints specified in the Schedule of Procedures/Assessments (Table 6 and Table 7). Results of these tests will be entered into the eCRF.

Refer to Appendix 2 for specific quantities of blood to be drawn during the study.

9.5.1.4.4 PHYSICAL EXAMINATIONS

PEs will be performed at the time points listed in the Schedule of Procedures/Assessments (Table 6 and Table 7). Refer to Section 9.5.1.1.2 for additional details.

9.5.1.4.5 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained at the time points listed in the Schedule of Procedures/Assessments (Table 6 and Table 7). Complete, standardized, 12-lead ECG recordings that permit all 12-leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.4.1) and the eCRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.4.2) the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.5.4.1).

9.5.1.4.6 ECOG PERFORMANCE STATUS

All subjects will be assessed for ECOG Performance Status (Appendix 3) at Screening and at the time points listed in the Schedule of Procedures/Assessments (Table 6 and Table 7).

9.5.1.4.7 ADVERSE EVENTS OF INTEREST

Immunologic symptoms associated with hypersensitivity reactions are possible with administration of any monoclonal antibody and should be considered AEs and recorded in the eCRF.

Hypersensitivity

The following signs and symptoms are considered hypersensitivity AEs if they occur within 24 hours of Test Article infusion:

- Cytokine release syndrome
- Flushing
- Fever
- Rigors/chills
- Sweating/diaphoresis
- Pruritus/itching

- Urticaria
- Bronchospasm/wheezing
- Bronchial edema

Hypersensitivity AEs are to be graded according to CTCAE v4.03 (National Cancer Institute, 2010). Hypersensitivity AEs are to be recorded in the eCRF and, if serious, should also be reported in an expedited manner using the SAE form as well in the same manner and timeframe as reporting of SAEs (Section 9.5.4.1).

All subjects will be assessed for ADA responses. Blood samples will be collected for this purpose at Screening and at various time points throughout the study, as described in the Schedule of Procedures/Assessments (Table 6 and Table 7).

Hypersensitivity AEs have been seen in the Phase 1 and 2 clinical trials of farletuzumab during and immediately following the administration of farletuzumab. In general, hypersensitivity AEs to monoclonal antibodies are immediate, typically occurring during the first few minutes of the first infusion. However, up to 30% of reactions to monoclonal antibodies are delayed and may occur in later infusions (Lenz, 2007).

Treatment of Hypersensitivity AEs

If a hypersensitivity AE occurs during infusion of Test Article, the rate of infusion should be decreased by at least 50% and then advanced back to the highest rate that was well-tolerated. Otherwise, the infusion should be terminated completely in accordance with standard practice at the investigational site or based on the CTCAE.

In the event of a hypersensitivity AE, the subject may be treated with an additional 650 mg acetaminophen orally, either alone or in combination with diphenhydramine 25-50 mg orally (Grade 1 reaction) or IV (Grade 2 reaction). At any point at which the investigator deems necessary, other therapeutic interventions should be initiated based on the signs and symptoms and the severity associated with the event.

Secondary Prophylaxis of Hypersensitivity AEs

For subjects who have experienced hypersensitivity AEs, secondary prophylaxis is recommended and given at the investigator's discretion. Details of secondary prophylaxis are outlined in Section 9.4.8.1.1 and below:

- Subjects experiencing hypersensitivity AEs consisting of Grade 1 events can be managed with secondary prophylaxis for subsequent infusions. Along with an antipyretic of choice (acetaminophen to a dose of 1000 mg orally has been used) and concurrent use of diphenhydramine, an H2 receptor antagonist can be considered, such as ranitidine (50 mg IV). Secondary prophylaxis should be administered approximately 30-60 minutes prior to dosing with Test Article.

- Subjects experiencing hypersensitivity AEs consisting of Grade 2 events can be managed with secondary prophylaxis for subsequent infusions, along with diphenhydramine 50 mg IV, ranitidine 50 mg IV, and dexamethasone 20 mg IV. Secondary prophylaxis should be administered approximately 30-60 minutes prior to dosing with Test Article.

Prophylaxis regimens are given at the investigator's discretion and should be recorded in the eCRF.

If a Grade 3 hypersensitivity AE occurs, the subject may be continued at the discretion of the investigator, provided the reaction can be reduced to and maintained at Grade 2 or lower. In the event that a Grade 4 hypersensitivity AE occurs, the subject will be discontinued from Test Article and moved to the Follow-Up Phase of the study.

Interstitial Lung Disease

Interstitial lung disease AEs are defined as AEs identified within the narrow-search Standardized Medical Dictionary for Regulatory Affairs Query (SMQ) for "interstitial lung disease," including, but not limited to:

- Interstitial lung disease
- Pulmonary fibrosis
- Pneumonitis

These events have been seen in clinical studies with other monoclonal antibodies; therefore, they will be monitored in this study and analyzed by CTCAE grade separately from other AEs.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 6 and Table 7 present the Schedule of Procedures/Assessments for the study.

Table 6 Schedule of Procedures/Assessments 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											
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		

Table 6 Schedule of Procedures/Assessments for PLD/Carboplatin Chemotherapy Arm

	Screen Phase[a]	Combination Treatment Phase								Maintenance Treatment Phase					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					
Evaluations	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	Test Article Admin Only Visits	EOT Visit[b]	30-Day Safety Visit	60-Day Visit	Follow-up Phone Call
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.

Table 6 Schedule of Procedures/Assessments 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					

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 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).

Table 6 Schedule of Procedures/Assessments 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					
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).																	

Table 7 Schedule of Procedures/Assessments 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		
Survival contact, anticancer treatment													X	X	X

Table 7 Schedule of Procedures/Assessments 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					

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; 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

Table 7 Schedule of Procedures/Assessments 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					
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 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).															

9.5.2.2 Description of Procedures/Assessments Schedule

Refer to the Schedules of Procedures/Assessments (Table 6 and Table 7), for details regarding the procedures and assessments required for this study.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in oncology studies.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Other Events of Interest

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study drug, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event.

Reporting deaths due to PD as SAEs is not necessary unless required per local regulations, as death associated with disease progression is included in the efficacy analysis.

SAEs, regardless of causality assessment, must be collected from date of informed consent signature through 30 days following the last dose of Test Article (farletuzumab or placebo). SAEs that are ongoing at the time of discontinuation of Test Article will be followed until resolution (or until stable if resolution is not expected).

Any SAE judged by the investigator to be related to Test Article or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided for the investigator in the Investigator Study File.

For SAE reporting purposes, please call/fax information to the following:

North America Safety Hotline:
Phone: PPD
Fax: PPD

EMA/Asia-Pacific Safety Hotline:
Phone: PPD
Fax: PPD

For urgent safety issues call: PPD **(24/7 number)**.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the CRO monitor to be filed in the sponsor's trial master file (TMF).

9.5.4.2 Reporting of Pregnancy and Exposure to Test Article Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the EOT Visit of the study or within 6 months following Test Article (farletuzumab or placebo) discontinuation, whichever is longer, or any exposure to study drug through breastfeeding during study treatment or within 30 days of the last Test Article administration, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1 Reporting of Serious Adverse Events).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Other Events of Interest

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of Test Article in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of Test Article not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of Test Article accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate Test Article use or subject harm while Test Article is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Section 9.5.4.1 Reporting of Serious Adverse Events, even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as non-serious on the SAE form and the Adverse Event eCRF.

9.5.4.3.2 Reporting of Study-Specific Events

Hypersensitivity AEs and Interstitial lung disease (ILD) AEs will be monitored in this study and analyzed by CTCAE grade separately from other AEs. Separate summaries and listings of hypersensitivity and ILD AEs will be presented. Hypersensitivity AEs and ILD AEs meeting serious criteria should be reported in the same manner and timeframe as any SAE.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the Test Article given (farletuzumab or placebo), the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break. Refer to Section 9.4.7 for additional details regarding blinding of treatment assignments.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects from Study (EOS)

Once a subject discontinues Test Article for any reason, the EOT procedures should be completed and documented in the eCRF and the EOT form should be completed.

Subjects who choose to discontinue Test Article administration but agree to continue participation in the study should still continue to be followed for OS. In addition, subjects who discontinue Test Article prior to having documented disease progression by RECIST 1.1 (Appendix 4) should continue to be followed radiographically to progression.

A subject may elect to discontinue participation in the study at any time for any reason. All subjects who discontinue the study are to complete the study's EOT procedures indicated in the Schedule of Procedures/Assessments (Table 6 and Table 7). In addition, the EOT and EOS eCRF forms should be completed. The investigator will promptly explain to the subject involved that all study procedures will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Following discontinuation of survival follow-up, disposition information will be collected on the EOS eCRF.

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.5.8 Data Monitoring Committee

A DMC will be established for this protocol to enhance safety monitoring by providing unblinded, independent oversight of the safety of study participants. The unblinded DMC will comprise 3 clinicians, all independent from Eisai and investigative sites and selected as to avoid conflict of interest. Eisai representatives from the study team will be appointed to attend the DMC open portion of meetings but will be independent of the recommendations derived from any closed portions of meetings.

The primary objectives of this DMC are to provide independent safety monitoring of unblinded data comparing adverse event rates between treatment arms, and to provide recommendations at each planned analysis. The DMC will review summary tabulations and comparative statistics to determine whether there appears to be an excess of any important AEs in either of the study treatment arms.

The safety evaluation will focus on AEs, tolerability, and clinical laboratory measurements. All subjects included in the Safety Population will be evaluated by treatment. All treatment emergent AEs will be summarized (by incidence) for each treatment arm and listed by the System Organ Class (SOC), preferred term, toxicity/severity grade, and causal relationship to Test Article. In addition, separate summaries of SAEs, deaths on study, Grade 3 or 4 AEs, and drug hypersensitivity and ILD AEs will be presented for each treatment arm.

In addition, the DMC may review any individual event thought to be of major significance as requested by the DMC; such events would generally include deaths or other serious outcomes for which a causal connection with the intervention is plausible.

Interim reports will be prepared for review and analysis by a statistician independent of Eisai and investigators to protect against inadvertent or inappropriate access. The independent statistician will retain the randomization code for unblinding data as outlined in the charter or as requested by the DMC. Unblinded interim data will not be accessible by anyone other than DMC members or the independent statistician(s) performing these analyses and presenting them to the DMC.

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. This will be followed by ongoing DMC safety reviews, to be conducted at a minimum frequency of every 6 months. The frequency of planned data reviews may also be increased as needed, based on accrual rates or emerging safety information as outlined in the DMC charter, and ad hoc safety reviews may also be convened when warranted to enhance safety oversight.

A DMC charter will be written to establish well-defined standard operating procedures including meeting proceedings and structure, data assessments, documentation and recordkeeping, process for DMC recommendations, and regulatory reporting as applicable. The charter will be written with procedures to ensure the minimization of bias, such as maintaining confidentiality of any interim data.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures (SOPs), working practice documents, and applicable regulations and guidelines.

Before any subjects can be enrolled at an investigational site and prior to the conduct of any protocol-specific procedures, formal training of investigational site personnel will be conducted. The investigator and all relevant investigational site staff are to be trained on aspects of the trial for which they are responsible. Site personnel may be trained at a formal initiation visit, at an Investigator's Meeting, or by another means, as necessary.

Imaging-Related Data

Investigator-assessed PFS is the primary efficacy endpoint for this study. However, all CT or MRI scans will be collected and stored in an independent central imaging laboratory for quality control purposes. The central imaging laboratory assessment of the study images will address the following objectives:

- Review of baseline CT/MRI images to confirm the eligibility status of each subject in terms of evaluable disease based on the protocol inclusion criteria
- Review of the images to monitor the investigator assessment of disease progression based on RECIST 1.1

Details on the collection and assessment of the study images and communication between the central imaging laboratory and the study sites will be included in the imaging manual.

eCRF-Related Data

Onsite verification of the eCRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters will be performed on a regular basis. Where appropriate, remote verification of source information will also be performed. The investigational site will be monitored immediately following enrollment of the first subject at the site (ie, within approximately 2 weeks or the earliest time point feasible) to verify that inclusion/exclusion criteria have been fulfilled. Subsequent monitoring visits will occur at regular intervals while subjects are actively enrolled into the clinical trial. Through frequent communications with the investigational site, the CRA will ensure that the investigation is conducted according to protocol design and all applicable regulatory requirements. Additional details on the monitoring of this clinical trial are provided in Section 11.3.

Additionally, ongoing data review of eCRF data will be performed by Data Management. External validation checks will be applied to assess data quality for completeness, consistency and conformance with the requirements of the protocol. Data review findings that impact eligibility will be reviewed by the Study Team and findings will be documented in the sponsor's TMF.

Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study. During the course of the clinical trial, investigational sites, the clinical trial database, and all associated clinical trial documentation may be subject to quality assurance audits by the sponsor, or their appointed representatives, on a planned or an as-needed basis. In addition, representatives of associated regulatory bodies may conduct inspections at their discretion. The investigator is responsible for assuring direct access to all study-related materials for the purpose of these activities.

9.6.1 Data Collection

Data required by the protocol will be collected on the electronic CRFs (eCRFs) and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the eCRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission fromEisai, except for authorized representatives Eisai or appropriate regulatory authorities.

The following apply to eCRFs:

- The sponsor will supply the eCRFs for data collection
- All eCRFs are to be completed by authorized study personnel and reviewed and signed by the investigator(s)
- Each investigator is responsible for ensuring that all discontinued orders or changes in the study or other medications entered on the subject's eCRF correspond to the entries on the subject's medical records
- eCRFs should be completed within 10 business days of the subject visit completion
- eCRFs must accurately reflect data contained in subject's records (eg, source documents)

At the beginning of the study, an investigator's study file will be established at the study center. The investigator/institution is responsible for maintaining the study documents as specified in the guideline for ICH GCP and US 21 CFR Part 312 and as required by the applicable regulatory requirement(s). The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

The following guidelines, instructions, and certifications are regarded as relevant supplements and will be provided for the investigator's study file at each center:

- Global Investigator's Brochure
- Instructions for completion of the eCRF
- Sample shipment details
- Pharmacy Manual
- Laboratory Manual
- Imaging Manual

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. Data, both eCRF and external (eg, Central laboratory data), will be entered into a clinical system.

This clinical trial will utilize an electronic data capture system for the management of clinical data. The data will be collected in electronic form (ie, via an eCRF) to allow for data entry at the investigational site from source documentation directly into the electronic database. Source documentation will be collected in accordance with ICH GCP, US 21 CFR Part 312, and the site's standard procedures.

The eCRF and eCRF Completion Guidelines will be supplied by the sponsor or its designee. Access to the electronic system will be restricted, and only authorized users will be able to access the system via individualized, password-protected accounts. Authorized site personnel will enter the information required by the protocol onto the eCRFs in accordance

with the eCRF Completion Guidelines. All changes to data in the database will be tracked and time stamped automatically, including updates to data entries and resolution of data queries generated by the CRA or data reviewer. Each investigator must review the subject data and approve the eCRFs by providing electronic signature.

Training will be provided to all system users based on their individual access role and use requirements prior to granting access and ongoing throughout the course of the clinical trial as needed. Documentation of training will be kept in the investigational site regulatory file and the sponsor's TMF.

A comprehensive set of data management documents that describe database set-up, testing, data review, and external data handling procedures will be prepared and filed in the sponsor's TMF. The standard operating procedures, internal/external security safeguards, system and change controls, and training procedures utilized to manage the trial will be outlined. A cumulative record will also be kept of the user access privileges for all authorized users across the clinical trial.

The system and procedures for electronic database set-up, entry, review, access, security, and auditing are designed in specific compliance with 21 CFR Part 11 and the FDA's Part 11 Guidance for Industry supplement "Computerized Systems Used in Clinical Investigations" (US Department of Health and Human Services, FDA, 2007). Any additional electronic systems that may be used by vendors (eg, PK) must comply with the same regulatory standards. Clinical sites (eg, electronic medical records used as source documents) must comply with local standards.

9.7 Statistical Methods

9.7.1 Statistical and Analytical Plans

A detailed statistical analysis plan (SAP) will be prepared as a separate document. The SAP includes a more technical and detailed description (including templates for tables, listings, and figures) of the planned statistical summaries. The SAP will supersede the study protocol for any differences between the two documents in the plans for data analysis. Details on censoring rules and handling rules for missing values will be specified in the SAP, as well as an outline of potential sensitivity analyses with regard to missing values. The SAP will be finalized and approved before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary efficacy endpoint for this study is PFS based on the investigators' radiographic assessments utilizing RECIST 1.1 criteria (Appendix 4). 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 time will be censored at the date of last tumor assessment without

evidence of progression prior to the date of initiation of further anticancer treatment or the cut-off date, whichever is earliest. Detailed censoring rules will be outlined in the SAP.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary efficacy endpoints for the study are as follows:

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 vs Second Platinum-Free Interval: Length of first platinum-free interval is defined as the period of time (in months) from the date of completion of previous platinum based chemotherapy until date of first relapse (ie, first observation of progression), as recorded on the eCRF. The date of first relapse is the progression date based on a radiographic assessment. Similarly, 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 until the date of progression based on the investigator's radiographic assessment (RECIST 1.1 [Appendix 4]).

Tumor Response (OR, TTR, DR per RECIST 1.1): OR is defined as either a CR or a PR using RECIST 1.1 criteria (Appendix 4). 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). DR 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.

9.7.1.1.3 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.

9.7.1.2 Definitions of Analysis Sets

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

The Safety Analysis Set (SAS) 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, analyzed by the treatment received. All safety endpoints will be analyzed using this set of subjects.

The Evaluable Population 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 assessment performed. They will be used to evaluate tumor response, farletuzumab serum drug levels, ADA, and other biomarker defined populations.

9.7.1.3 Subject Disposition

The number of subjects in each analysis population and the reasons for exclusion, along with any randomization errors will be summarized by treatment group. In addition, subjects that discontinue study treatment or study follow-up will also be summarized by treatment group, along with reasons for discontinuation of study treatment and study follow-up.

9.7.1.4 Demographic and Other Baseline Characteristics

Subject demographics and characteristics at baseline will be summarized by treatment group in frequency tables or with summary statistics for continuous variables in the ITT population. Unless specified otherwise, the baseline value will be taken as the last value prior to the first study drug administration (or closest to date of enrollment for subjects not treated). Laboratory values will be graded, when possible, using CTCAE criteria.

The stratification factor profiles will be evaluated among the treatment groups, as well as other potential imbalances in subject characteristics.

Continuous demographic and baseline variables include, but are not limited to: age, weight, BSA, CA125, and length of first platinum-free interval, etc. Categorical variables include, but are not limited to: race, ethnicity, reproductive status, ovarian cancer primary site, original disease stage, ECOG status, and ascites, etc.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (March 2014 release, or later). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the SAS population by treatment group, Anatomical Therapeutic Chemical (ATC4) class, and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of Test Article. Concomitant medications will be defined as medications that (1) started before the first dose of Test Article and were continuing at the time of the first dose of Test Article, or (2) started on or after the date of the first dose of Test Article up to 30 days after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

PFS is defined in Section 9.7.1.1.1. The cut-off date for PFS will be based on one of the following milestones: a) at least a total number of 143 PFS events, or b) a minimum of

6 months PFS follow-up from last subject enrolled, whichever occurs later. The cut-off date for PFS will be used for all secondary efficacy variables, as well as survival data supporting the interim survival analysis.

The stratified log rank test will be utilized 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 vs. carboplatin plus PLD), and (2) length of platinum-free interval following first line therapy (6-12 months vs. >12-36 months). The HR will be estimated based on Cox's proportional hazards model stratified by the same two factors. PFS will be summarized using Kaplan-Meier curves and will be further characterized in terms of the median and PFS probabilities at 6, 12, 18, and 24 months. Sensitivity analysis will be performed using the unstratified log-rank test. Multivariate Cox's proportional hazards model will be utilized to evaluate the treatment effect modified by prognostic factors, which will be specified in the SAP. Additional sensitivity analysis could be specified in the SAP.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

OS is defined in Section 9.7.1.1.2. 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. OS will be analyzed using methods similar to the PFS analyses.

DR will be analyzed using the methods described in Section 9.7.1.6.1 except for the multivariate and additional sensitivity analyses. Time to tumor response will be characterized with descriptive statistics. Both time-to-tumor response and DR are analyzed on responders.

The proportion of subjects in the ITT population who experienced a platinum-free interval during the study that is longer than their first platinum-free interval will be summarized within each treatment group, stratified by length of first platinum-free interval (6-12 months, >12-36 months). Treatment estimates and two-sided 95% CIs will be presented.

For OR, the RR is defined in Section 9.7.1.1.2, and will be compared between farletuzumab and placebo using the Cochran-Mantel-Haenszel (CMH) test stratified by the same factors used in the primary PFS analysis. The CMH analysis will be conducted in the ITT (primary) and Tumor Response Evaluable (secondary) populations. Treatment estimates and differences in proportions will be presented with corresponding two-sided 95% CIs.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

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 ≤ 3 x ULN (105 U/mL).

Exploratory analyses for efficacy endpoints including PFS, OS, OR, and DR will also be conducted in each of the two chemotherapy strata (paclitaxel, PLD).

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

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.

9.7.1.7.2 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.

9.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment group, will be summarized on an "as treated" basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables). Safety variables include treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs), clinical laboratory parameters, tolerability (treatment discontinuations, treatment delays, and dose reductions), 12-lead ECG results, ECOG performance status, and 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 SAS population will be evaluated by treatment group in the safety analysis. In addition, analyses will be provided for the Combination Treatment and single-agent Maintenance Treatment safety sub-populations. All these analyses will also be repeated for each chemotherapy (paclitaxel vs. PLD).

9.7.1.8.1 EXTENT OF EXPOSURE

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

Extent of exposure parameters will be summarized by treatment group in the SAS population and 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, number of dose delays. A summary of AEs leading to dose delay and/or reduction will also be provided. Additionally, cumulative dose, dose intensity, and relative dose intensity (actual dose intensity divided by the planned dose intensity) will also be summarized by treatment group. Summaries for the farletuzumab treatment will include duration of exposure, number of infusions received, and number of dose delays. A summary of AEs leading to dose delay will also be provided. Additionally, cumulative dose (mg/kg), dose intensity (mg/kg/week) and relative dose intensity (actual dose intensity divided by the planned dose intensity) will also be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) (version 17.0 or higher) terminology and the severity of the toxicities will be graded according to the CTCAE.

The focus of the analyses will be on TEAEs and TRAEs. A TEAE is defined as an 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 TRAE is defined as a TEAE that was classified by the investigator as related to treatment with Test Article. All TEAEs and TRAEs will be summarized (by incidence) and listed by the System Organ Class (SOC), preferred term, toxicity/severity grade, and causal relationship to study drugs (only TEAEs). In addition, separate summaries of SAEs and Treatment-related SAEs, TEAEs and TRAEs leading to death on study, TEAEs and TRAEs leading to study drug discontinuation, Grade 3 and 4 AEs, hypersensitivity AEs, and ILD AEs, as well as separate listings, will be presented.

Drug Hypersensitivity Adverse Events (DHAEs) are defined as the subset of programmatically-identified hypersensitivity AEs noted in Section 9.5.1.4.7 that also have serologic evidence of an immunologic response to the Test Article (ie, positive ADA which is defined as a treatment induced or treatment-boosted ADA). The determination of DHAE status for each of the programmatically-identified AEs described in Section 9.5.1.4.7 is dependent upon serum ADA sample results obtained on or subsequent to the onset date of the AE. There could be multiple subsequent ADA samples. If the serum ADA results are positive for at least 1 of these samples, the AE will be considered a DHAE. Any event captured within the predetermined MedDRA codes for hypersensitivity AEs and having a

positive ADA titer on that day or subsequent to the occurrence of the hypersensitivity AE will be considered a DHAE.

9.7.1.8.3 LABORATORY VALUES

Hematology and chemistry laboratory parameters will be graded according to the CTCAE criteria where applicable. For each parameter based on the worst grade observed by the subject during the on-treatment period, the number and percentage of subjects with any abnormality (ie, Grade 1 or higher) and with Grade 3 or 4 will be tabulated by treatment group. Shift tables (comparing worst on-study grade vs. baseline) may also be used to summarize selected parameters of interest. When the CTCAE scale is not applicable for a parameter, analyses will be performed based on out-of-normal laboratory range values.

9.7.1.8.4 CARDIAC SAFETY EVALUATION

Descriptive statistics for ECG results and changes from baseline will be presented by visit and treatment group.

All cardiac function data, including cardiac assessment, will be presented in a data listing.

9.7.1.8.5 OTHER SAFETY ANALYSES

Blood samples will be drawn before the administration of Test Article at time points specified in the Schedule of Procedures/Assessments (Table 6 and Table 7) for the evaluation of the development of immunogenicity (ADA) responses. 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).

9.7.2 Determination of Sample Size

Sample size considerations are based on the primary PFS endpoint comparing 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 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 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 at 1-sided 10%, the following sequential testing scheme will be employed for the PFS primary analysis and the OS analyses:

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

9.7.3 Interim Analysis

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.

An interim analysis for OS will be performed to accompany the primary PFS analysis of the study. 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.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

The SAP will be finalized at the earliest time possible, at minimum prior to formal database lock for analysis. The details of any revisions to protocol specified analyses or changes to the planned analyses outlined in the final SAP will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor (or appropriate study team member) and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required, the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

In general, protocol violations include deviations from inclusion/exclusion criteria, from concomitant medication restrictions, and from any other protocol requirement that could, at least hypothetically, result in significant risk to the subject and/or affect the outcome of the clinical trial. Protocol violations will be noted in the final CSR.

A deviation is defined as nonadherence to the protocol procedures or schedule as defined by the protocol or the primary endpoint that does not place the subject at any added or significant risk or affect the data quality or the outcome of the clinical trial (eg, a missed procedure, an out-of-window site visit).

Only subjects who meet protocol-defined eligibility criteria may be enrolled in this clinical trial. If any protocol eligibility criteria or procedures are unclear, the investigator or investigational site personnel should contact the CRA. If the question requires medical interpretation, the sponsor's medical monitor should be consulted. All protocol violations should be reported to the IRB/IEC according to the standard practices of the investigational site and applicable regulatory requirements.

Data and document review will be performed in an ongoing manner during trial conduct to assess protocol deviations and violations. The sponsor will convene a data review meeting at least once prior to database lock to classify findings as either protocol deviations or violations.

11.3 Monitoring Procedures

The sponsor's and/or the CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned blinded and unblinded CRAs, as described in the monitoring plan. For the purpose of maintaining the blind of this study, all pharmacy and study drug accountability monitoring will be performed by an unblinded CRA assigned by the sponsor or CRO. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with ICH GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as x-rays, and other imaging reports (eg, sonograms, CT scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalograms, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- eCRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

Prior to the start of the clinical trial, each investigational site will be initiated with training on the protocol and discussion of the responsibilities of the investigator. The investigator must participate in this meeting, as must any other investigational site personnel who are involved in the conduct of the clinical trial.

The CRA will perform the first onsite monitoring visit at each site approximately 2 weeks after the first subject is enrolled at that site to ensure that clinical trial procedures are being followed. After the first visit, monitoring visits will occur at regular intervals, as agreed upon with the sponsor. At these interim monitoring visits, the CRA (or unblinded CRA, where noted) will perform the following tasks:

- Compare data entered into the eCRFs with the corresponding source documents
- Check for protocol compliance (including documentation of adequate written informed consent, appropriate subject visit dates, documentation of AEs and concomitant medications, key safety and biological endpoint observations, and study agent dosing)
- Review the site regulatory binder to ensure that all regulatory documentation has been updated as necessary and filed appropriately, and reconcile the contents of the site regulatory binder against the TMF
- (Unblinded CRA only) Review Test Article accountability (and chemotherapy accountability [only if provided by the sponsor]) and verify compliance with the study Protocol and the Pharmacy Manual

After the last subject at the site has completed the clinical trial, the CRA will return to the site for final source data verification and close-out visit. At this visit, any outstanding issues will be resolved and the investigator's responsibilities for retention of clinical trial documentation will be reviewed.

11.4 Recording of Data

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as the source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected. The investigator must electronically sign each subject's eCRF.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated

representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Global Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor and as required per local regulations, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

At the completion of the required retention period or in the event that the investigator retires or relocates during the retention period, the investigator is asked to contact the sponsor to provide the location where the records are archived, including contact information for the responsible party(ies). This will allow the sponsor to assist in arranging for permanent archiving of the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Test Article

All farletuzumab will be supplied to the designated, unblinded pharmacist by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked) in its original packaging, and stored according to the conditions specified on the label. The unblinded pharmacist must maintain records of farletuzumab delivery to the study site, inventory at the site, use for each subject, and farletuzumab destruction or return. Throughout the study, partially-used and empty vials, as well as any investigational product deemed unusable (eg, as a result of a temperature excursion) must be accounted for.

On close-out of the site, all remaining used vials and unused vials may be destroyed onsite, according to the investigational site's local destruction policy/standard operating procedures, following review of drug accountability records by the unblinded site monitor. The investigational product may also be returned to the sponsor's designated location if previously arranged with the sponsor. The sponsor will assure that a final report of drug accountability to the vial level is prepared and maintained by the investigative site.

A Drug Dispensing Log will be supplied by the sponsor. This log must be kept current and should contain the following information:

- Initial and subsequent inventory on receipt of farletuzumab at the investigational site
- Identification (subject number) of each subject to whom the farletuzumab was dispensed
- Number of vials of farletuzumab used at each visit per subject
- Dates and lot numbers of all farletuzumab dispensed
- Number and lot numbers of farletuzumab vials destroyed
- Number and lot numbers of farletuzumab vials returned

All records and inventory must be available for inspection by the sponsor or its designee (ie, the unblinded clinical study monitor), the IRB/IEC, and the relevant regulatory agencies.

Additional details on the storage, handling and inventory of farletuzumab will be provided in the Pharmacy Manual.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator’s staff, and the IRB/IEC, and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

The study will be listed on www.clinicaltrials.gov and other registries, as appropriate.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations. The terms of insurance will be kept in the regulatory files.

12 APPENDICES

Appendix 1 Sample Collection Procedures and Bioanalytical Methods for Serum Farletuzumab levels and ADA

METHODS:

Blood samples for farletuzumab level analyses and ADA in the clinical studies with farletuzumab should be processed for serum. A blood sample (5.0 mL) will be collected for each test into sterile tubes and placed at room temperature for at least 30 minutes to allow clot formation. Centrifuge within 1 hour of collection at approximately 3000-3500 rpm for 15 minutes. Serum will be removed from the clot and divided into 2 equal aliquots. Within 2 hours of collection time, freeze and store samples at -70°C to -80°C (if not available -20°C) until instructed to ship to central laboratory.

Complete instructions for processing and shipping samples will be located in the laboratory manual.

FARLETUZUMAB LEVEL IN SERUM:

This fluorescent immunoassay format measures free forms of farletuzumab in human serum based on direct capture by a biotin-farletuzumab complementarity determining region (CDR)-specific bivalent Fab mini-antibody immobilized on streptavidin coated columns within a bioaffy 200 CD, followed by direct detection using an Alexa Flour labeled murine antifarletuzumab and subsequent fluorescence detection via Gyros Workstation.

FARLETUZUMAB ANTI-DRUG ANTIBODY (ADA) ASSAY:

A tiered analysis approach will be employed using risk-based statistical methods to detect, confirm and characterize the presence of farletuzumab-specific human anti-drug antibodies in subject samples. First, samples generating a signal at or above an established floating screening cut point (one-tailed, upper 95% CI), will be identified as potential ADA positives. These samples will be subsequently assessed for ADA specificity to farletuzumab through competitive inhibition of immuno-complex formation by addition of excess unlabeled farletuzumab and evaluating the relative change in signal responses compared to unspiked samples. Lastly, positive and specific ADA samples are serially diluted to generate a relative titer value to establish the magnitude of the ADA response.

The validated bridging format immunoassay detects the presence of farletuzumab-specific immunoglobulins based on the formation and capture of immuno-complexes between biotinylated farletuzumab, antifarletuzumab and reporter labeled farletuzumab antibody. Bound anti-drug antibody immuno-complexes are then detected in a quasi-quantitative manner via electrochemiluminescence signal generation. Sample signal responses are evaluated against a statistical threshold derived from drug naïve individuals, and confirmed for specificity to farletuzumab via competitive binding signal depletion.

Appendix 2 Quantity of Fluid and Tissue to be Collected

The anatomical sites from which blood samples are drawn and drug is administered must be documented in the medical record. A breakdown of the approximate amounts of blood to be collected for each investigation, as specified in the Schedule of Procedures/Assessments (Table 6 and Table 7), is provided below.

Investigation	Quantity/Volume	Additional Notes
Archived tumor tissue	Tumor block or 15-20 (4-5 micron) slides	Slides to be created from serial sections cut from the archival tumor tissue sample taken at the time of initial diagnosis of ovarian cancer; serial sections to be identified sequentially as cut. If a minimum of 15 slides are not available, contact the CRA to discuss.
Hematology panel	3.0 mL	
Chemistry panel	4.0 mL	Screening pregnancy test analyzed from the same vial as the Chemistry panel
hCG pregnancy test		
CA125	5.0 mL	
Biomarker levels	11.0 mL*	5.0 mL for serum, 6.0 mL for plasma; *add an additional 11.0 mL at Screening; to be collected within 2 weeks of Randomization
Urine biomarker	10.0-20.0 mL	Screening only; to be collected within 2 weeks of Randomization
Farletuzumab levels	5.0 mL	10.0 mL total per specified visit
ADA levels	5.0 mL	

Appendix 3 Eastern Cooperative Oncology Group Performance Status

Grade	ECOG
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

(Oken, et al., 1982)

The ECOG Performance Status is in the public domain and made available by the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Co-Chair.

Appendix 4 Protocol-Specific Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Quick Reference

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) Eur J Cancer. 2009;45:228–247.

Methods of Measurement

- As part of the disease assessment by RECIST 1.1 criteria, 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 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 (eg, 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 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 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 ≥ 10 mm and < 15 mm

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

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

Measurable lesions 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 patients 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 patients who have measurable disease at baseline.

Time Point Response: Patients With Target (+/– Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
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
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

For additional guidance on evaluation of tumor response according to RECIST 1.1, please refer to the RECIST 1.1 guideline (Eisenhauer, et al., 2009).

PROTOCOL SIGNATURE PAGE

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
Investigational Product Name:	Farletuzumab (MORAb-003)
IND Number:	BB12219
EudraCT Number:	2014-003812-36

SIGNATURES

Authors:

PPD

06 NOV, 2018
Date

Oncology Business GroupEisai Inc.

PPD

06 Nov 2018
Date

Oncology Business Group, Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

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I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date